Living Well with MS: Therapies to Prevent Damage to the Brain.

Timothy Vollmer, MD
Professor of Neurology
University of Colorado Denver
Co-Director
Rocky Mountain MS Center
at Anschutz Medical Center
MS: The Disease

- >400,000 American victims, 2.7 million world wide.
- 80% of MS Patients develop MS between 16 and 45 yrs.
- Female:Male Ratio  2.5:1
- 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.
Truths about treating MS:

- Optimal treatment of MS requires a comprehensive approach including:
  - Optimizing Diet
  - Adopting an effective exercise program
  - Developing an "Active Lifestyle"
  - Using medications to manage symptoms when necessary
  - Preventing further injury to the brain, spinal cord and optic nerves through the effective use of disease modifying therapies for MS (DMAMS)

- Optimal management of MS requires a knowledgeable patient and family. (knowledge is power)
Effect of Co-Morbidities on Disability in MS:

<table>
<thead>
<tr>
<th>Comorbidity category</th>
<th>Adjusted†</th>
<th></th>
<th></th>
<th>Adjusted for diagnostic delay†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Vascular</td>
<td>1.51</td>
<td>1.12-2.05</td>
<td>1.06</td>
<td>0.77-1.44</td>
<td>1.32</td>
<td>0.97-1.80</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1.54</td>
<td>1.04-2.28</td>
<td>1.81</td>
<td>1.25-2.63</td>
<td>1.35</td>
<td>0.91-2.01</td>
</tr>
<tr>
<td>Mental</td>
<td>1.29</td>
<td>0.97-1.71</td>
<td>1.62</td>
<td>1.23-2.14</td>
<td>1.23</td>
<td>0.92-1.63</td>
</tr>
<tr>
<td>Overweight†</td>
<td>1.08</td>
<td>0.78-1.50</td>
<td>1.03</td>
<td>0.74-1.42</td>
<td>1.02</td>
<td>0.74-1.43</td>
</tr>
<tr>
<td>Obesity†</td>
<td>1.38</td>
<td>1.02-1.87</td>
<td>1.24</td>
<td>0.91-1.67</td>
<td>1.33</td>
<td>0.98-1.80</td>
</tr>
</tbody>
</table>

Table 3. Odds ratios and 95% CIs for the association of comorbidity category at diagnosis and degree of disability at diagnosis in white NARCOMS participants enrolled within 2 years of diagnosis (n = 2,237)
Effect of Diet Related Diseases on Disability in MS:

Figure: Proportion of NARCOMS participants enrolled within 2 years of diagnosis who reported severe disability at diagnosis by number of physical comorbidities present.
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
Longitudinal Comparison of Cognitive Reserve Groups by Performance Scales 5-year Trajectories

- Mobility
- Pain
- Hand Function
- Vision
- Spasticity
- Sensory
- Fatigue
- Bladder
- Cognition

- High Active / Low Passive
- Low Active / High Passive
- High Active / High Passive
Selecting the best DMAMS for an individual patient:
Please Keep in Mind:

The following are my opinions.

There is no consensus within neurology on what therapy is best for each patient.
Evolving Therapeutic Goals with DMAMS:

- **1993-2007:** Slow Progression of Disease
- **2007-2010:** Seek Disease Activity Free State
- **2010-??:** Seek Disease Activity Free State and remission of symptoms.
Steps involved in selecting a DMAMS:

- First, confirm the diagnosis is correct.
- Second, use MRI, patient history and neurological examination to determine life time risk of disability.
- Third, identify concomitant health issues relevant to selection of DMAMS.
- Fourth, obtain “biomarker studies” to determine personal risk/benefit profile for each patient (personalized medicine).
- Fifth, select optimal agent based on lifetime risk of disability and personalized risk/benefit analysis of available agents.
- Finally, be ready to change therapy if MS is not completely controlled or safer therapies emerge.
Risk Categories for MS:

- **Low Risk of Disability:** 10% of MS patients.
  - May treat or monitor by MRI

- **Average Risk of Disability:** 60% of MS patients
  - Treat but minimize risks.

