MULTIPLE SCLEROSIS IN A PRIMARY CARE SETTING:
Employing Strategies for Early Diagnosis & Improved Patient Outcomes

May 1, 2013
10:45am—12:15pm
Anaheim Convention Center

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Department of Neurology, Baylor College of Medicine
Houston, Texas

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ACTH Vs MP Trial Department
Neurology Keck School of Medicine of USC
Los Angeles, California

EDUCATION PARTNER
Horizon CME
Session 3: Multiple Sclerosis in a Primary Care Setting:
Employing Strategies for Early Diagnosis and Improved Patient Outcomes

Learning Objectives

1. Recognize early multiple sclerosis (MS) symptoms and facilitate accurate diagnosis according to recommended MS diagnostic and imaging criteria.
2. Be familiar with strategies for managing the symptoms and complications of MS in the primary care setting.
3. Outline the risks and benefits of currently available disease modifying therapies in the treatment of patients with MS.
4. Monitor MS patients on disease modifying therapies for effectiveness and safety.

Faculty

Regina R. Berkovich, MD, PhD
Assistant Professor, Clinical Neurology Principal Investigator
ACTH Vs MP Trial Department
Neurology Keck School of Medicine
University of Southern California
Los Angeles, California

Dr. Regina Berkovich is an assistant professor of Clinical Neurology at the Comprehensive MS Care Center of the Keck School of Medicine, University of Southern California (USC). She has specific training and expertise in Multiple Sclerosis and is one of the key opinion leaders in her field. The USC MS Center is the largest in Southern California; serving over 2500 patients with MS. She has a large clinical practice where she consults and follows up with MS patients on a regular basis.

Dr. Berkovich also carries out extensive clinical research in MS and has participated in many multicenter clinical trials in the capacity of principal investigator (PI) and co-PI. She developed several investigator initiated protocols and has been awarded research grants for originally designed Investigator Initiated Studies (IIS) from National Multiple Sclerosis Society, Questcor, and Teva Pharmaceutical. The Investigational New Drug Application (IND) was granted to her by the FDA for potential new indicator for the adrenocorticotropic hormone. Her recent American Academy of Neurology (AAN) poster was included in official 65th AAN Press release.

Over years of working in clinical trials, Dr Berkovich developed close professional relationships with top scientists in the MS field. She designed and carried on collaborative ancillary studies, such as the Immunology study of ACTH in collaboration with Professor Lawrence Steinman, MD at Stanford University and MRI metrics of monthly ACTH in collaboration with Professor Rohit Bakshi, MD, PhD at Harvard University.

In 2010, Dr Berkovich was awarded the Top Doctors Certificate by the Pasadena Magazine. She is a member of Los Angeles Society of Neurologists, Association of California Neurologists, American Neurology Association (ANA), and American Academy of Neurology (AAN).

Victor M. Rivera, MD, Sr, FAAN
Distinguished Emeritus Professor of Neurology
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Department of Neurology
Baylor College of Medicine
Houston, Texas

Dr. Victor M. Rivera is the distinguished emeritus professor of Neurology at Baylor College of Medicine, adjunct professor of Research at the University of Houston, senior member and fellow of the American Academy of Neurology. He is also the founder of the Mexican Academy of Neurology and the Latin American Committee for Treatment and Research in MS (LACTRIMS); serving as its president for two consecutive terms. He is also the founder and first director of the Maxine Mesinger Multiple Sclerosis Comprehensive Care Center & Clinic of Baylor College of Medicine at The Methodist Hospital in Houston, Texas.
Faculty Financial Disclosure Statements
The presenting faculty reports the following:

Dr Berkovich served as a consultant for Acorda, Avanir, Bayer, Biogen Idec, Genzyme, Questcor, Teva.

Dr Rivera has no financial relationships to disclose.

Education Partner Financial Disclosure Statement
The content collaborators at Horizon CME have report the following:

Brian Lee, PharmD, Elizabeth Wilkerson, CHES, Cara Williams, PharmD, and Arianna Sunford, BHA, have no financial relationships to disclose.

Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDMS</td>
<td>Clinically Definite Multiple Sclerosis</td>
<td>PML</td>
<td>Progressive Multifocal Leukoencephalopathy</td>
</tr>
<tr>
<td>CIS</td>
<td>Clinically Isolated Syndrome</td>
<td>PPMS</td>
<td>Primary Progressive Multiple Sclerosis</td>
</tr>
<tr>
<td>DMT</td>
<td>Disease Modifying Therapy</td>
<td>RRMS</td>
<td>Relapsing-Remitting Multiple Sclerosis</td>
</tr>
<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
<td>SPMS</td>
<td>Secondary Progressive Multiple Sclerosis</td>
</tr>
<tr>
<td>IPIR</td>
<td>Immediate Postinjection Reaction</td>
<td>VEP</td>
<td>Visual Evoked Potentials</td>
</tr>
<tr>
<td>ITP</td>
<td>Idiopathic Thrombocytopenia Purpura</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JCV</td>
<td>John Cunningham Virus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suggested Reading List


SESSION 3
10:45 AM – 12:15 PM

Multiple Sclerosis in a Primary Care Setting: Employing Strategies for Early Diagnosis and Improved Patient Outcomes

SPEAKERS
Regina R. Berkovich, MD, PhD
Victor M. Rivera, MD, Sr, FAAN

Presenter Disclosure Information

The following relationships exist related to this presentation:

• Dr Berkovich served as a consultant for Acorda, Avanir, Bayer, Biogen Idec, Genzyme, Questcor, Teva.

