Multiple Sclerosis

Disease State Insights and Clinical Updates

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- Disease of immune dysregulation and neurodegeneration
  - Most common cause of neurological disability in young adults
  - Onset: 20-50 yrs
  - More common in women (2-3x more likely) than men
  - More common in individuals of northern European descent
- Chronic disease with unpredictable, variable course
- MS is a syndrome with heterogeneous clinical expression
  - Different clinical subtypes
  - Growing evidence supports pathologic heterogeneity
  - Immunologic heterogeneity also likely

2. NMSS-Who gets MS?
### MS Symptoms

<table>
<thead>
<tr>
<th>Visual</th>
<th>Sensory</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neuritis</td>
<td>• Paresthesia</td>
<td>• Weakness</td>
</tr>
<tr>
<td>• Diplopia</td>
<td>• Dizziness</td>
<td>• Paralysis</td>
</tr>
<tr>
<td>• Vision loss</td>
<td>• Vertigo</td>
<td>• Spasticity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mental</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cognitive Impairment</td>
<td>• Fatigue/Sleep</td>
</tr>
<tr>
<td>• Depression</td>
<td>• Urinary/bowel</td>
</tr>
<tr>
<td>• Speech</td>
<td>• Sexual dysfunction</td>
</tr>
<tr>
<td>• Psychosis</td>
<td>• Societal</td>
</tr>
<tr>
<td>• Euphoria</td>
<td>• Problems with everyday activities</td>
</tr>
</tbody>
</table>

### Risk Factors for Multiple Sclerosis

**Genetic**
- SNPs
- Disease modifier and susceptibility genes
- Methylation
- Retroviral sequences
- microRNAs

**Environment**
- Pathogens
- Chemicals
- Smoking
- Diet
- Sun and Vitamin D
- Salt
- Alcohol

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Oksenberg J. and Baranzini S. Nat Rev Neurol, 2010;6:429-437
Females vs Males

- MS is 2-3 times more common in women vs. men
- Women are more likely than men to have MS that follows a “benign” course
- Male sex was associated with a higher probability of developing secondary progressive disease and a shorter time to progression

Immune dysregulation
- Inflammation
- Breakdown of BBB
- Demyelination
- Relapses-inflammation

Neurodegeneration
- Axonal damage/loss
- Plaque formation in CNS
- Gliosis
- Progression-disability

Hallmarks of MS Pathology
Disease Progression in RRMS

Disability vs Time

RRMS
85% of MS diagnoses
50% of RRMS convert over 10 years
90% of RRMS convert over 25 years

PPMS
10% of MS diagnoses

SPMS

Disease Courses of MS

http://www.nationalmssociety.org/What-is-MS/Types-of-MS/RRMS
http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS
http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS
Diagnosis of MS

Clinical, Radiological

Diagnosis of MS: McDonald Criteria

McDonald criteria allows diagnosis of CDMS after a single attack, if additional MRI criteria are met:

- Lesion dissemination in both space and time
- Requirement for CDMS can be satisfied clinically, radiologically, or both
- Allows earlier diagnosis and treatment initiation

### Diagnosis of MS: 2010 McDonald Criteria

**Summary**

<table>
<thead>
<tr>
<th>Clinical Attacks</th>
<th>Lesions</th>
<th>Additional Criteria Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>≥ 2</td>
<td>none</td>
</tr>
<tr>
<td>≥ 2</td>
<td>1</td>
<td>DIS (≥1 T2 lesions in MS brain regions)</td>
</tr>
<tr>
<td>1</td>
<td>≥ 2</td>
<td>DIT (simultaneous contrast-enhancing and non-enhancing lesions)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>DIS (≥2 T2 lesions in MS brain regions AND DIT (enhancing and non-enhancing lesions)</td>
</tr>
<tr>
<td>0 (progression from onset)</td>
<td>1 year of disease progression AND 2/3 of the following: 1. DIS in the brain 2. DIS in sp. cord based on ≥2 T2 lesions 3. Positive CSF</td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis**

- **Diagnosis of MS: 2010 McDonald Criteria**
  - Clinical Attacks
  - Lesions
  - Additional Criteria Needed

**Monitoring Disease Progression in MS**

- **Disability, MRI**
Expanded Disability Status Score (EDSS)

10-point scale of disease severity

- Low Range
  - EDSS 0-3.5
  - EDSS is based on change in one or more of the functional systems (FS)

