Therapeutic Advances in the Management of Multiple Sclerosis

A CME webcast jointly sponsored by the Postgraduate Institute for Medicine and AcademicCME

Fred D. Lublin, MD
Course Chair Moderator
Saunders Family Professor of Neurology
Corinne Goldsmith Dickinson Center for Multiple Sclerosis
Mount Sinai School of Medicine
New York, NY
Faculty

Clyde Markowitz, MD
Director, Multiple Sclerosis Center
Associate Professor of Neurology
University of Pennsylvania
Philadelphia, PA

Daniel Kantor, MD
President, Neurologique
President, Florida Society of Neurology
Ponte Vedra, FL

Patricia Coyle, MD
Professor and Acting Chair
Department of Neurology
SUNY at Stony Brook
Stony Brook, NY
Case 1

A healthy 29 year old woman awoke with numbness in the legs which over the next 2 days rose to her ribcage. She thought her walking was affected but denied any weakness or bladder difficulty. A physical exam by her primary care physician was found to be normal. She was sent for an MRI of the brain. Results concluded 3 periventricular lesions. She was then referred by her PCP for a neurological evaluation.
Clinically Isolated Syndrome

- A first neurologic episode that lasts at least 24 hours
- Caused by inflammation/demyelination in the central nervous system (CNS)
- Can be monofocal or multifocal
- Various factors determine risk of developing clinically definite multiple sclerosis (CDMS)
- CIS should be treated like it is MS!

## CDMS by McDonald Criteria

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 relapses with objective evidence</td>
<td>None</td>
</tr>
<tr>
<td>≥ 2 relapses with objective evidence of 1</td>
<td>DIS by MRI or ≥ 2 MRI lesions with positive CSF or another relapse</td>
</tr>
<tr>
<td>1 relapse; objective evidence of &gt;2 lesions</td>
<td>DIT by MRI or second relapse</td>
</tr>
<tr>
<td>1 relapse; evidence of 1 lesion (e.g. CIS)</td>
<td>DIS by MRI or ≥ 2 MRI lesions with positive CSF and DIT by MRI or second relapse</td>
</tr>
<tr>
<td>Insidious progression suggesting MS</td>
<td>1 year progression and 2 of: A. MRI with 9 T2 or ≤ 4 T2 and Pos. CSF B. Pos. SC MRI (2 focal T2 lesions) C. Pos. CSF</td>
</tr>
</tbody>
</table>
## Diagnostic Criteria for MS: Application of MRI

<table>
<thead>
<tr>
<th>Dissemination in Time</th>
<th>McDonald 2001(^1)(^2)</th>
<th>McDonald 2005(^1)(^3)</th>
<th>MAGNIMS 2010 Proposal(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>≥ 1 gadolinium-enhancing lesion ≥ 3 months after CIS onset (if not related to CIS)</td>
<td>≥ 1 gadolinium-enhancing lesion ≥ 3 months after CIS onset (if not related to CIS)</td>
<td>Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time</td>
</tr>
<tr>
<td>2)</td>
<td>A new T2 lesion with reference to a prior scan obtained ≥ 3 months after CIS</td>
<td>A new T2 lesion with reference to a prior scan obtained ≥ 30 days after CIS</td>
<td>A new T2 and/or gadolinium-enhancing lesion on follow-up MRI irrespective of timing of baseline scan</td>
</tr>
</tbody>
</table>

## Diagnostic Criteria for MS: Application of MRI

<table>
<thead>
<tr>
<th>Dissemination in Space (on Either Baseline or Follow-Up Magnetic Resonance Imaging [MRI])</th>
<th>McDonald 2001(^1,2)</th>
<th>McDonald 2005(^1,3)</th>
<th>MAGNIMS 2010 Proposal(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3 of:</td>
<td>≥ 3 of:</td>
<td>≥ 1 lesion in each of ≥ 2 characteristic locations</td>
<td></td>
</tr>
<tr>
<td>≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion</td>
<td>≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion</td>
<td>Periventricular</td>
<td></td>
</tr>
<tr>
<td>≥ 3 periventricular lesions</td>
<td>≥ 3 periventricular lesions</td>
<td>Juxtacortical</td>
<td></td>
</tr>
<tr>
<td>≥ 1 juxtacortical lesion</td>
<td>≥ 1 juxtacortical lesion</td>
<td>Posterior fossa</td>
<td></td>
</tr>
<tr>
<td>≥ 1 posterior fossa lesion</td>
<td>≥ 1 posterior fossa lesion</td>
<td>Spinal cord</td>
<td></td>
</tr>
<tr>
<td>1 cord lesion can replace 1 brain lesion</td>
<td>Any number of lesions can be included in lesion count</td>
<td>All lesions in symptomatic regions excluded in brain stem and spinal cord syndromes</td>
<td></td>
</tr>
</tbody>
</table>
Natural Progression of MS