• Dr Rivera has no financial relationships to disclose.

Off-Label/Investigational Discussion

• In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Multiple Sclerosis in a Primary Care Setting: Employing Strategies for Early Diagnosis and Improved Patient Outcomes

Learning Objectives

• Recognize early MS symptoms and facilitate accurate diagnosis according to recommended MS diagnostic and imaging criteria
• Be familiar with strategies for managing the symptoms and complications of MS in the primary care setting
• Outline the risks and benefits of currently available disease modifying therapies in the treatment of patients with MS
• Monitor MS patients on disease modifying therapies for effectiveness and safety

Demographic Question

How many patients with multiple sclerosis do you see each week?

1. None
2. 1-10
3. 11-20
4. 21-30
5. Over 30

Outcomes Question #1

Which of the following criteria are required for a diagnosis of MS?

1. A single clinical episode and characteristic visual evoked potential (VEP) findings
2. A single clinical episode and evidence of a plaque anywhere in the CNS
3. Evidence of plaques in at least two different locations in the CNS and evidence that plaques occurred at different points in time
4. Evidence of plaques in at least two different locations in the CNS regardless of when they developed
Outcomes Question #2

When should disease-modifying MS therapies be initiated?

1. After a first attack
2. At definite diagnosis of MS with active, relapsing disease
3. For acute exacerbations
4. For incomplete remission from acute exacerbations

Outcomes Question #3

Which of the following signs indicate MS disease progression and/or the need to adjust disease-modifying therapy?

1. New T2 lesions on MRI
2. Gadolinium-negative lesions on MRI
3. No improvement in Expanded Disability Status Scale (EDSS)
4. No decrease in frequency of relapse

Drug List

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>US Trade Name</th>
<th>Generic Drug Name</th>
<th>US Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (corticotrophin)</td>
<td>H.P. Acthar Gel</td>
<td>dimethyl fumarate (BG-12) oral</td>
<td>Tecfidera</td>
</tr>
<tr>
<td>fingolimod (oral)</td>
<td>Gilenya</td>
<td>glatiramer acetate (injection)</td>
<td>Copaxone</td>
</tr>
<tr>
<td>interferon β-1a (intramuscular)</td>
<td>Avonex</td>
<td>interferon β-1a (subcutaneous)</td>
<td>Rebif</td>
</tr>
<tr>
<td>interferon β-1b (subcutaneous)</td>
<td>Betaseron</td>
<td>methylprednisolone acetate (injection)</td>
<td>Solumedrol</td>
</tr>
<tr>
<td>mitoxantrone (injection)</td>
<td>Novantrone</td>
<td>natalizumab (injection)</td>
<td>Tysabri</td>
</tr>
<tr>
<td>teriflunomide (oral)</td>
<td>Aubagio</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EPIDEMIOLOGY & ETIOLOGY
Epidemiology of MS

- Inflammatory, demyelinating and degenerative disease of the CNS
- About 350,000 people in the US, 2.5 million worldwide
- Incidence is rising
- MS is the leading cause of chronic neurologic disability in young adults (1:1000)
- Female : male ratio is 2:1
- Average age of diagnosis is 32, but can occur at any age (generally 20-40); increasingly recognized in children

Cause of MS is Unknown

- Genetic Predisposition
- Environmental Trigger
- Autoimmunity
- Loss of myelin & nerve fibers

Demyelination and Axonal Damage

Sources of Inflammation in MS

- Immune mechanisms most likely start in the periphery, rather than in the CNS
- Myelin-specific immune response in T cells involves
  - T and B Lymphocytes, NK cells, Macrophages, Neutrophils, mast cells
- Immune cells gain entry to the CNS via several mechanisms involving
  - integrins, adhesion molecules, chemokines
  - dynamic changes in the blood brain barrier
- Activation of microglia, astrocytes and production of their inflammatory mediators also occur

Summary

- MS is an inflammatory, demyelinating and degenerative disease of the CNS
  - Incidence rising; leading cause of chronic neurologic disability in young adults
  - Cause is unknown
    - Genetic predisposition + environmental trigger → autoimmune response
  - Autoimmune response
    - T-cells and demyelinating antibodies from systemic circulation enter CNS
    - Release proinflammatory cytokines, stimulate other proinflammatory mediators, trigger enhanced immune attack of myelin
    - Results in loss of myelin (demyelination) and damaged axons (poor transmission of action potentials)

DIAGNOSIS OF MULTIPLE SCLEROSIS: SYMPTOMS, MRI & PARA CLINICAL FINDINGS
Clinically Isolated Syndrome

- Most common presentations as the very first event
  - Optic Neuritis
    - Usually unilateral ocular/orbital pain; Blurred or total loss of vision; Central scotoma; RAPD; Dyschromatopsia
  - Myelitis
    - Sensory disturbance involving affected dermatome(s); paralysis may develop if motor pathways involved; spasticity with abnormal reflexes; gait affected; sphincter control difficulties may occur
  - Brain Stem/Cerebellar Syndrome
    - Double vision; nystagmus; ophthalmoplegia; facial numbness and/or facial weakness; dysarthria; dysphagia; ataxia.