- Middle Range
  - EDSS >4.0
  - Scoring is based primarily on gait dysfunction

- Mid-High Range
  - EDSS 6-7.5
  - Exclusively dependent on walking function

- High Range
  - EDSS 8-10
  - Loss of ambulation, function, & death

Lesions are bright (hyperintense)

- The bright signal is non-specific
  - Edema, demyelination, remyelination, gliosis, inflammation, axon loss

- Highly sensitive to above tissue changes
  - Used to understand accumulation of lesion burden
  - Lack of specificity = poor marker for disease progression

**T2-Weighted Lesions**

Thus, hyperintense = edema, demyelination, or destruction

**T1-Weighted Lesions (Without Gd)**

- **Lesions appear** **DARK** (hypointense)
  - Chronic tissue injury or severe inflammatory edema
  - Acute MS lesions are often isointense w/NAWM

- **T1 lesions can resolve:** “acute”
  - Typically within 6 months
  - Same possible underlying pathology as T2 lesion

- **Chronic Black Hole**
  - 40% of lesions evolve into persistent or chronic black holes over a 6 month period
  - Correlate pathologically with permanent demyelination and severe axonal loss

NAWM = Normal Appearing White Matter
Virtually all new lesions go through a phase of enhancement.
- Typically persisting for two to eight weeks.

Immunopathogenesis of MS

Immune System, T and B cells, BBB Trafficking
**Immunopathogenesis of MS**

Immune cells and inflammatory mediators play a central role in the ongoing damage to CNS structures.

**Potential Role for B Cells in MS**

- **Antibodies are produced intrathecally**

- **Oligoclonal bands (OCBs)**
  - Present in the CSF but not in serum
  - Unclear specificity or functional relevance

- **Epstein-Barr virus infection**
  - Non-specific activation of the intrathecal B-cell pool
Environmental Factors in MS

Vitamin D, Salt Intake, Alcohol, Gut Microbiome


http://multiplesclerosis.net/what-is-ms/statistics/

- A distinct latitudinal variation in MS frequency, with higher latitude correlating with increased prevalence, incidence, and mortality

- Vitamin D levels and exposure to UV light appear to have independent contributions to MS risk
**Vitamin D Link to MS**

- High incidence of vitamin D deficiency among MS patients\(^1\)\(^-\)\(^2\)
- Higher MS risk in individuals with low vitamin D intake or low circulating 25(OH)D\(^2\),\(^3\)
- Vitamin D levels early in life may be critical for conferring protection from MS\(^2\)
- Low vitamin D levels inversely correlate with MS disease activity\(^4\)\(^-\)\(^7\)

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**Higher Serum Vitamin D Predicts Reduced MS Activity**

In the BENEFIT trial, serum 25(OH)D levels in the first 12 months following a CIS predicted MS activity and progression in the subsequent 4 years.

- Higher 25(OH)D levels predicted:
  - Slower conversion to CDMS (p = .05)
  - Fewer new active lesions (p = .002)
  - Reduced T2 lesion volume (p = .008)
  - Less brain volume loss (p = .005)
### Inverse Correlation between Serum 25(OH)D Levels and Clinical Disability

For patients with serum 25(OH)D levels ≥50 nmol/L:
- 27% reduction in relapses from baseline to 60 months (p = .19)
- Significant effect on relapses only observed from 12 to 60 months (57% reduction, p = .03)

### Annualized Change in EDSS by 25(OH)D Levels

<table>
<thead>
<tr>
<th>25(OH)D, nmol/L</th>
<th>50</th>
<th>70</th>
<th>90</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.04</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- 50 nmol/L increase in 25(OH)D levels associated with a reduction of 0.16 in EDSS score (p = .11)
- Annualized change in EDSS score was lower among patients with high (≥50 nmol/L) 25(OH)D

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### Gut Microbiome and MS

- **The gut microbiome:**
  - Plays a key role in shaping the immune repertoire
  - Plays an important role in disease susceptibility in the EAE model
  - Has been described in many diseases but not yet fully in multiple sclerosis

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### Environmental Factors Summary

<table>
<thead>
<tr>
<th>Possible Benefit?</th>
<th>Increased Risk?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>High Salt Diet</td>
</tr>
<tr>
<td>Alcohol (moderation)</td>
<td>Smoking (not oral tobacco)</td>
</tr>
<tr>
<td>Exercise</td>
<td>High BMI, dietary fat</td>
</tr>
<tr>
<td></td>
<td>Vitamin B12 deficiency</td>
</tr>
<tr>
<td>Gut Microbiome?</td>
<td>EBV infection early in life</td>
</tr>
</tbody>
</table>

