MS: A Clinical Update

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Cause of MS?

- Immunologic/autoimmune
  - Molecular mimicry
  - Vitamin D
- Microbial
  - Viral
    - EBV
    - HHV 6
  - Chlamydia
- Oligodendroglialopathy
- Vascular
  - Small vessel
  - CCSVI
- Toxic/environmental
  - Diet
MS and the immune system: a complicated situation!

Dhib-Jalbut S, Marks S. Neurology 2010;74:S17-S24
Risk Factors - Gender

• 2 to 3 times higher risk in women
  – Ratio appears to be increasing

• Parent of Origin Effect – slightly higher risk of inheritance if affected patient is female
Risk Factors - Genetics

- Prevalence in U.S. 1/1000

- Risk for identical twin = 25-35%

- Risk for fraternal twin/first degree relative = 2-5%

- Adoptees have risk of general population

Risk Factors - Genetics

MS cases vs Controls
Comparing one variant between many individuals

Genetic variants statistically associated with MS
GWAS & meta-analysis
Resequencing follow-up studies

Summary of the genetic load of a single individual
MSGB score
Multiple sclerosis genetic burden

Information on ~ 200 MS variants
HLA-DRB1
IL7R
EVI5
IRF8
CD6
IL12A
etc...

Immunological Reviews
Volume 248, issue 1 pages 87-103, 21 JUN 2012 DOI: 10.1111/j.1600-065X.2012.01134.x
Risk Factors – Geographic Risk
MS: Vitamin D

• First implicated 30 years ago in association with latitudinal gradient

• Vitamin D has immunological properties in addition to role in calcium homeostasis
  – Inhibitor of dendritic cell maturation
  – Activator of the innate immune system
• U.S. Military Study
  • In whites the highest rate of MS occurred in lowest 20% of Vit D levels, lowest rate in highest 20% of Vit D levels
  • Based on this study, it has been postulated that Vit D supplementation might prevent up to 70% of MS cases

• Nurses Study
  • Nurses who took Vitamin D supplement showed a trend towards lower risk for MS

• Another Nurses Health Study
  • Increased risk for MS in Nurses whose mothers had lowest milk consumption
• Recommendations
  – Check Vitamin D in MS patients
  – Replete with goal to keep level in normal range
  – patients with first degree relative with MS may also benefit from vitamin d monitoring/repletion

• A large randomized trial is now underway to determine whether Vitamin D is an adjunct MS therapy
Smoking

- Multiple large studies now suggest association between Smoking and risk for MS
- Studies also show that smokers have shorter time for transition from RRMS to SPMS
- Smoking is likely neurotoxin, may also have effects on the immune system
Effects of Pregnancy on MS

- It is now well recognized that relapse rate decreases during pregnancy.
- There is a rebound in relapse in first 3 months after delivery.

Confavreux, 1998

Figure 2. Rate of Relapse per Woman per Year for Each Three-Month Period before, during, and after Pregnancy in 227 Pregnancies Resulting in a Live Birth among Women with Multiple Sclerosis. The values shown are means and 95 percent confidence intervals.
The Diagnosis of MS

Lesions of the central nervous system, disseminated in time and space

Caveat: No better explanation
Clinical Presentation: The Relapse

• “patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection.”

• When possible, symptoms should be correlated to signs on examination

Clinical Presentation: Progression

- Typically presents as a progressive myelopathy
- May present as progressive brainstem or cerebellar syndrome
- Characterized by difficulties with gait, balance, spasticity, weakness, and bladder and/or bowel
- Less sensory symptoms than relapsing patients

Clinical presentation: Other Symptoms

– Bladder
– Bowel
– Sexual dysfunction
– Cognitive dysfunction
– Mood
– Paroxysmal sx
– Hearing loss
– Taste dysfunction
MS: A Dual Phase Disease?

Inflammatory

Axonal loss

Degenerative

Transitional

Inflammation

Dhib-Jalbut, S 2005
Natural History of MS
Multiple Sclerosis: Clinical Subtypes

RRMS = relapsing-remitting; SPMS = secondary progressive; PRMS = progressive relapsing; PPMS = primary progressive.

Applying the diagnostic criteria: The essence of MS

• Dissemination in Time
• Dissemination in Space
• Objective Evidence
• Exclude other Causes

Charil et al. MRI and the diagnosis of multiple sclerosis: expanding the concept of “no better explanation”. Lancet Neurology 2006
Diagnosis of MS: McDonald 2010

- 2 clinical attacks meets DIT. You can meet DIS either with:
  - Clinical evidence for 2 lesions OR
  - Clinical evidence of 1 lesion **PLUS** MRI DIS

- 1 clinical attack means you need both DIS and DIT
  - DIS can be met with either:
    - Clinical Evidence of 2 lesions OR
    - Clinical evidence of 1 lesion and MRI DIS
  - DIT can be met by MRI
# Evolution of Diagnostic Criteria for MS: Magnims 2010 “Any 2, Any New”