RAPD=relative afferent pupillary defect.

How is MS Diagnosed?

- Multiple Sclerosis is a clinical diagnosis
  - Signs and symptoms
  - Medical history
  - Laboratory tests
  - Requires dissemination in space and time
    - Space: evidence of plaques in at least two different locations in the CNS
    - Time: evidence that plaques occurred at different points in time
  - There is no other explanation for the symptoms
    - Differential diagnosis to rule out other diseases and radiographic mimics.

Confirming the Diagnosis

- What tests are used?
  - Magnetic Resonance Imaging (MRI)
    - Approximately 10% of MS cases show a normal MRI upon first presentation in the clinic
  - Visual evoked potentials (VEPs)
  - Lumbar puncture (CSF)
  - Clinically Isolated Syndrome (CIS) or Clinically Definite Multiple Sclerosis (CDMS)?
    - With single clinical episode and minimal MRI changes the condition is likely to be called CIS
    - CIS may also be diagnosed if there is a single clinical episode and characteristic VEP or CSF findings (ie, presence of oligoclonal bands in the CSF but not the serum)
    - More than one episode of neurological dysfunction, "disseminated in space and time" define Clinically Definite Multiple Sclerosis (CDMS)

Mimics of MS

- Neuromyelitis optica
- Acute disseminated encephalomyelitis (ADEM)
- Systemic Lupus Erythematosus
- Lyme disease
- Neurosarcoidosis
- Adrenoleukodystrophy and metachromatic dystrophy

Magnetic Resonance Imaging

- FLAIR/T2: all lesions" (edema, inflammation, demyelination, axonal loss)
- Gadolinium-enhancing lesion: breakdown of blood-brain barrier, active inflammation
- T1 hypointense: axonal loss, tissue destruction

MTR=magnetization transfer ratio.


Cerebrospinal Fluid (CSF) Tap

- CSF testing can provide evidence of chronic CNS inflammation
  - The CSF is tested for oligoclonal bands found in 90% to 95% of patients with definite MS
  - Combined with MRI and clinical data, the presence of oligoclonal bands in the CSF but not the serum helps facilitate a diagnosis of MS

Visual Evoked Potentials (VEPs)

- VEPs can be used to reveal otherwise asymptomatic demyelination
  - The brain of a person with MS often responds less actively to stimulation of the optic and sensory nerves
  - In conjunction with other tests, VEPs can help elucidate the overall nerve involvement required for a definitive diagnosis of MS

Diagnostic Criteria for Clinically Definite MS

- The criteria for a diagnosis of MS have evolved over time
- Poser criteria (1983)
  - 2 attacks and evidence of separate lesions
  - Incorporated MRI, neurology history, examination, and paraclinical laboratory examinations into diagnosis
  - Over time, changes in diagnostic criteria have incorporated clinical advances and improvements in imaging technology to allow for earier diagnosis and treatment

2010 Revised McDonald Diagnostic Criteria

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Additional data needed for MS diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 attacks, objective clinical evidence of 2 lesions</td>
<td>None</td>
</tr>
<tr>
<td>2 attacks, objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by: + MRI or 2 detected lesions consistent with MS plus positive CSF or Await future clinical attack implicating a different site</td>
</tr>
<tr>
<td>1 attack, objective clinical evidence of 2 lesions</td>
<td>Dissemination in time, demonstrated by: + MRI or Second clinical attack</td>
</tr>
<tr>
<td>1 attack, objective clinical evidence of 1 lesion (monosymptomatic presentation; CIS)</td>
<td>Dissemination in space, demonstrated by: + MRI or 2 detected lesions consistent with MS plus positive CSF and Dissemination in time, demonstrated by: + MRI or second clinical attack</td>
</tr>
<tr>
<td>Infrequent neurologic progression suggestive of MS</td>
<td>1 year of disease progression (retrospectively or prospectively determined) and 2 of the following: + Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive VEPs), Positive spinal cord MRI (2 focal T2 lesions) + Positive CSF</td>
</tr>
</tbody>
</table>

Multiple Sclerosis Clinical Types

- CIS (Clinically isolated syndrome)
  - 15-40% will be CDMS
- RRMS (Relapsing-remitting multiple sclerosis)
  - 50% at onset
- SPMS (Secondary progressive multiple sclerosis)
  - 50% of RRMS
- PPMS (Primary progressive multiple sclerosis)
  - 10-15%
- PRMS (Progressive-relapsing multiple sclerosis)
  - 5%

Clinical Types of MS and Natural History

- Disease type at diagnosis
  - 15% Primary progressive MS (PPMS)
  - 85% Relapsing-remitting MS (RRMS)
  - 42% Secondary progressive MS (SPMS)
  - Disease type 11-15 years after diagnosis among patients with RRMS at diagnosis
  - 58%
**Disease Progression**

- **Relapse Remitting**
- **Secondary Progressive**

**Clinical disability**
- Brain volume
- Inflammation
- Time

Adapted from Ziemssen T. J Neurol 2005;252(suppl 5):V38-V45.