#### Genetic Factors in MS

**Susceptibility Genes**
Genetics in MS

- Genetic susceptibility to MS exists
  - Concordance rate in monozygotic twins estimated 25-30%\(^1,2\)
    - MZ females = 34%
  - Concordance rate in dizygotic twins estimated 3-11.4%\(^1,2\)
    - DZ females = 3.8%
  - Risk to sibling 1.9%-3.9%\(^3\)

- Racial subgroups have different susceptibility to MS\(^3\)
  - Susceptible: Caucasians from Scandinavia and Scotland
  - Resistant: African American, Mongolian, Japanese, Chinese, American Indian, Inuit

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Potential Triggers of MS

- Genetic Predisposition?\(^1\)
- Infectious Agent?\(^2\)
- Environmental Factors?\(^1\)

Abnormal immunologic response \(\rightarrow\) MS

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2. Willer CJ et al. PNAS. 2003;100(22)12877-12882.
Clinical Correlates
Cognitive Issues, Spasticity, Fatigue, Bladder/bowel

Cognitive Impairment in MS

- Cognitive capacity is most robustly connected to vocational status/disability\(^1\)
- Prevalence of cognitive impairment 45-65%\(^2,3\)

**Areas affected\(^3,4\)**
- Episodic memory
- Working memory
- Processing speed*
- Executive function*
- Visual/spatial processing
- Language

**Frequency of Impairment\(^2\)**
- Language 8-9%
- Visuospatial abilities 12-19%
- Attention span 7-8%
- Information processing 22-25%
- Memory 22-31%
- Problem solving 13-19%

\(^*\) Can also be related to depression

Impairment defined as % of MS patients scoring <5th percentile for normal population

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Definition of spasticity:

“An unusual tightening of muscles that feels like leg stiffness, jumping of legs, a repetitive bouncing of the foot, muscle cramping in the legs or arms, legs going out tight and straight or drawing up”


Epidemiology

- Spasticity affects up to 80% of MS patients to some degree

- Approximately 40-83.4% of MS patients rate their spasticity as moderate to severe

Fatigue in MS has been defined as a:

“reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion. It can occur at anytime but is usually worse in the afternoon.”


Fatigue in Multiple Sclerosis

Fatigue in MS

• Cause remains completely unknown, is complex and multifactorial
• Affects between 50%-80% of patients
• The most disabling and chronic symptom
• Distinctly different than fatigue reported in healthy individuals or other diseases
• Effort required to perform a task becomes disproportionately high
• Impacts mood, sleep and quality of life

Urinary symptoms occur in ≥80% of MS patients

Mechanism - lesions can disrupt normal process by interfering with transmission of signals between the brain and the urinary system.

References:
Bowel Dysfunction

- Constipation is the most common bowel complaint in MS and can be due to:
  - MS related neurological damage
  - Lack of exercise
  - Inadequate fluids
  - Poor diet
  - Certain medications such as anti-depressants

Bowel & Bowel Management Approach

- Successful management of these symptoms is an ongoing process, requiring effective doctor-patient communication and teamwork

- Symptoms can often be managed by
  - Medication
  - Diet modification (fruit, vegetables, water)
  - Self catheterization
  - Exercises to strengthen pelvic floor muscles
  - Walking
### Disease Modifying Therapies
**FDA-Approved DMDs**

### 13 FDA-Approved DMDs for MS

<table>
<thead>
<tr>
<th>Generic (Brand) Name</th>
<th>Summary of U.S. Indication in MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Glatiramer acetate (Glatopa)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Interferon β-1a, IM (Avonex)</td>
<td>Relapsing forms of MS, to reduce relapses and physical disability</td>
</tr>
<tr>
<td>Interferon β-1a, SC (Rebif)</td>
<td>Relapsing forms of MS, to reduce relapses and physical disability</td>
</tr>
<tr>
<td>PEG-Interferon β-1a, SC (Plegridy)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Interferon β-1b, SC (Betaseron)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Interferon β-1b, SC (Extavia)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Dimethyl fumarate, oral (Tecfidera)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Fingolimod, oral (Gilenya)</td>
<td>Relapsing forms of MS, to reduce relapses and physical disability</td>
</tr>
<tr>
<td>Teriflunomide, oral (Aubagio)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Natalizumab, IV (Tysabri)</td>
<td>Relapsing forms of MS, as a monotherapy</td>
</tr>
<tr>
<td>Alemtuzumab, IV (Lemtrada)</td>
<td>Relapsing forms of MS</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>SPMS, PRMS, or worsening RRMS to reduce disability and clinical relapses</td>
</tr>
</tbody>
</table>
Types of IFNβ Preparations