- Subclinical
  - Initial demyelinating event
- Monosymptomatic
- Relapsing–Remitting
  - Clinically definite MS
- Secondary Progressive
  - Relapse

Level of disability
Accumulated MRI lesion burden
Acute (new and Gd+) MRI activity
Cognitive dysfunction
Brain volume
Rationale for Early Treatment

• Treatment with disease-modifying therapies has demonstrated
  - Reduction in the frequency of relapses
  - Slowing of disability progression
  - Reduction in number of brain lesions observed on MRI in patients with RRMS

• Studies have also shown that silent damage, as well as irreversible axonal damage, may occur

• Questions remain, such as:
  - Will treatment provide better long-term outcomes?
  - If we treat after only one event and patients remain stable, how will we be sure they really have MS?

MRI = magnetic resonance imaging; RRMS = relapsing-remitting MS.
## Disease-Modifying Therapy in CIS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Follow-up</th>
<th>On Tx</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAMPS¹</td>
<td>Interferon beta-1a 30 µg IM Qwk</td>
<td>383</td>
<td>3 y</td>
<td>35%</td>
<td>50%</td>
<td>.002</td>
</tr>
<tr>
<td>ETOMS²</td>
<td>Interferon beta-1a 22 µg SC once weekly</td>
<td>309</td>
<td>2 y</td>
<td>34%</td>
<td>45%</td>
<td>.047</td>
</tr>
<tr>
<td>REFLEX³</td>
<td>Serum-free interferon beta-1a 22 µg TIW or QW</td>
<td>517</td>
<td>≤2 y</td>
<td>62.5% (TIW)</td>
<td>85.8%</td>
<td>&lt;.000001</td>
</tr>
<tr>
<td>BENEFIT⁴</td>
<td>Interferon beta-1b 250 µg SC q48h</td>
<td>468</td>
<td>2 y</td>
<td>28%</td>
<td>45%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PreCISE⁵</td>
<td>Glatiramer acetate 20 mg/d</td>
<td>481</td>
<td>3 y</td>
<td>61%</td>
<td>77%</td>
<td>.0005</td>
</tr>
</tbody>
</table>

Risk Factors Contributing to “More Aggressive” Disease

- Age at onset
- Symptoms at onset
- MRI status
- Interval between first and second attack
- Incomplete recovery from initial attacks
- Attack frequency in first 2 years (relapse rate)
- Sex (in post-hoc analysis)
  - Females have higher incidence of MS (approximately 2:1)
  - Males have higher risk of poor outcomes

Classification of risk groups

- Low-risk group—patients with 0 to 1 risk factor
- Medium-risk group—patients with 2 to 3 risk factors
- High-risk group—patients with 4 to 6 risk factors

Benefits to Current MS Therapies

• Reduction in the number and severity of relapses (about 30-68%)
• Delay disease progression by clinical measures (about 30-40%)
• Reduction of lesions on MRI
  - Gad enhancing and T2 (about 40-90%)
  - Atrophy
• Slow cognitive decline

Current Disease Modulating Treatments

• Interferon-1a: weekly IM, 6 M units
• Interferon-1b: QOD SQ, 8 M units
• Interferon-1a: QOD SQ, 12 M units
• Glatiramer acetate: QD SQ, 20 mg
• Mitoxantrone: Q 3 months- 12mg/m²
• Natalizumab: Q monthly
• Fingolimod: Oral- Q daily
Natalizumab vs Placebo
(1801 Study—AFFIRM)

Annualized Relapse Rate (95% CI)

Placebo
n=315

0.81

P<0.0001

Natalizumab
n=627

0.26

68%

Updated Natalizumab-Associated PML Incidence by Treatment Duration

PML = progressive multifocal leukoencephalopathy
145 cases of PML have been documented in MS patients treated with natalizumab as of July 22, 2011. Available at: http://chefarztfrau.de/?page_id=716