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**The EDSS: Assessing the Course of Disease**

EDSS = Expanded Disability Status Score

Summary

- Multiple Sclerosis is a clinical diagnosis
- Confirming diagnosis
  - Magnetic Resonance Imaging (MRI)
  - Visual evoked potentials (VEPs) used to reveal otherwise asymptomatic demyelination
  - Lumbar puncture (oligoclonal bands in CSF)
- 2010 Revised McDonald Diagnostic Criteria
  - Requires dissemination in space and time
- Progressive disease over time
  - Relapsing-remitting (RRMS) ➔ Secondary-progressive (SPMS)
  - Increasing disability (EDSS)
  - Episodic inflammation

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**What are the Treatment Strategies?**

1. Treatment of relapses (aka exacerbations, flare-ups, attacks—that last at least 24 hours)
2. Symptom management
3. Disease modification
4. Rehabilitation (maintain/improve function)
5. Psychosocial support

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**TREATMENT STRATEGIES**

**Acute MS Exacerbations (MS Relapse)**

- New neurologic symptom that last >24 hours in the absence of a fever or infection
- Worsening of a neurologic symptom that had previously been stable for ≥30 days
- Exacerbations can last days, weeks, or months
- At least 80% of patients with MS have an acute exacerbation during the course of the disease
- Average acute exacerbation rate of 0.5 to 1.0 per year in the US
- Incomplete remission from an exacerbation may result in permanent neurologic deficit

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**The EDSS: Assessing the Course of Disease**

EDSS = Expanded Disability Status Score

**MS Relapse Treatment**

- IV methylprednisolone at a dose of 1000 mg/day for 3 to 7 days with or without rapid oral tapering, could be a safe and effective protocol.
- Alternatively, IM or SQ ACTH 80 Units (1 cc/day) can be given for 7-10 days.
- Cost difference may be substantial.

**Management of Primary Symptom**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>amantadine, fluoxetine, and modafinil</td>
</tr>
<tr>
<td>Spasticity</td>
<td>onabotulinumtoxin A, dantrolene, baclofen, diazepam, tizanidine</td>
</tr>
<tr>
<td>Ambulation difficulties</td>
<td>dalfampridine</td>
</tr>
<tr>
<td>Depression</td>
<td>venlafaxine, paroxetine, fluoxetine, bupropion, sertraline</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
<td>desmopressin, oxybutynin, darifenacox, alpha blockers (tamsulosin, terazosin, etc...), propanteline bromide, tropium chloride, sildeniox sucratne</td>
</tr>
<tr>
<td>Pain and sensory dyesthesias or paresthesias</td>
<td>duloxetine hydrochloride, phenyloin, amitriptyline, gabapentin, nortriptilnine, carbamazepine</td>
</tr>
</tbody>
</table>

**General Secondary Symptoms**

- Prevention and Management
  - Vitamin D3
  - Cease smoking
  - Involvement in physical activities
  - Support Groups
- Overall fewer patients with advanced disability
  - Wheel-chair bound → bed ridden (EDSS 7.0 – 9.5)
  - Skin care and usual DVT prophylaxis indicated in these cases.

**Patients Own Report of Symptoms (n=300)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>58%</td>
</tr>
<tr>
<td>Spasticity</td>
<td>37%</td>
</tr>
<tr>
<td>Difficulty Walking</td>
<td>35%</td>
</tr>
<tr>
<td>Depression</td>
<td>35%</td>
</tr>
<tr>
<td>Bladder/Bowel sx</td>
<td>33%</td>
</tr>
<tr>
<td>Pain</td>
<td>29%</td>
</tr>
<tr>
<td>Paroxysmal sx</td>
<td>24%</td>
</tr>
<tr>
<td>None</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Management of Primary Symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertigo &amp; dizziness</td>
<td>medazolam</td>
</tr>
<tr>
<td>Tremor</td>
<td>clonazepam, lorazipid</td>
</tr>
<tr>
<td>Constipation</td>
<td>dicoulate, mineral oil, bisacodyl, pyrium hydrophilic mucoidid, magnesium hydroxide, glycerol</td>
</tr>
<tr>
<td>Gait &amp; balance problems</td>
<td>physical therapy and rehabilitation procedures</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>low vision clinics, prism to correct diploia</td>
</tr>
<tr>
<td>Cognitive problems</td>
<td>computer-based cognitive retraining</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>papaverine, tadalfil, vardenafli, alprostadil, sildenafil</td>
</tr>
<tr>
<td>Speech problems</td>
<td>speech therapy</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>physical therapy, strengthening exercises, rehabilitation</td>
</tr>
</tbody>
</table>

**Disease Modifying Therapy**

**Treatment Recommendations for Physicians**

"Initiation of treatment with an interferon beta medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS."

—National Clinical Advisory Board of the National Multiple Sclerosis Society (NMSS), Treatment Recommendations for Physicians, Disease Management Consensus Statement, 2008.

