DMAMS: Disease Modifying Therapies for Multiple Sclerosis

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MS: The Disease

- MS is a relapsing inflammatory disease of the brain, spinal cord and optic nerves.
- >400,000 American victims, 2.7 million worldwide.
- 80% of MS Patients develop MS between 16 and 45 yrs.
- Female:Male Ratio 2.5:1
- Untreated, 30% will ultimately end up in wheelchair
- Total lifetime disease related costs in excess of 2.2 million dollars.
- MS is the leading cause of irreversible disability in young women and second leading cause of disability in young men.

Goals of Therapy with DMAMS:

- Old goal: Slow progression of disability in MS.
- New goal: Put patient in a “Disease Activity Free State”
  - No relapses
  - No progression of disability
  - No new lesions on MRI
- Better Goal: Maximize chance patient will be better after 1 to 2 years on treatment.
  - Less fatigue
  - Better strength and coordination
  - Less pain
  - Less cognitive problems
- Future Goal: Cure MS

Disclosure (Last 4 Years)

- I have received personal compensation for:
  - Activities such as advisory boards, lectures and consultancy with the following companies/organizations: Biogen Idec, Consortium of MS Centers, Daiichi Sankyo, Elan Pharma, Eli Lilly and Co, Global Prairie, Guidepoint Global, Hoffman-LaRoche, Medical Logic, MSDx, Prime Education, Projects in Knowledge, Teva Pharmaceutical Industries, Xenoport, Esai Pharmaceuticals, Schering-Plough Biopharma, Acorda, Novartis
  - Research support from the following: Biogen Idec, Teva Pharmaceutical Industries, Lilly Research Laboratories, Genzyme, Ono Pharmaceuticals, Elan Pharmaceuticals, Novartis, NIH, Dept of Defense.
Prognosis in MS:

- Worrisome Prognostic Indicators:
  - Early Age of Onset
  - Incomplete recovery from early relapses
  - Early onset of progressive disability

- MRI metrics
  - High T-2 Burden of Disease = Frequent Inflammation
  - High ratio of T-1 to T-2 disease
  - Location - Location - Location
  - Presence of Brain Atrophy

MS MRI: T-2 vs T-1 Lesion Load

Spinal Cord MS Lesions:

Very Mild Cerebral MS:
Very Bad Spinal Cord MS:

Brain Atrophy

Grey Matter Lesions in MS:


13 patients with clinically definite RRMS with no treatment
- Mean age 36.4 years and mean disease duration 1.9 years (from first symptom onset)
- Significant difference in rate of change between MS patients and normal controls in gray matter fraction (GMF, \(P=0.010\))
- Gray matter atrophy did not occur in concurrence with white matter atrophy

**Extensive Grey Matter Demyelination is Associated with Meningeal B Cell Follicles**

**Early Neurodegeneration is Masked by Compensation and Reorganization**

- Clinical exam reveals fully normal functioning of right hand during simple motor task in patient
- fMRI reveals functional cortical changes
- Ongoing damage may go unrecognized until it is too late

**T-cell Mediated Inflammatory Pathway in MS**

- Residental inflammation
- Myelin/Oligodendrocytes
- Axons/Neurons
- Blood brain barrier
- Peripheral inflammation
CNS Resident Degenerative Pathway in MS


CNS Resident Degenerative Pathway in MS

- Oligodendrocyte
- Astrocyte
- Activated Astrocytes
- Astrocyte Glial scar formation
- Myelin Residue
- Proinflammatory Cytokines
- Axonal Damage
- TNF-α, NO, O2

MS: A Single Disease?
Loss of Neural Reserve for Adaptation to ongoing CNS Injury and onset of progressive disability

- Relapsing Phase
- Transitional Phase
- Progressive Phase

Stages of MS:
- Relapsing MS
- Transitional MS
- Progressive MS

Brain Atrophy

MRI GD Lesion:
- RRMS
- SPMS
- PPMS

Relapses:
- Inflammation
- Stopping Declining Neural Reserve
- Brain Atrophy

Aging contributes to progression

Treatments for MS

Quick Comparison of Current Agents:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relapse reduction RR</th>
<th>Decreased Sustained Disability</th>
<th>Reduction of MRI Activity</th>
<th>Effect on Brain Atrophy</th>
<th>Ease of Use</th>
<th>Risk of Serious AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose INF beta: Avonex</td>
<td>18%</td>
<td>15%</td>
<td>70%</td>
<td>no</td>
<td>2</td>
<td>2</td>
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<tr>
<td>High dose INF beta: Betaseron, Rebif, Xetava</td>
<td>30-32%</td>
<td>5-10%</td>
<td>80-90%</td>
<td>no</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Glatiramer: Copaxone</td>
<td>28-32%</td>
<td>13%</td>
<td>40%</td>
<td>yes</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Natalizumab: Tysabri</td>
<td>68%</td>
<td>54%</td>
<td>92%</td>
<td>yes</td>
<td>4-JVC+</td>
<td>1-JVC-</td>
</tr>
<tr>
<td>Teriflunomide: Aplastic</td>
<td>54-60%</td>
<td>30%</td>
<td>82%</td>
<td>yes</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Laquinimod</td>
<td>7%</td>
<td>36%</td>
<td>40%</td>
<td>yes (30%)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>MG-122</td>
<td>35%</td>
<td>38%</td>
<td>30%</td>
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<tr>
<td>Rituximab, Ocrelizumab</td>
<td>68%</td>
<td>63%</td>
<td>92%</td>
<td>yes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Teriflunomide: Aplastic</td>
<td>31%</td>
<td>30%</td>
<td>82%</td>
<td>yes</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Alemtuzumab</td>
<td>79%</td>
<td>30%</td>
<td>90%</td>
<td>yes</td>
<td>2</td>
<td>4</td>
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</table>
Quick Comparison of Current Agents:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relapse Reduction (1-3)</th>
<th>Decreased Sustained Disability (1-3)</th>
<th>Reduction of MRI Activity (1-3)</th>
<th>Effect on Brain Atrophy (1-3)</th>
<th>Risk of Serious AE (1-4)</th>
<th>Total Score: Lower is Better</th>
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<tbody>
<tr>
<td>Avonex</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
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<td>13</td>
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<td>Betaseron, Rebif, Xela</td>
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<td>2</td>
<td>3</td>
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<td>13</td>
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<tr>
<td>Glatiramer acetate</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
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<td>11</td>
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<tr>
<td>Natalizumab</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>8</td>
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<tr>
<td>Copaxone</td>
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<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>5</td>
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<td>Fingolimod</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
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<tr>
<td>Laquinimod</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>BG-12</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>9</td>
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<tr>
<td>Rituximab</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Alemtuzumab</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