PML Risk Stratification in MS Patients Based on the 3 Known Risk factors

Anti-JCV Antibody Status

- Negative*
  - Prior Immunosuppressant Use
    - No
      - Natalizumab Exposure
        - 0 – 2 Years
          - Anti-JCV Antibody Negative
            - 0.35/1000 (95% CI: 0.19-0.60)
        - > 2 Years
          - Anti-JCV Antibody Positive with No Prior Immunosuppressant Use
            - 2.8/1000 (95% CI: 2.0-3.8)
    - Yes
      - Anti-JCV Antibody Positive with Prior Immunosuppressant Use
        - 1.2/1000 (95% CI: 0.58-2.2)

- Positive†
  - Prior Immunosuppressant Use
    - No
      - Natalizumab Exposure
        - 0 – 2 Years
          - Anti-JCV Antibody Negative
            - ≤ 0.11/1000 (95% CI: 0.00-0.59)
        - > 2 Years
          - Anti-JCV Antibody Positive with No Prior Immunosuppressant Use
            - 0.35/1000 (95% CI: 0.19-0.60)
    - Yes
      - Anti-JCV Antibody Positive with Prior Immunosuppressant Use
        - 8.1/1000 (95% CI: 5.4-11.6)

*Estimate based on all anti-JCV antibody negative patients receiving at least 1 dose of natalizumab and 1 hypothetical PML case that was anti-JCV antibody negative at the time of PML diagnosis.

†PML incidence in anti-JCV antibody positive patients was calculated on the basis of the following assumptions: 55% of natalizumab-treated MS patients were anti-JCV antibody positive, the proportion of natalizumab-treated patients with prior IS use was 20% based on TYGRIS data, and 100% confirmed cases of PML were anti-JCV antibody positive prior to the onset and diagnosis of PML.

Questions About Natalizumab

• Is the PML risk acceptable to patients and physicians (1:100-1:1000?)
• Which patients should we use it for?
• How long should we keep patients on natalizumab, drug holiday?
• Antibodies to JC virus assay
• Washout period before and after treatment, prior immunosuppression
• Can we detect PML early enough to prevent irreversible damage
• What algorithm should be used to treat cases of PML
The FREEDOM Study (Fingolimod):
Annualized Relapse Rate

Annualized relapse rate was consistently reduced in both treatment-naive patients and patients previously treated with DMT ($P<0.01$ for all comparisons)

Fingolimod- Monitoring

• Blood
  - Liver enzymes/billirubin, CBC+diff, anti-VZV IgG/IgM
• Ophthalmologic
  - Macular edema, repeated in 4 months
• EKG
  - Cardiac issues or medication
  - 6-hour evaluation with first dosing
• Dermatologic?
• Pulmonary

Questions About Fingolimod

• What are the short term safety issues?
• What are the long term safety concerns?
• What should the washout be for patients on previous DMT prior to starting fingolimod?
• What type and how frequently should patients be monitored? Who will do all the monitoring? PMD? Neurologist?
• Should this be a first line therapy?
Case 1 Discussion

A healthy 29 year old woman awoke with numbness in the legs which over the next 2 days rose to her ribcage. She thought her walking was affected but denied any weakness or bladder difficulty. A physical exam by her primary care physician was found to be normal. She was then sent for an MRI of the brain. Results concluded 3 periventricular lesions. Subsequently, her PCP referred her for a neurological evaluation.
Case 2

A 38 year old man had optic neuritis in 2007. In 2008 he developed diplopia and an INO. An MRI revealed multiple lesions, many periventricular, and 3 enhancing. In September 2008 he was started on interferon beta 1-a thrice weekly. In April 2009 he had an episode of L facial numbness and weakness and horizontal diplopia which improved 90% after IV steroids. In August 2009 he developed numbness and weakness in both legs. MRI of the C spine revealed an enhancing lesion at C 7.
Case 2 Continued

- Relapsing MS for 2 years
- 4 attacks
- Worrisome features
  - demographics (older male)
  - initial brain MRI (multiple, enhancing lesions)
  - relapses (motor; brainstem, spinal cord)
- Suboptimal responder to IFNβ
- Need to modify therapy
  - potential novel strategies
Potential Agents

- Teriflunomide
- Daclizumab
- Anti CD20 Class
  - Rituximab
  - Ocrelizumab
  - Ofatumumab
Teriflunomide- Background

- Oral agent
- Active metabolite of leflunomide (approved for rheumatoid arthritis since 1998)
- Noncompetitive reversible inhibition of mitochondrial enzyme dihydroorotate dehydrogenase (de novo pyrimidine synthesis pathway)
- Salvage pathway remains intact
- Cytostatic for proliferating T and B cells; noncytotoxic