In 2008, only interferon and glatiramer acetate were available for a first attack. This statement applies to Disease Modifying Therapy in general.
**Currently Available Disease Modifying Therapies**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-1b</td>
<td>Glatiramer Acetate</td>
<td>Mitoxantrone</td>
<td>Fingolimod</td>
<td>Natalizumab</td>
<td>Dimethyl Fumarate (BG 12)</td>
<td>IFN-1a (SQ)</td>
<td>Teriflunomide</td>
</tr>
</tbody>
</table>

**Disease Modifying Therapies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose IFN-1a</td>
<td>20 mcg</td>
<td>IM</td>
<td>Weekly</td>
</tr>
<tr>
<td>High-dose IFN-1b</td>
<td>250 mcg</td>
<td>SC</td>
<td>Every other day</td>
</tr>
<tr>
<td>High-dose IFN-1a</td>
<td>22 mg or 44 mcg</td>
<td>SC</td>
<td>3x weekly</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>20 mg</td>
<td>SC</td>
<td>Daily</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>300 mg</td>
<td>IV</td>
<td>Monthly</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 mg/m²</td>
<td>IV</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>0.5 mg</td>
<td>Oral</td>
<td>Daily</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>7 mg or 14 mg</td>
<td>Oral</td>
<td>Daily</td>
</tr>
<tr>
<td>Dimethyl fumarate (BG 12)</td>
<td>240 mg</td>
<td>Oral</td>
<td>Twice daily</td>
</tr>
</tbody>
</table>

**Efficacy of Disease Modifying Therapies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Annualized Relapse Rates (ARR)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.4¹</td>
<td>-</td>
</tr>
<tr>
<td>Low-dose IFN-1a</td>
<td>0.33²</td>
<td>-</td>
</tr>
<tr>
<td>High-dose IFN-1b</td>
<td>0.38³</td>
<td>-</td>
</tr>
<tr>
<td>High-dose IFN-1a (44 mcg)</td>
<td>0.36⁴</td>
<td>-</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>0.28⁵</td>
<td>-</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>0.2⁶</td>
<td>-</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>0.47⁷</td>
<td>-</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>0.18⁸</td>
<td>-</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>0.37⁹</td>
<td>-</td>
</tr>
<tr>
<td>Dimethyl fumarate (BG 12)</td>
<td>0.17¹⁰</td>
<td>-</td>
</tr>
</tbody>
</table>

**Efficacy – MRI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean (Median) Number of Enhancing Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl fumarate (BG 12)</td>
<td>Active</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Placebo</td>
</tr>
<tr>
<td>Natalizumab</td>
<td></td>
</tr>
<tr>
<td>INF-1a SQ</td>
<td></td>
</tr>
<tr>
<td>INF-1a IM</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment of the First Clinical Event Suggestive of MS**

- Multicenter, double-blind, placebo-controlled, randomized trials of DMTs in CIS
  - CHAMPS² = IFN-β-1a IM
  - ETOMS² = IFN β-1A SQ
  - BENEFIT² = IFN β-1b
  - PreCISE Study² = GA
- Efficacy of DMTs on the rate of conversion to CDMS has been evaluated.
- The IFNβ-1a IM, IFNβ-1b and GA are approved for the CIS indication.

**MOA of Interferon β and Glatiramer Acetate**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Mechanism of Action (MOA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ</td>
<td>Immune Modulation</td>
<td>Reduces proinflammatory cytokine levels and increases levels of anti-inflammatory mediators</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>Immune Modulation</td>
<td>Induces a shift from Tₐ₁ to Tₐ₂ cells</td>
</tr>
</tbody>
</table>

**Notes:**

**References:**
- http://www.accessdata.fda.gov/drugsatfda/index.cfm
Safety Considerations
Glatiramer Acetate and Interferon β

<table>
<thead>
<tr>
<th>Agent</th>
<th>Common Side Effects</th>
<th>Pregnancy Category</th>
<th>Liver Monitoring</th>
<th>Laboratory Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-β-1a</td>
<td>Depression, decreased peripheral blood counts, anaphylaxis, hepatic injury, flu-like symptoms, asthma, anemia, headache, gastrointestinal upset</td>
<td>C</td>
<td>+</td>
<td>Required</td>
</tr>
<tr>
<td>IFN-β-1b</td>
<td>Depression, injection-site necrosis, anaphylaxis, hepatic injury, injection-site reactions, flu-like symptoms, hematologic abnormalities</td>
<td>C</td>
<td>+</td>
<td>Required</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>Injection-site and post-injection reactions, vasodilatation, chest pain, asthma, pain, nausea, infections, arthralgia, anorexia, hyperesthesia</td>
<td>B</td>
<td>–</td>
<td>Not required</td>
</tr>
</tbody>
</table>

MOA of Other Disease Modifying Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Mechanism of Action (MOA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>Cell Trafficking</td>
<td>• Strongly reduces proinflammatory cell recruitment to the CNS</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Cell Sequestration</td>
<td>• Significantly decreases the number of lymphocytes from leaving the lymph nodes and entering the bloodstream and CNS compartment</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Immune Modulation</td>
<td>• An immunomodulatory agent with anti-inflammatory properties that inhibits “de novo” pyrimidine synthesis</td>
</tr>
<tr>
<td>Dimethyl fumarate (BG12)</td>
<td>Immune Modulation</td>
<td>• Inhibits the expression of adhesion molecules and proinflammatory cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Induces a shift from TH1 to TH2 cells</td>
</tr>
</tbody>
</table>

Injection-Site Reactions

Results from an open-label study conducted by chart review and interviews of patients receiving MS therapies over 5 years

<table>
<thead>
<tr>
<th>Agent</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer acetate (n=101)</td>
<td>90%</td>
</tr>
<tr>
<td>High dose IFN-β-1a/High dose IFN-β-1b (n=93)</td>
<td>78%</td>
</tr>
<tr>
<td>Low dose IFN-β-1a (n=79)</td>
<td>40%</td>
</tr>
</tbody>
</table>

FDA-approved labeling includes up to 3 years of clinical data.