Interferonβ-1b SC

- Betaseron
- Extavia
- Rebif

Interferonβ-1a IM

- PEG-Interferonβ-1a SC

Interferonβ-1a SC

IFNβ MOA

- VCAM
- MMPs
- VLA-4
- Reduced BBB penetration
- Endothelial cells


IFNβ Clinical Study Results

<table>
<thead>
<tr>
<th>IFNβ Study Group</th>
<th>Jacobs</th>
<th>PRISMS</th>
<th>ADVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Betaseron, 250ug)</td>
<td>(Avonex, 30ug)</td>
<td>(Rebif, 44 ug)</td>
<td>(Plegridy, 125ug)</td>
</tr>
<tr>
<td>ARR</td>
<td>34% ↓</td>
<td>18% ↓ (32% ↓ for 104 wk subset)</td>
<td>NR</td>
</tr>
<tr>
<td># relapses</td>
<td>NR</td>
<td>NR</td>
<td>32% ↓</td>
</tr>
<tr>
<td>% relapse-free for Pbo</td>
<td>36% vs. 18%</td>
<td>38% vs. 26% for Pbo</td>
<td>32% vs. 16% for Pbo</td>
</tr>
<tr>
<td>3M CDP</td>
<td>NS</td>
<td>ND</td>
<td>38% ↓</td>
</tr>
<tr>
<td>6M CDP</td>
<td>ND</td>
<td>21.9% vs. 34.9% Pbo</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = Not Done  NS = Not Significant  NR = Not Reported


Interferonβ Selected Safety Information

- Flu-Like Symptoms
  - Running nose, Sore throat
- Depression
- Leukopenia
- Injection Site Reactions/Necrosis
- Neutralizing Antibodies
- Hepatic Toxicity

Flu-Like Symptoms

FDA Package Inserts for Betaseron, Rebif, Avonex, and Plegridy; accessed July 2015
Mixture of acetate salts of synthetic polypeptides containing four amino acids:

- L-glutamic acid (E)
- L-lysine (K)
- L-alanine (A)
- L-tyrosine (Y)

Average length of 20-200 aa

Molar ratio similar to myelin basic protein (MBP)

- 0.14:0.43:0.09:0.34 for Glu, Ala, Tyr and Lys

Glatiramer Acetate
Copolymer-1, Copaxone®

GA MOA
GALA Trial Results: ARR

![Graph showing ARR comparison between Placebo and GA 40 mg tiw.]

RR = 0.656, \( p < 0.0001 \)

\[ \text{ARR} \pm \text{SEM} \]

Placebo (n=461) vs. GA 40 mg tiw (n=943)

\[ \downarrow 34.4\% \]

GA Selected Safety Information

- Immediate Post-Injection Reaction
- Chest Pain (Usually Transient)
- Injection Site Reactions/Necrosis
- Lipoatrophy

Injection Site Reaction
Natalizumab binds to the $\alpha_4$ subunit of $\alpha_4\beta_1$ integrin on T cells to block its interaction with VCAM1, thus inhibiting T cell entry into the CNS.

Natalizumab MOA

Natalizumab binds to the $\alpha_4$ subunit of $\alpha_4\beta_1$ integrin on T cells to block its interaction with VCAM1, thus inhibiting T cell entry into the CNS.
Natalizumab Clinical Study Results

<table>
<thead>
<tr>
<th></th>
<th>AFFIRM</th>
<th>SENTINEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR (year 1)</td>
<td>68% ↓</td>
<td>54% ↓</td>
</tr>
<tr>
<td>ARR (year 2)</td>
<td>68% ↓</td>
<td>55% ↓</td>
</tr>
<tr>
<td>ARR with</td>
<td>18% ↓</td>
<td>ND</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3M CDP</td>
<td>42% ↓</td>
<td>24% ↓</td>
</tr>
<tr>
<td>6M CDP</td>
<td>54% ↓</td>
<td>18% ↓ (NS)</td>
</tr>
<tr>
<td>MSFC</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gd #</td>
<td>92% ↓</td>
<td>89% ↓</td>
</tr>
<tr>
<td>T2 #</td>
<td>83% ↓</td>
<td>83% ↓</td>
</tr>
<tr>
<td>Atrophy (8PF)</td>
<td>40% ↑ in year 1</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>NS for 0-24 M</td>
<td></td>
</tr>
</tbody>
</table>