**Teriflunomide - Background (cont.)**

- Inhibits protein kinase activity
  - ↓ T-cell proliferation, activation, cytokine production
- $T_\frac{1}{2}$ 2 weeks
- Hepatic metabolism
- Teratogenic in rabbits, rats
- Rapid clearance requires cholestyramine, activated charcoal

TEMSO- TEriflunomide Multiple Sclerosis Oral

Phase III, 2-year study
- RRMS or SPMS with relapses (N=1080)
- Placebo vs daily teriflunomide (7 mg or 14 mg)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Teriflunomide (7 mg)</th>
<th>Teriflunomide (14 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>0.54</td>
<td>0.37 (↓ 31%, P=0.0002)</td>
<td>0.37 (↓ 32%, P=0.0005)</td>
</tr>
<tr>
<td>Sustained disability</td>
<td>27.3%</td>
<td>21.7% (NS)</td>
<td>20.2% (↓ 30%, P=0.03)</td>
</tr>
<tr>
<td>Combined unique active lesions</td>
<td>2.5</td>
<td>1.3 (↓ 47%, P=0.001)</td>
<td>0.8 (↓ 69%, P&lt;0.001)</td>
</tr>
<tr>
<td>Brain MRI total lesion volume</td>
<td>--</td>
<td>↓ 39%</td>
<td>↓ 67%</td>
</tr>
</tbody>
</table>

Teriflunomide—Safety

- LFTs (ALT)
- Nasopharyngitis
- Alopecia
- Nausea, diarrhea
- Paresthesias
- Back pain, limb pain
- Arthralgias

Proposed Mechanisms: Daclizumab

- Humanized mAb directed against IL-2 receptor-α chain (CD25)
  - IL-2 stimulates T-cell proliferation
- Originally engineered to block IL-2 binding
- Recent findings:
  - Daclizumab induces activation of CD56^{bright} NK cells

Daclizumab in RRMS (Phase II CHOICE Study): Gd-Enhancing MRI Lesions


*P < 0.05 versus interferon beta and placebo
SELECT

- Phase 2b one year trial of SC daclizumab (high yield process) (N=600)
  - 150mg (N=201) or 300mg (N=203) SC DAC HYP monthly
  - Placebo (N=196)

- ARR ↓54% (p<0.0001), ↓50% (p=0.0002)

- Relapse proportion ↓55% (p<0.0001), ↓51% (p=0.0003)
SELECT

• EDSS disability (12 weeks) ↓57% (p=0.021), ↓43% (p=0.091)

• Cumulative contrast MRI lesions in subset 8-24 weeks ↓69%, ↓78% (p<0.0001)
  - new contrast lesions at wk 52 ↓79%, ↓86% (p<0.0001)

• New/ enlarging T2 lesions ↓70%, ↓79% (p<0.0001)

• Adverse events include cutaneous hypersensitivity, ↑LFTs, infection
Anti-CD20 Therapies

• Target B cells (APCs, immune regulation, antibody secretion)

• CD20 present on >95% of B cells (pre, immature, mature, activated, memory B cells)

• Includes
  - Rituximab (IgG1 chimeric, approved for NHL, refractory RA)
  - Ocrelizumab (humanized)
  - Ofatumumab (human; approved for CLL)
Rituximab

• Phase II 48 week relapsing MS trial (N=104)
  - 1,000 mg IV on days 1, 15 (N=69)
  - Placebo (N=35)
  - Contrast MRI lesions ↓ 91% (p<0.001)
  - Proportion with relapses 20.3% vs. 40% (p<0.04)

• Phase II 96 week PPMS trial (N=439)
  - 1,000 mg IV on days 1 and 15 every 24 weeks (N=292)
  - Placebo (N=147)
  - Confirmed progression 30.2% vs. 38.5% (NS)
  - Progression slowed in subgroup (age <51 years, Gd + MRI)
  - Less T2 lesions volume increase (p<0.001)
Ocrelizumab Phase II Trial

- **Relapsing MS (N=220)**
  - 1000 mg or 300 mg ocrelizumab days 0, 15 vs placebo vs IFNβ-1a IM

- **1° outcome**
  - Total number of contrast MRI lesions at 9, 12, 16, 20, and 24 weeks
  - 5.5 placebo vs 6.9 (IFNβ-1a IM), 0.6 ocrelizumab 600 mg, ↓ 89%, 0.2 ocrelizumab 2000 mg, ↓ 96%
  - ARR 0.636 vs 0.354, 0.125 (↓ 80%), 0.169 (↓ 73%)