Safety Considerations

Natalizumab – Safety

- Most common side effects:
  - Headache, fatigue, arthralgia, UTI, lower respiratory tract infection, gastroenteritis, vaginitis, abdominal discomfort, diarrhea, NOS, and rash
- Hepatotoxicity
- Risk of progressive multifocal leukoencephalopathy (PML)
  - Opportunistic viral infection of the brain that usually leads to death or severe disability
  - Only available through a restricted distribution program (TOUCH Program)

Incidence of PML Related to Natalizumab Stratified by Known Risk Factors

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<thead>
<tr>
<th>Agent</th>
<th>Common Side Effects</th>
<th>Pregnancy Category</th>
<th>Safety Precautions</th>
</tr>
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<tbody>
<tr>
<td>Natalizumab</td>
<td>PML, infections, immunosuppressant reactions, immunosuppressant headache, fatigue, arthralgia, UTIs, gastroenteritis, vaginitis, depression, others</td>
<td>C</td>
<td>Monitor for signs of PML, infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monitor liver enzymes</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Skin malignancies, cardiac arrhythmias, macular edema, HTN, Herpes infections, headaches, increased liver enzymes, diarrhea</td>
<td>C</td>
<td>Regular blood monitoring, including liver enzymes</td>
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<tr>
<td>Teriflunomide</td>
<td>Potential hepatotoxicity, myelosuppression, hair thinning, GI symptoms, pernicious anemia, UTIs, neuro- &amp; lymphoproliferative</td>
<td>X</td>
<td>Regular blood monitoring, including liver enzymes</td>
</tr>
<tr>
<td>Dimethyl fumarate (BG12)</td>
<td>Lymphoproliferative, flushing, pruritus</td>
<td>C</td>
<td>Monitor for signs of PML, infection</td>
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Safety Considerations

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</table>
**Treatment of progressive multiple sclerosis**

- The effects of IFN-β or Glatiramer Acetate in secondary progressive multiple sclerosis are controversial.
- The European Study Group on IFN-β-1b in Secondary Progressive MS trial
  - 718 patients treated with either IFN-β-1b or placebo for 3 years
  - Primary outcome = time to progression in disability
  - Significant difference in time to progression favoring IFN-β-1b (p=0.0008)
- Other trials with IFN-β-1b, IFN-β-1a or Glatiramer Acetate failed to confirm this
- Existing and new DMTs are being studied

*Defined as a 0.5 increase in EDSS from baseline or a 0.5 increase in baseline EDSS 6.0 or 6.5.
Kappos L, and European Study Group on Interferon Beta 2b in Secondary Progressive MS. The authors.
http://dx.doi.org/10.1002/2050-313X.ddd.6149

**Cost Considerations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-β-1a (Avonex®)</td>
<td>30 mcg IM once per week</td>
<td>$3,745</td>
</tr>
<tr>
<td>IFN-β-1a (Rebif®)</td>
<td>22 mcg or 44 mcg SC 3x per week</td>
<td>$3,500</td>
</tr>
<tr>
<td>IFN-β-1b (Betaseron® or Extavia®)</td>
<td>0.25 mg SC every other day</td>
<td>$3,500-$3,740</td>
</tr>
<tr>
<td>Glatiramer Acetate (Caspazone®)</td>
<td>10 mg SC daily</td>
<td>$4,000</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone®)</td>
<td>12 mg/m² IV every 3 months</td>
<td>$1,500</td>
</tr>
<tr>
<td>Natalizumab (Tyasr®)</td>
<td>300 mg IV every 4 weeks</td>
<td>$3,800</td>
</tr>
<tr>
<td>Fingolimod (Gilenya®)</td>
<td>0.5 mg PO once daily</td>
<td>$4,400</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio®)</td>
<td>7 mg or 14 mg PO once daily</td>
<td>$3,400</td>
</tr>
<tr>
<td>Dimethyl Fumarate (Tecfidera®)</td>
<td>120 mg PO twice daily x 7 days, then 240 mg PO twice daily</td>
<td>$5,000</td>
</tr>
</tbody>
</table>

**Monitoring DMT Safety and Efficacy**

**Safety**
- Liver function tests
- Thyroid function
- Signs of hepatic injury
- Cardiac evaluations
- Blood cell counts
- Pulmonary evaluations as clinically indicated
- Blood pressure tests
- Ophthalmologic evaluations
- JCV antibody status
- MRI