- **High Risk of Disability:** 30%
  - Treat, may be appropriate to accept somewhat more risk.
Relevant CoMorbid Health Conditions:

- History of Cancer- Gilenya, Teriflunomide, Alemtuzumab
- History of liver disease- Interferons, Gilenya
- History of heart disease- Gilenya
- History of Diabetes- Gilenya, Interferons
- Other autoimmune diseases- Interferons
  - Inflammatory Bowel Disease- Tysabri
- Hepatitis B or C-rituximab, Gilenya
When Selecting a DMAMS consider:
(in order of priority)

- Reduction of risk of sustained disability
- Reduction of Brain atrophy
- Probability of “Disease Activity Free State”
- Probability of improved function over 2 years.
- Reduction of Annualized relapse rate

- Risk of “serious adverse effects”
- Negative impact on Quality of Life and finances
- Tolerability issues
- Need for regular safety monitoring
- Comparable Risks: Life time risk of Death:
  - Heart Disease= 1/4
  - Cancer= 1/20
  - Car Accident= 1/164
  - Airline crash= 1/20,000
# 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, 88% yr 2, 96% 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>
Natalizumab Withdrawal Syndrome

- Incidence:
  - Clinical Symptoms: 30-40%
  - MRI Gad+ Lesions: 40-60%
- Mean Time to onset: 3.1 Months after last dose of natalizumab, range 8 weeks to 6 months.
- Mean EDSS change: Baseline EDSS=3.3, EDSS at last dose of Natalizumab=2.8, EDSS at 6 months after last dose of Natalizumab=4.0.
- Mean # Gad+ lesions at relapse=6 (range 3-16)

# Quick Comparison of Current Agents:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relapse reduction : RRR</th>
<th>Decreased Sustained Disability</th>
<th>Reduction of MRI Activity</th>
<th>Effect on Brain Atrophy</th>
<th>Ease of Use 1-3</th>
<th>Risk of Serious AE 1-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose INF beta Avonex</td>
<td>18%</td>
<td>15%</td>
<td>70%</td>
<td>yes</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>High dose INF beta: Betaseron, Rebif, Xtavia</td>
<td>30-32%</td>
<td>5-10%</td>
<td>80-90%</td>
<td>no</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Glatiramer Copaxone</td>
<td>29-32%</td>
<td>13%</td>
<td>40%</td>
<td>yes</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Natalizumab Tysabri</td>
<td>68%</td>
<td>54%</td>
<td>92%</td>
<td>yes</td>
<td>1</td>
<td>4-JVC+ 2-JVC-</td>
</tr>
<tr>
<td>Fingolimod Gilenya</td>
<td>54-60%</td>
<td>30%</td>
<td>82%</td>
<td>yes</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>27%</td>
<td>36%</td>
<td>40%</td>
<td>yes (33%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BG-12</td>
<td>53%?-</td>
<td>38%?-</td>
<td>??</td>
<td>??</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab Ocrealizumab</td>
<td>68% 80%</td>
<td>63% - PPMS &gt;60%</td>
<td>92% &gt;90%</td>
<td>??</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>31%</td>
<td>30%</td>
<td>69%</td>
<td>30%</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>79%</td>
<td>30%?</td>
<td>90%</td>
<td>??</td>
<td>2</td>
<td>4-5</td>
</tr>
</tbody>
</table>
Relevant Biomarker Studies:

- **JC Virus antibody status:**
  - If negative very low risk of PML
  - If positive high risk of PML with Tysabri, others?