ND = Not Done       NS = Not Significant       NR = Not Reported

Natalizumab Selected Safety Information

- Progressive Multifocal Leukoencephalopathy (PML)
- Reduced Immune Response
- Hepatic Toxicity
- Anaphylaxis
- Neutralizing Antibodies

Only available through REMS program
# PML Risk Stratification

1. JCV Status  
2. Tysabri Duration  
3. Prior immunosuppressant use

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Negative</th>
<th>TYSABRI Exposure*</th>
<th>Anti-JCV Antibody Positive</th>
<th>No Prior Immunosuppressant Use</th>
<th>Prior Immunosuppressant Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1/1000</td>
<td>1-24 months</td>
<td>&lt; 1/1,000</td>
<td>1/1,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25-48 months</td>
<td>3/1,000</td>
<td>12/1,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>49-72 months</td>
<td>6/1,000</td>
<td>13/1,000</td>
<td></td>
</tr>
</tbody>
</table>

* Data beyond 6 years are limited
**Fingolimod MOA**

- **Drug Attributes:**
  - Pro-drug
  - Phosphorylated form is a structural analog of S1P

- **Cell types affected:**
  - CD3,4,8+
  - CD45R7+ (naïve T cells)
  - CD45R7- (effector memory T cells)
  - CD19+

**Fingolimod Clinical Study Results**

<table>
<thead>
<tr>
<th></th>
<th>FREEDOMS 1</th>
<th>TRANSFORMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>55% ↓</td>
<td>52% ↓</td>
</tr>
<tr>
<td>3M CDP</td>
<td>26% ↓</td>
<td>NS</td>
</tr>
<tr>
<td>6M CDP</td>
<td>34% ↓</td>
<td>NR</td>
</tr>
<tr>
<td>EDSS Change</td>
<td>0.00 vs. 0.13 for Pbo</td>
<td>NS</td>
</tr>
<tr>
<td>MSFC Change</td>
<td>0.03 vs. -0.06 for Pbo</td>
<td>0.04 vs. -0.03 for IFN</td>
</tr>
<tr>
<td>Gd #</td>
<td>82% ↓</td>
<td>55% ↓</td>
</tr>
<tr>
<td>T2 #</td>
<td>74% ↓</td>
<td>34% ↓</td>
</tr>
<tr>
<td>Atrophy</td>
<td>35% ↓ for 0-6 M</td>
<td>31% ↓</td>
</tr>
<tr>
<td></td>
<td>23% ↓ for 0-12 M</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45% ↓ for 12-24 M</td>
<td></td>
</tr>
</tbody>
</table>

**ND = Not Done  NS = Not Significant  NR = Not Reported**

**Fingolimod Selected Safety Information**

- Cardiovascular Impairment
- Reduced Immune Response
- Macular Edema
- Posterior Reversible Encephalopathy Syndrome
- Respiratory Function
- Hepatic Toxicity
- Progressive Multifocal Leuкоencephalopathy

**First Dose Monitoring (6 Hours)**
- Bradycardia
- AV Block
- Prolonged QTc Interval

**Teriflunomide**

AUBAGIO®, Genzyme/Sanofi
**Teriflunomide Clinical Study Results**

**14mg Results**

<table>
<thead>
<tr>
<th></th>
<th>TEMSO</th>
<th>TOWER</th>
<th>TENERE</th>
<th>TOPIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>31.5% ↓</td>
<td>36.3% ↓</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Time to Failure</td>
<td>ND</td>
<td>ND</td>
<td>NS</td>
<td>42.6% ↓ (CDMS)</td>
</tr>
<tr>
<td>3M CDP</td>
<td>26% ↓</td>
<td>31.5% ↓</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Gd #</td>
<td>80% ↓</td>
<td>ND</td>
<td>ND</td>
<td>88.8% ↓</td>
</tr>
<tr>
<td>T2 IV</td>
<td>76.7% ↓</td>
<td>ND</td>
<td>ND</td>
<td>NR</td>
</tr>
<tr>
<td>Atrophy</td>
<td>NS</td>
<td>ND</td>
<td>ND</td>
<td>NR</td>
</tr>
<tr>
<td>SF-36</td>
<td>ND</td>
<td>NS</td>
<td>ND</td>
<td>NR</td>
</tr>
<tr>
<td>FIS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>TSQM</td>
<td>ND</td>
<td>ND</td>
<td>11.6% ↑</td>
<td>NR</td>
</tr>
</tbody>
</table>