Ocrelizumab: Phase II Safety Outcomes

- No overall differences in AEs, SAEs, infections
- Higher incidence of infusion-related events on day 1–15
- 1 death in 2000 mg group secondary to systemic inflammatory response syndrome
- Supports phase III trials

Ocrelizumab Phase III Trials

- **OPERA I, II**
  - Phase 3 trials in RRMS (N=800 each)
  - Ocrelizumab 2x300 MU IV every 2 weeks vs IFNβ-1a SC 44 μg
  - 1° outcome ARR at 96 weeks; time to sustained disability progression (24 weeks)

- **ORATORIO**
  - Phase 3 in PPMS (N=360)
  - Age ≤55 years, EDSS 3-6.5, abnormal CSF
  - EDSS ≤5, disease duration <10 years
  - EDSS >5, disease duration <15 years

Ofatumumab* Phase II Study: T1 Gd-Enhancing Lesions

Monthly MRI scans from weeks 8 to 24

1 Patient receiving placebo with 95 total lesions not included

Ofatumumab Phase II Study: Safety Outcomes

- Main AEs related to infusion
- No increases in infections
- Well tolerated
- Safe

Late Stage Agents

- BG-12
- Alemtuzumab
- Laquinimod
BG-12

- An oral formulation of dimethylfumarate
- > 30 years of use of fumaric acids in the treatment of psoriasis (both topical and oral)
- Antiinflammatory effects
  - Inhibits the expression of adhesion molecules and proinflammatory cytokines
  - Induces a Th1 to Th2 shift
- Potential neuroprotective effects
  - Activates the Nrf2 pathway and induces antioxidant enzyme production
  - Protects oligodendrocytes against free-radical induced cytotoxicity
  - Increases neuronal survival and protects astrocytes against oxidative stress \textit{in vitro}
  - Preserves myelin, axons, and neurons in EAE

## BG-12

<table>
<thead>
<tr>
<th>DEFINE</th>
<th>CONFIRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS (&gt; 1200)</td>
<td>Basically same inclusion as DEFINE also Glatiramer Acetate arm</td>
</tr>
<tr>
<td>EDSS 0 – 5.0</td>
<td>Primary endpoint: Annualized relapse rate (ARR)</td>
</tr>
<tr>
<td>240 mg BG-12 240 mg BID - TID vs placebo</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint: Proportion of patients relapsing at 2 years</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoints: ARR, EDSS, # of new or enlarging T2 lesions, # of Gd+ lesions</td>
<td></td>
</tr>
</tbody>
</table>

# BG-12: DEFINE Trial

<table>
<thead>
<tr>
<th>DEFINE * ECTRIMS 2011</th>
<th>BG-12 BID</th>
<th>BG-12 TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion relapse free</td>
<td>↑ 51% (p&lt;0.001)</td>
<td>↑ 50% (p&lt;0.001)</td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>↓ 53% (p&lt;0.001)</td>
<td>↓ 49% (p&lt;0.001)</td>
</tr>
<tr>
<td>Mean # of new/enlarging T2 lesions</td>
<td>↓ 85% (p&lt;0.0001)</td>
<td>↓ 74% (p&lt;0.0001)</td>
</tr>
<tr>
<td>Mean # of Gad+ lesions</td>
<td>↓ 90% (p&lt;0.0001)</td>
<td>↓ 73% (p&lt;0.0001)</td>
</tr>
<tr>
<td>Confirmed 12-week EDSS progression</td>
<td>↓ 38% (p&lt;0.01)</td>
<td>↓ 34% (p&lt;0.05)</td>
</tr>
</tbody>
</table>

**Note:** All comparisons are vs. placebo

## BG-12: CONFIRM Trial

<table>
<thead>
<tr>
<th>CONFIRM</th>
<th>BG-12 BID</th>
<th>BG-12 TID</th>
<th>Glatiramer Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Press release 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>↓ 44% (p&lt;0.0001)</td>
<td>↓ 51% (p&lt;0.0001)</td>
<td>↓ 29% (p&lt;0.02)</td>
</tr>
<tr>
<td>Proportion relapse free</td>
<td>↑ 34% (p&lt;0.003)</td>
<td>↑ 45% (p&lt;0.0001)</td>
<td>↑ 29% (p&lt;0.01)</td>
</tr>
<tr>
<td>Mean # of new/enlarging T2 lesions</td>
<td>↓ 71% (p&lt;0.0001)</td>
<td>↓ 73% (p&lt;0.0001)</td>
<td>↓ 54% (p&lt;0.0001)</td>
</tr>
<tr>
<td>Confirmed 12-week EDSS progression</td>
<td>↓ 21% (NS)</td>
<td>↓ 24% (NS)</td>
<td>↓ 7% (NS)</td>
</tr>
<tr>
<td>Mean # of new T1 lesions</td>
<td>↓ 57% (p&lt;0.0001)</td>
<td>↓ 65% (p&lt;0.0001)</td>
<td>↓ 41% (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