- **Future possible biomarkers:**
  - Gene profile of super responders to copaxone
  - IL-17r for response to interferons
  - IL-21 expression for alemtuzumab
If JCV Antibody Negative and average risk of disability:

- Rank order based on safety and efficacy:
  - Tysabri 68% ARR 50% Disability
  - Rituximab 70% ARR 30% Disability
  - BG12 50% 30% Disability
  - Copaxone 29% ARR ?? Disability
  - Teriflunomide 30% ARR ?? Disability
  - Rebif 30% ARR 10-15% Disability
  - Avonex 20% ARR 30% ?Disability
  - Gilenya 55% ARR 30% Disability
  - Betaseron/Xtavia 30% ARR ?? Disability
  - Alemtuzumab 70% ARR 30% Disability
If JCV Antibody Negative and high risk of disability:

- Rank order based on safety and efficacy:
  - Tysabri 68% ARR 50% Disability
  - Rituximab 70% ARR 30% Disability
  - Alemtuzumab 70% ARR 30% Disability
  - Gilenya 55% ARR 30% Disability
  - BG12 50% 30% Disability
  - Copaxone 29% ARR ?? Disability
  - Teriflunomide 30% ARR ?? Disability
  - Rebif 30% ARR 10-15% Disability
  - Avonex 20% ARR 30% ?Disability
  - Betaseron/Xtavia 30% ARR ?? Disability
If JCV Antibody Positive and average risk of disability:

• Rank order based on safety and efficacy:
  – Rituximab 70% ARR 30% Disability
  – BG12 50% 30% Disability
  – Copaxone 29% ARR ?? Disability
  – Gilenya 55% ARR 30% Disability
  – Teriflunomide 30% ARR ?? Disability
  – Rebif 30% ARR 10-15% Disability
  – Avonex 20% ARR 30% ?Disability
  – Betaseron/Xtavia 30% ARR ?? Disability
  – Alemtuzumab 70% ARR 30% Disability
  – Tysabri 68% ARR 50% Disability
If JCV Antibody Positive and high risk of disability:

- Rank order based on safety and efficacy:
  - Rituximab 70% ARR 30% Disability
  - Alemtuzumab 70% ARR 30% Disability
  - Tysabri 68% ARR 50% Disability
    - Except Chemo exposure Pts
  - Gilenya 55% ARR 30% Disability
  - BG12 50% 30% Disability
  - Teriflunomide 30% ARR ?? Disability
  - Copaxone 29% ARR ?? Disability
  - Rebif 30% ARR 10-15% Disability
  - Avonex 20% ARR 30% ?Disability
  - Betaseron/Xtavia 30% ARR ?? Disability
Anticipating Pregnancy: A special case

- Copaxone
- Tysabri
- Interferons
- Gilenya
- BG12
Safety Monitoring for Tysabri:

• Baseline MRI
• Visits with neurologist every three months.
  – May go to every 6 months in second year if JCV antibody negative
• JCV antibody tests every 6 months.
• Liver enzyme tests every 3 to 6 months

• Urgent MRI if any new neurological symptoms to rule out PML in all cases.
Safety Monitoring for Gilenya:

- **First dose monitoring:**
  - Baseline and every hour ECG for 6 hours

- **Visits with neurologist every three months.**
  - May go to every 6 months in second year
  - Liver enzyme tests every 3 months
  - CBC every 3 months
  - ECG at 3 months
  - OCT at baseline and 3 months and again if any visual symptoms

- **Baseline MRI**

- **Annual MRI??**
Safety Monitoring for Alemtuzumab:

- Baseline MRI
- First dose monitoring:
  - For infusion reactions
- Visits with neurologist every three months.
  - CBC and Platelet Count every month !!!
  - Kidney tests every month !!
Safety Monitoring for Interferons, BG12 and Teriflunomide:

- Baseline MRI
- Visits with neurologist every three months year 1, possibly every 6 months year 2.
- CBC and LFTs every three months
- Annual MRI
Safety Monitoring for Copaxone:

- Baseline MRI
- Annual MRI
Recommendations:

• Talk with your neurologist about what your goals with therapy are and about any symptoms you have.

• Be willing to review your treatment with your neurologist at least yearly.

• Reassess if the therapy you are on is the best if you have a relapse or new lesions on MRI.

• If you are having side effects or suffering high costs talk with your neurologist about alternatives.

• Combine DMAMS with a comprehensive approach to managing your MS.