**Efficacy**
- Relapse frequency
- Changes in EDSS
- MRI findings

**Snapshot: Treatment Considerations Evolving**

<table>
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<tr>
<th>Disease Stage</th>
<th>Medical History/ Comorbidities</th>
<th>Safety/ Tolerability</th>
<th>Monitoring</th>
<th>Lifestyle Considerations</th>
</tr>
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<tbody>
<tr>
<td>CIS</td>
<td>Cardiac ischemia</td>
<td>Depression</td>
<td>Liver function tests</td>
<td>Age</td>
</tr>
<tr>
<td>RRMS</td>
<td>Hypertension</td>
<td>Diabetes</td>
<td>Thyroid Function</td>
<td>Smoking status</td>
</tr>
<tr>
<td>MS</td>
<td>Malignancy</td>
<td>Neutropenia</td>
<td>Visual Acuity</td>
<td>MS severity</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td>Infertility</td>
<td>Changes in EDSS</td>
<td>Employment status</td>
</tr>
<tr>
<td>BSS</td>
<td>Renal insufficiency</td>
<td>Substance use</td>
<td>Disability score</td>
<td>Substance use</td>
</tr>
<tr>
<td>Level of cognitive impairment</td>
<td></td>
<td>Blood Pressure</td>
<td>Disability score</td>
<td>Prescription</td>
</tr>
</tbody>
</table>

**Snapshot: DMTs in MS Management**

<table>
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<tr>
<th>Disease Stage</th>
<th>Medical History/ Comorbidities</th>
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**DMTs in MS Management**

- **Safety**
  - Liver function tests
  - Thyroid function
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  - Cardiac evaluations
  - Blood cell counts
  - Pulmonary evaluations as clinically indicated
  - Blood pressure tests
  - Ophthalmologic evaluations
  - JCV antibody status
  - MRI

- **Efficacy**
  - Relapse frequency
  - Changes in EDSS
  - MRI findings

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**DMTs in MS Management**

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  - Relapse frequency
  - Changes in EDSS
  - MRI findings

**DMTs in MS Management**

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  - Blood cell counts
  - Pulmonary evaluations as clinically indicated
  - Blood pressure tests
  - Ophthalmologic evaluations
  - JCV antibody status
  - MRI

- **Efficacy**
  - Relapse frequency
  - Changes in EDSS
  - MRI findings
Monitoring of DMT

<table>
<thead>
<tr>
<th>Agent</th>
<th>Laboratory Tests</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclizumab</td>
<td>None Requested</td>
<td>NA</td>
</tr>
<tr>
<td>IFN-1a</td>
<td>Liver Thyroid</td>
<td>1.5 and 6 months initially, then periodically. Every 6 months in pts w/ loss of vision/dysfunction.</td>
</tr>
<tr>
<td>IFN-1b</td>
<td>CBC Liver</td>
<td>1.5 and 6 months initially, then periodically. CBC w/ differential CBC and platelet counts, blood chemistry, and liver function tests.</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>PML Monitoring</td>
<td>Baseline MRI and JCV antibody every 6 months. Evaluate the patient 3 months after 1st infusion, then every 6 months thereafter. Monthly liver panel for 12 months, quarterly indefinitely in pts w/ normal liver panel. Discontinue drug if AST/ALT ≥3x ULN or total bilirubin ≥2x ULN. Monthly liver panel indefinitely for patients w/ elevated AST/ALT or bilirubin but w/ values below the threshold (AST/ALT ≥3x ULN and bilirubin ≥2x ULN).</td>
</tr>
</tbody>
</table>

Predictors of Disability Progression

<table>
<thead>
<tr>
<th>Frequency of relapse, is it black holes?</th>
<th>MRI: Are there new T2 lesions?</th>
<th>MRI: Are there new T1 lesions?</th>
<th>MRI: Are there new black holes?</th>
<th>MRI: Is there increase in brain atrophy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the answer is No – the treatment is adequate. However, if Yes – consider and discuss alternative DMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary

- MS is a common neurological disorder with approximately 200 new cases diagnosed each week.
- Diagnosis of MS involves assessment of neurological symptoms, MRI evidence, and/or laboratory tests.
- Over time, diagnostic criteria have evolved to allow for earlier diagnosis and treatment.
- Because it is impossible to predict how any individual MS patient will progress over time, initiation of treatment with an approved first-line therapy should be considered as soon as possible following a definitive diagnosis of MS.
- Treatment response should be assessed regularly – both clinically and radiologically.
- Awareness of suboptimal response and treatment failure signs is paramount for optimal management of MS patients.
- New DMTs, including oral, are emerging. Safety considerations remain very important in choosing DMT strategy.

Patient Cases
**Case 1**

- 33-year-old woman, housewife and mother of 2 children ages 4 years and 14 months, was previously healthy until June 2011 when she experienced Optic Neuritis affecting the right eye (blurred vision, right ocular and frontal pain). She was seen by an ophthalmologist. Symptoms dissipated gradually without treatment in about 3 weeks.
- In June 2012 she acutely developed a “strange” feeling around the neck and tingling of the legs. Although she felt a little unsteady while walking, there was no overt motor weakness of the lower extremities. There was no fever, malaise or any other associated symptom.

**Case 1 Continued**

- Since the uneventful birth of her second child in March 2012, she has experienced unusual and persistent overwhelming fatigue. Patient denied bladder, bowel or sexual dysfunction.
- She was worked in by her Family Physician (PCP) to be seen next morning. Blood work was performed and referred immediately to a neurologist in the same building.

**Case 1 Continued**

- Medical History: good health, no surgical antecedents. She recalls having had Infectious Mononucleosis during adolescence.
- Medications: Oral contraceptive and multivitamins.