BG-12 Safety

• Incidence of serious infections was similar across treatment groups

• No opportunistic infections in BG-12-treated patients

• No evidence of increased malignancy with BG-12

# BG-12 Tolerability

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Placebo (n=408)</th>
<th>BG-12 BID (n=410)</th>
<th>BG-12 TID (n=416)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>20 (5)</td>
<td>154 (38)</td>
<td>132 (32)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55 (13)</td>
<td>62 (15)</td>
<td>78 (19)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (9)</td>
<td>53 (13)</td>
<td>54 (14)</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>28 (7)</td>
<td>40 (10)</td>
<td>52 (13)</td>
</tr>
<tr>
<td>Proteinuria*</td>
<td>34 (8)</td>
<td>38 (9)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>22 (5)</td>
<td>46 (11)</td>
<td>37 (9)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>19 (5)</td>
<td>42 (10)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (6)</td>
<td>40 (10)</td>
<td>30 (7)</td>
</tr>
</tbody>
</table>

Alemtuzumab

- IV monoclonal humanized antibody directed against CD52 antigen
- Prolonged lymphocyte depletion (B cells, T cells, and monocytes)
  - < 1 hour following dose, WBCs no longer detectable in circulation
  - Long term CD4+, CD8+ T cells depletion
    - Median recovery time to baseline levels
      - CD4+ T cells – 61 months
      - CD8+ T cells – 30 months
      - Monocytes – 3 months
      - B cells – 3 to 6 months
      - After recovery, rise to 124% of pretreatment levels at 27 months

Alemtuzumab: CARE-MS I & II

<table>
<thead>
<tr>
<th>CARE-MS I</th>
<th>CARE-MS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS (n=581)</td>
<td>RRMS (n=840)</td>
</tr>
<tr>
<td>Treatment naive</td>
<td>Relapse despite &gt; 6 months of treatment</td>
</tr>
<tr>
<td>EDSS 0 – 3.0</td>
<td>EDSS 0 – 5.0</td>
</tr>
<tr>
<td>Onset of MS symptoms within 5 years</td>
<td>Onset of MS symptoms within 10 years</td>
</tr>
<tr>
<td>IV alemtuzumab vs. IFN-Beta-1a SC</td>
<td>IV alemtuzumab vs. IFN-Beta-1a SC</td>
</tr>
<tr>
<td>Primary endpoint: Reduction in relapse rate and time to 6 month sustained disability</td>
<td>Primary endpoint: Reduction in relapse rate and time to 6 month sustained disability</td>
</tr>
<tr>
<td>Secondary endpoints: ARR, EDSS, # of new or enlarging T2 lesions, # of Gd+ lesions</td>
<td>Secondary endpoints: ARR, EDSS, # of new or enlarging T2 lesions, # of Gd+ lesions</td>
</tr>
</tbody>
</table>

## Alemtuzumab: CARE-MS I

<table>
<thead>
<tr>
<th>CARE-MS I * ECTRIMS 2011</th>
<th><strong>Alemtuzumab</strong></th>
<th><strong>IFN Beta-1a SC</strong></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>0.18</td>
<td>0.39</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>% with sustained 6 month EDSS worsening</td>
<td>8%</td>
<td>11%</td>
<td>p = 0.22 (NS)</td>
</tr>
<tr>
<td>Proportion relapse free</td>
<td>78%</td>
<td>59%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Reduction in T2-hyperintense lesion volume</td>
<td>- 9.3</td>
<td>- 6.5</td>
<td>p = 0.31 (NS)</td>
</tr>
<tr>
<td>Proportion with new/enlarging T2 lesions</td>
<td>49%</td>
<td>58%</td>
<td>p = 0.035</td>
</tr>
<tr>
<td>Proportion with new Gad+ lesions</td>
<td>15%</td>
<td>27%</td>
<td>p = 0.0006</td>
</tr>
<tr>
<td>Proportion with new T1 lesions</td>
<td>24%</td>
<td>31%</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>Change in brain parenchymal volume</td>
<td>- 0.87</td>
<td>- 1.49</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