ND = Not Done     NS = Not Significant     NR = Not Reported

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**Teriflunomide Selected Safety Information**

- Hepatic Toxicity
- Risk of Teratogenicity
- Reduced Immune Response
- Peripheral Neuropathy
- Renal Toxicity
- Toxic Epidermal Necrosis
- Blood Pressure Changes
- Respiratory Function

Only pregnancy category X*

* Pregnancy categories are no longer being used by the FDA

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Dimethyl Fumarate (DMF)
TECFIDERA®, Biogen Idec

Nrf2 Pathway Activation

- 100s of genes are modulated by Nrf2
- Many are 'antioxidant' genes that help cells deal with stress
- Mitochondrial support – Cellular Energy
### DMF Clinical Study Results

#### BID Results

<table>
<thead>
<tr>
<th>DEFINE</th>
<th>CONFIRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>53% ↓</td>
</tr>
<tr>
<td></td>
<td>44% ↓</td>
</tr>
<tr>
<td>% of patients relapsed</td>
<td>27% vs. 46% for Pbo</td>
</tr>
<tr>
<td>3M CDP</td>
<td>38% ↓</td>
</tr>
<tr>
<td>Gd #</td>
<td>90% ↓</td>
</tr>
<tr>
<td>T2</td>
<td>88% ↓</td>
</tr>
<tr>
<td>Atrophy</td>
<td>30% ↓ for 6-24 M</td>
</tr>
<tr>
<td>SF-36</td>
<td>NR</td>
</tr>
</tbody>
</table>

| NS = Not Significant | NR = Not Reported |

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### DMF Selected Safety Information

- **Progressive Multifocal Leukoencephalopathy (PML)**
- **Lymphopenia**
- **Flushing**
- **Hepatic Toxicity**
- **GI Events (diarrhea, nausea)**
- **Anaphylaxis**

---

NS = Not Significant       NR = Not Reported
DMF Selected Safety Information

Dosage and Administration

• Starting dose: 120mg BID, 7 days
• Maintenance dose: 240mg BID
• Swallow TECFIDERA tablets whole and intact (do not crush, chew, or sprinkle tablet onto food)

Alemtuzumab
Lemtrada®, Genzyme/Sanofi
Alemtuzumab MOA

Cytotoxic Leukopenia

**Humanized monoclonal anti-CD52 antibody**

- CD52 on T and B cells, NK cells, monocytes, macrophages, eosinophils
- Antibody-mediated cytotoxicity, complement-mediated cell lysis
- B cells return by ~6mo, long-term depletion of CD8+ (3yr) and CD4+ (5yr) T cells


**Alemtuzumab Clinical Study Results**

<table>
<thead>
<tr>
<th></th>
<th>CARE MS-I</th>
<th>CARE MS-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>62% ↓</td>
<td>50% ↓</td>
</tr>
<tr>
<td>% relapse-free</td>
<td>78% vs. 59% for IFN</td>
<td>65% vs. 47% for IFN</td>
</tr>
<tr>
<td>6M CDP</td>
<td>NS</td>
<td>42% ↓</td>
</tr>
<tr>
<td>Gd+ (# patients)</td>
<td>63% ↓</td>
<td>61% ↓</td>
</tr>
<tr>
<td>T2 (# patients)</td>
<td>17% ↓</td>
<td>32% ↓</td>
</tr>
<tr>
<td>Atrophy</td>
<td>42% ↓</td>
<td>23% ↓</td>
</tr>
</tbody>
</table>

NS = Not Significant
Alemtuzumab Administration

Long-Term Efficacy (ie: Disease Activity-Free)

Herpetic Prophylaxis  Annual Skin Exam

Year 1 Year 2 Year 3 Year 4 Year 5

Monthly Labs

12mg/day 5 days 12mg/day 3 days

Alemtuzumab Selected Safety Information

Only available through REMS program

Autoimmunity
Infusion Reactions/Anaphylaxis
Malignancies
Glomerular Nephropathies
Thyroid Disorders (34% patients)
Infections