Inflammatory Trafficking into the CNS in Multiple Sclerosis

- **Systemic Circulation**
  - Blood-Brain Barrier
  - 1: Immune cells cross through Blood-brain barrier
  - 2: Immune cells may re-activate and produce cytokines

- **Central Nervous System**
  - 3: Immune cells stimulate auto-immune attack against myelin

α4-integrin Plays a Central Role in Adhesion and Migration at the Blood-Brain Barrier

- Leukocyte
- α4-integrin
- Blood-Brain Barrier
- Endothelial Cells
- VCAM-1

In CNS Inflammation, Natalizumab Blocks the Transmigration of Lymphocytes into the BRAIN

- Circulation
- 4: Natalizumab
- Blood-brain barrier
- Endothelial Cell
- α4-integrin
- VCAM-1
- Tissue
- Extracellular Matrix (ECM)
**Recovery of Function on Natalizumab**

<table>
<thead>
<tr>
<th>Area of Improvement</th>
<th>Observations:</th>
<th>ECTRIMS Poster #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Superior to INF and GA</td>
<td>495, 925, 837, 207</td>
</tr>
<tr>
<td>Memory, Cognition</td>
<td>All components</td>
<td>495, 837, 464, 231</td>
</tr>
<tr>
<td>Hand Function</td>
<td></td>
<td>652</td>
</tr>
<tr>
<td>Disease Free State</td>
<td>68% yr 1, 68% yr 2, 90% yr 3.</td>
<td>896</td>
</tr>
<tr>
<td>EDSS, walking distance</td>
<td>3.4-3.1, 1185m to 1391m</td>
<td>892, 652</td>
</tr>
<tr>
<td>Daily Function</td>
<td></td>
<td>495</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Superior to INF and GA</td>
<td>495, 942, 837</td>
</tr>
<tr>
<td>Employability, work Capacity, Cost of Disease</td>
<td>Superior to INF and GA</td>
<td>659, 234</td>
</tr>
</tbody>
</table>

**Effect of Co-Morbidities on Disability in MS:**

- **Benefits of Exercise in MS:**
  - Improved Aerobic Capacity
  - Improved Strength
  - Improved Endurance
  - Improved Balance
  - Improved Fatigue
  - Improved Bowel/Bladder Function
  - Improved Quality of Life
  - Improved Self Efficacy
  - Improved Depression
Laquinimod: A Possible New Therapy for the “CNS Resident Immunopathology of MS”

Molecular Effects of Laquinimod on Resident CNS Cells: Laquinimod Interferes With NF-κB to Inhibit Activation of Astrocytes

- In MS, increased activation of NF-κB contributes to both:
  - Relapses: due to activation of the pro-inflammatory T-cell response and peripheral inflammation
  - Neurodegeneration: due to activation of astrocytes and microglial cells leading to resident CNS inflammation
- Laquinimod has been shown to block activation of NF-κB in astrocytes, thereby reducing their activation and subsequent astroglial scar formation.

Bravo study design & purpose

Purpose: To assess the efficacy, safety, and tolerability of laquinimod over placebo in a double-blind design and of a reference arm of Interferon β-1a (Avonex<sup>®</sup>) in a rater-blinded design.
Primary endpoint – annualized relapse rate

LAQUINIMOD 0.6mg

21% Reduction
p=0.02

PLACBO

0.37

0.29

AVONEX® 30mcg

20% Reduction
p=0.002

0.27

*Adjusted for baseline EDSS, number of relapses in 2y pre-study, country, baseline T2 lesion volume and GdE-T1 status at baseline.

Laquinimod reduced the risk for 3-months confirmed disease progression

Laquinimod vs. Placebo – 33.5% Reduction, p=0.04

AVONEX® vs. Placebo – 28.7% Reduction, p=0.09

MRI-measured brain volume loss (sienna)

PLACBO

LAQUINIMOD 0.6mg

AVONEX® 30mcg

-1.14%

-0.83%

-1.25%

27% Improvement
p=0.0001

4% Deterioration
p=0.14

*Adjusted for baseline EDSS, number of relapses in 2y pre-study, country, baseline T2 lesion volume and GdE-T1 status at baseline.

Cure?

- Combination Therapies
- MS Vaccine
Future Combinations to Consider:

- Rituximab and Copaxone
- Laquinimod plus any other DMAMS
- Rituximab and BG12
- Copaxone and BG12
- Interferon and Teriflunomide

QUESTIONS?