### Alemtuzumab: CARE- MS II

<table>
<thead>
<tr>
<th>CARE-MS II * Press release 2011</th>
<th>Alemtuzumab vs. IFN Beta-1a SC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>↓ 49%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>% with sustained 6 month EDSS worsening</td>
<td>↓ 42%</td>
<td>p = 0.0084</td>
</tr>
</tbody>
</table>

Alemtuzumab Safety

- **Serious adverse events**
  - CARE-MS I
  - Alemtuzumab – 18.4%
  - IFN Beta-1a SC – 14.4%

- **Antibody-mediated autoimmunity**
  - ITP
    - CARE-MS I – 0.8%
    - CARE-MS II – ~1%
  - Thyroid dysfunction
    - CARE-MS I – 18.1%
    - CARE-MS II – ~16%
  - Older trials: Anti-glomerular basement membrane disease 0.5%

Alemtuzumab Safety

- Mild or moderate infections (respiratory tract, UTIs, herpes, influenza) - 66%
  - CARE-MS I and CARE-MS II – No life threatening or fatal infections

- Infusion reactions - 99%
  - Mild to moderate
  - Headache, rash, nausea, hives, fever, itching, insomnia, and fatigue

- CD52 expressed on epidydimitis, mature sperm

- Rare: Burkitt’s Lymphoma

Laquinimod

• Antiinflammatory effects
  - Induces a Th1 to Th2 shift
  - Influence the expression of cytokines, MMPs, and integrins
  - Reduces infiltration of CD4+ T cells and macrophages into the CNS

• Potential neuroprotective effects
  - Ameliorates EAE via a BDNF pathway
  - Reduces astrogliosis and limits demyelination and oligodendrocyte and axonal damage in the cuprizone model

• Preserves immune surveillance

<table>
<thead>
<tr>
<th></th>
<th><strong>ALLEGRO</strong></th>
<th><strong>BRAVO</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RRMS</strong></td>
<td>(n=1,106)</td>
<td>RRMS (n=1,331)</td>
</tr>
<tr>
<td><strong>EDSS</strong></td>
<td>0 – 5.5</td>
<td>EDSS 0 – 5.5</td>
</tr>
<tr>
<td><strong>24 months</strong></td>
<td></td>
<td>24 months</td>
</tr>
<tr>
<td><strong>Primary endpoint:</strong></td>
<td>Annualized relapse rate</td>
<td>Annualized relapse rate</td>
</tr>
<tr>
<td><strong>Secondary endpoints:</strong></td>
<td>Confirmed 12 and 24 week disability progression, # of new or enlarging T2 lesions, # of Gd+ lesions, brain atrophy</td>
<td>Confirmed 12 and 24 week disability progression, # of new or enlarging T2 lesions, # of Gd+ lesions</td>
</tr>
</tbody>
</table>

### Laquinimod

<table>
<thead>
<tr>
<th>ALLEGRO * AAN 2011</th>
<th>Laquinimod</th>
<th>Placebo</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>0.30</td>
<td>0.39</td>
<td>↓ 23% (p=0.0024)</td>
</tr>
<tr>
<td>Confirmed 3-month EDSS progression</td>
<td></td>
<td>↓ 36% (p=0.0122)</td>
<td></td>
</tr>
<tr>
<td>Confirmed 6-month EDSS progression</td>
<td></td>
<td>↓ 48% (p=0.0023)</td>
<td></td>
</tr>
<tr>
<td>Mean cumulative # of Gd+ lesions</td>
<td>1.3</td>
<td>2.1</td>
<td>↓ 37% (p=0.0003)</td>
</tr>
<tr>
<td>Mean cumulative # of new T2 lesions</td>
<td>5.0</td>
<td>7.1</td>
<td>↓ 30% (p=0.0002)</td>
</tr>
<tr>
<td>% brain volume change from baseline</td>
<td>-0.87</td>
<td>-1.29</td>
<td>↓ 33% (p&lt;0.0001)</td>
</tr>
<tr>
<td>Whole Brain Magnetization Transfer Ratio</td>
<td>+0.045</td>
<td>-0.438</td>
<td>n = 88 (p = 0.0180)</td>
</tr>
</tbody>
</table>