**Case 1 – Question 1**

This patient has experienced two separate neurological events and has objective findings to examination. In this clinical setting what tests are indicated to make the appropriate diagnosis?

1. Brain MRI and MRA of neck vessels
2. Brain and Spinal Cord MRI, CSF and VEP
3. Spinal cord MRI and Electromyography of legs
4. Only spinal cord MRI or CT scan of spine
5. Only brain MRI

**MRI STUDIES**

- CSF study showed 5 Oligoclonal Bands.
- VEP showed slowing of conduction on right Optic Nerve.
Case 1 – Question 2

How should this patient be treated for this acute relapse?

1. Epidural methylprednisolone acetate suspension injections in upper neck
2. The patient should simply be observed (no Rx)
3. Intravenous methylprednisolone pulses (1000 mg each) for three days with or without oral taper with methylprednisolone or prednisone
4. Oral low-dose chemotherapy
5. Extensive physical therapy without medications

Case 1 Cont’d

- The patient has no cardiac, liver, or laboratory abnormalities that are concerns for treatment of her MS with chronic therapy.
- The patient plans to quit smoking.
- She is not sure if she will have more children.
- She expressed substantial phobia to needles and would decline injectable therapies.

Case 1 – Question 3

- Which of the treatment options is most appropriate for the patient at this time?

1. She is a good candidate for oral fingolimod
2. Traditionally a SC interferon should be tried first
3. Occasional intramuscular injections of interferon could be considered until the fear to needles is overcome
4. Once a month Intravenous natalizumab could be offered as alternative
5. The patient can wait until next attack then use glatiramer acetate

Case 2

- 45-year-old male, trial lawyer, single. Was diagnosed with Relapsing/Remitting MS at age 39 after he had an episode of vertigo, double vision and ataxia. Brain MRI showed 9 T2 lesions at that time, some enhancing after intravenous contrast. CSF showed 3 Oligoclonal Bands. VEP was normal. After IV steroids he was initiated on interferon beta 1-a high dose with poor tolerance due to persistent side effects (flu-like symptoms) leading to lack of adherence.
- He had a relapse at age 41 with significant leg weakness and residual spastic gait (EDSS 3.5). His daily activities have been substantially affected since. MRI showed more lesions in brain and 2 in the thoracic spinal cord. He received intravenous steroids and was switched to glatiramer acetate daily injections.

Case 2

- Despite treatment with glatiramer acetate and adequate adherence, the patient has continued to have relapses about one per year with increasing EDSS (4.5) and MRI burden of disease. His neurologist suggests natalizumab as second line therapy. JC Virus antibody test ordered. The patient never has been exposed to immunosuppressive agents.

Last MRI Study - EDSS 4.5

- Gd-enhancing: Active lesions
- T2-hyperintense: Increased burden of disease
Case 2 Continued

• Medical History: Unremarkable. He had a concussion playing football in College. Vitamin D level was low in two separate occasions.

• Medications: Glatiramer acetate 20 mg SC daily; Baclofen 10 mg tid for spasticity; Fampridine 10 mg bid for walking; Vitamin D3 2000 IU daily.

Case 2 – Question 1

• The patient is considered for natalizumab therapy. All of the following are reasons to use natalizumab for second line (rescue) therapy except:
  1. Failure to tolerate a first line therapy
  2. Failure to respond to a first line therapy
  3. Persistent relapsing disease
  4. Increasing disability and burden of disease by worsening MRI
  5. Absence of JCV antibodies

Case 2 – Question 2

The patient is considered for natalizumab therapy. He never received chemotherapy but he is JCV antibody positive. The discussion regarding risk for Progressive Multifocal Encephalopathy (PML) should include:

1. Risk of > 100/1000
2. Risk of <1/1000
3. Natalizumab is generally contraindicated in this setting
4. The patient can be treated but therapy should be for less than a year then resume glatiramer acetate
5. Natalizumab could be added to glatiramer acetate as combination therapy

Case 2 – Question 3

The patient is considered for natalizumab therapy. He never received chemotherapy but he is JCV positive. The discussion regarding PML risk should include which of the following?

1. Risk increases after 25 infusions therefore closer follow-ups and MRIs are in order
2. Current predictive data is not reliable
3. Natalizumab is the only MAB that causes PML
4. Natalizumab beneficial effects last 24 months

Outcomes Question #1

Which of the following criteria are required for a diagnosis of MS?

1. A single clinical episode and characteristic visual evoked potential (VEP) findings
2. A single clinical episode and evidence of a plaque anywhere in the CNS
3. Evidence of plaques in at least two different locations in the CNS and evidence that plaques occurred at different points in time
4. Evidence of plaques in at least two different locations in the CNS regardless of when they developed
Outcomes Question #2
When should disease-modifying MS therapies be initiated?
1. After a first attack
2. At definite diagnosis of MS with active, relapsing disease
3. For acute exacerbations
4. For incomplete remission from acute exacerbations

Outcomes Question #3
Which of the following signs indicate MS disease progression and/or the need to adjust disease-modifying therapy?
1. New T2 lesions on MRI
2. Gadolinium-negative lesions on MRI
3. No improvement in Expanded Disability Status Scale (EDSS)
4. No decrease in frequency of relapse

Question & Answer