**MFIS (MS Fatigue Impact Scale) and SF-36 – maintained or improved on laquinimod vs. placebo**

<table>
<thead>
<tr>
<th>BRAVO * ECTRIMS 2011</th>
<th>Laquinimod</th>
<th>IFN Beta-1a IM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annualized relapse rate</strong></td>
<td>0.29 ↓ 21.3% (p=0.026)</td>
<td>0.27 ↓ 29% (p=0.002)</td>
</tr>
<tr>
<td><strong>Confirmed 3-month EDSS progression</strong></td>
<td>↓ 33.5% (p=0.044)</td>
<td>↓ 28.7% (NS)</td>
</tr>
<tr>
<td><strong>Confirmed 6-month EDSS progression</strong></td>
<td>↓ 40.6% (p=0.04)</td>
<td>↓ 28.3% (NS)</td>
</tr>
<tr>
<td><strong>Mean cumulative # of Gd+ lesions</strong></td>
<td>↓ 22% (NS)</td>
<td>↓ 60% (p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Mean cumulative # of new T2 lesions</strong></td>
<td>↓ 19% (p=0.037)</td>
<td>↓ 52% (p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>% brain volume change from baseline</strong></td>
<td>-- 0.83 ↓ 27.5% (p&lt;0.0001)</td>
<td>-- 1.25 ↓ 9% (p=0.14)</td>
</tr>
</tbody>
</table>

* BRAVO data after correction for baseline differences

Placebo: 0.37

Placebo: - 1. 14

### Laquinimod: Safety

<table>
<thead>
<tr>
<th>Adverse Event (ALLEGRO)</th>
<th>Laquinimod</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased ALT</td>
<td>38 (6.9%)</td>
<td>15 (2.7%)</td>
<td>2.6</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>32 (5.8%)</td>
<td>16 (2.9%)</td>
<td>2.0</td>
</tr>
<tr>
<td>Back Pain</td>
<td>90 (16.4%)</td>
<td>50 (9%)</td>
<td>1.8</td>
</tr>
<tr>
<td>Cough</td>
<td>41 (7.5%)</td>
<td>25 (4.5%)</td>
<td>1.7</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>40 (7.3%)</td>
<td>25 (4.5%)</td>
<td>1.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44 (8%)</td>
<td>34 (6.1%)</td>
<td>1.3</td>
</tr>
<tr>
<td>Headache</td>
<td>125 (22.7%)</td>
<td>99 (17.8%)</td>
<td>1.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>36 (6.5%)</td>
<td>31 (5.6%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>47 (8.5%)</td>
<td>42 (7.6%)</td>
<td>1.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (6.2%)</td>
<td>32 (5.8%)</td>
<td>1.1</td>
</tr>
<tr>
<td>Depression</td>
<td>31 (5.6%)</td>
<td>35 (6.3%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>101 (18.4%)</td>
<td>118 (21.2%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>42 (7.6%)</td>
<td>48 (8.6%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>35 (6.4%)</td>
<td>38 (6.8%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Influenza</td>
<td>33 (6%)</td>
<td>44 (7.9%)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- Serious Adverse Events: 22.2% (Laquinimod) vs. 16.2% (placebo). No fatalities on laquinimod
- Herpes: viral infections 3.1% (laquinimod) vs. 3.6% (placebo)
- Neoplasm: 1.5% (laquinimod) vs. 1.1% (placebo)
Case 2 Discussion

A 38 year old man had optic neuritis in 2007. In 2008 he developed diplopia and an INO. An MRI revealed multiple lesions, many periventricular, and 3 enhancing. In September 2008 he was started on interferon beta 1-a thrice weekly. In April 2009 he had an episode of L facial numbness and weakness and horizontal diplopia which improved 90% after IV steroids. In August 2009 he developed numbness and weakness in both legs. MRI of the C spine revealed an enhancing lesion at C 7.
Case 3

The patient is a 37 year old male clinical psychologist whose illness began in 1987 with transient numbness in the feet and band-like sensation in the back. In 1989 he had right optic neuritis with full recovery. In 1991 he first noticed difficulty running and a diagnosis of MS was made. He had several exacerbations over the next five years, each one leaving a “greater deficit.” The patient felt he became “secondary progressive” in 1996 when he first required a cane because of right leg weakness.

In 1998 he needed two canes and in late 1999 began to use a wheelchair intermittently because of frequent falls and involvement of his left leg. For about one year prior to this consultation, he also noticed progressively increasing stiffness of the right hand which interfered with his handwriting. He also experienced increasing difficulty with urination, with severe urgency and incontinence. For about a year he had been unable to maintain an erection.
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Summary

- Clinically Isolated Syndrome
- Relapsing Remitting Multiple Sclerosis
- Secondary Progressive Multiple Sclerosis
- Therapeutic Options for each Stage of Disease
- Pipeline
Therapeutic Advances in the Management of Multiple Sclerosis