<table>
<thead>
<tr>
<th></th>
<th>McDonald 2001</th>
<th>McDonald 2005</th>
<th>MAGNIMS 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dissemination in Space</strong></td>
<td>≥ 3 of: ≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion ≥ 3 periventricular lesions ≥ 1 juxtacortical lesion ≥ 1 posterior fossa lesion</td>
<td>≥ 3 of: ≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion ≥ 3 periventricular lesions ≥ 1 juxtacortical lesion ≥ 1 posterior fossa lesion</td>
<td>≥ 1 lesion in each of ≥ 2 characteristic locations Periventricular Juxtacortical Posterior fossa Spinal cord</td>
</tr>
<tr>
<td><strong>(DIS; on either baseline or follow-up MRI)</strong></td>
<td>1) ≥ 1 gadolinium-enhancing lesion ≥ 3 months after CIS onset (if not related to CIS) 1) A new T2 lesion with reference to a prior scan obtained ≥ 3 months after CIS</td>
<td>1) ≥ 1 gadolinium-enhancing lesion ≥ 3 months after CIS onset (if not related to CIS) 2) A new T2 lesion with reference to a prior scan obtained ≥ 30 days after CIS</td>
<td>1) Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time 2) A new T2 and/or gadolinium-enhancing lesion on follow-up MRI irrespective of timing of baseline scan</td>
</tr>
<tr>
<td></td>
<td>2) A new T2 lesion with reference to a prior scan obtained ≥ 3 months after CIS</td>
<td>2) A new T2 lesion with reference to a prior scan obtained ≥ 30 days after CIS</td>
<td>All lesions in symptomatic regions excluded in brain stem and spinal cord syndromes</td>
</tr>
</tbody>
</table>

Typical appearance of MS lesions on MRI

Axial FLAIR image demonstrating juxtacortical lesions

Sagittal FLAIR image demonstrating periventricular lesions, including in the corpus callosum, giving rise to “Dawson fingers” appearance.

Axial FLAIR image demonstrating infratentorial lesions

Sagittal T2-weighted image demonstrated lesions in the cervical spinal cord

A 32-year-old woman with left heminumbness and left leg weakness. No prior medical history. Examination demonstrates diminished sensation in the left upper and lower extremities; mild weakness of the left leg with extensor plantar response and asymmetrically hyperreflexic. Brain MRI shows:

- Patient Meets Criteria for MS Using the MAGNIMS 2010 Criteria

Images courtesy of Omar Khan, MD.
Not all white spots are MS

Clues that this is not MS:

- Peripheral dots: not periventricular
- Circular, not oval with long axis
- Not radiating outward
- None enhance with gadolinium
- No involvement of:
  - corpus callosum,
  - infratentorial/brainstem
  - spinal cord

Diagnosis: Migraine
CSF in Multiple Sclerosis

- **Protein**: Normal or mildly increased (50%)
- **Glucose**: Normal
- **Cells**: Normal 66%, remainder 5 to 20 lymphocytes/mm³
- **IgG Synthetic Rate**: Increased in 70%
- **Oligoclonal bands**: present in 90%
- **Myelin basic protein**: Normal <1 ng/mL. Can be increased during acute relapses
“No Better Explanation”
the Differential Diagnosis of MS

- Metabolic: $B_{12}$ deficiency
- Infectious: Lyme, syphilis, HIV, HTLV-1
- Vascular: AVM, vasculitis, CADASIL
- Malignancy: spinal cord tumor
- Genetic: LHON, leukodystrophies
- Inflammatory/autoimmune: lupus, Sjögren’s, sarcoidosis, antiphospholipid syndrome
- Structural: cervical spondylosis

AVM=arteriovenous malformation; CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LHON=Leber hereditary optic neuropathy.
Is This MS?

• 281 patients referred to University of Colorado with possible MS
  – 33% diagnosed with MS or possible MS by McDonald criteria
  – 31.5% had other neurological disease
  – 22.5% had psychiatric disorder
  – 12.5% had no clear diagnosis
• Referrals for clinical features in 63% and 37% for MRI abnormalities
  – 46% of those with clinical disease had MS
  – 11% of those with MRI abnormalities had MS

Case #1

• A 40-year-old Guatemalan woman developed left optic neuritis in 9/01, with pain on eye movement and VA of <20/800. Orbital MRI showed enhancement in the L optic nerve, but brain MRI was normal. CSF was normal. She was told she had MS and began treatment with glatiramer acetate.
Case #1

- In March ’04 she developed numbness and tingling on the left side of the body. Serological studies for toxoplasma and Lyme disease were negative and angiotensin converting enzyme level was normal. Spinal MRI in 3/04 showed a long lesion from C6 to T3 with an area of enhancement only at T1-2.
Case #1

• In 5/04, she developed severe visual impairment in the right eye. Brain MRI remained normal. She was treated at each episode with IVMP and her vision improved markedly.
Case #1

• Treatment was changed to IFNB-1b. However, in late 7/04 she again developed visual impairment in the left eye. She was referred for another opinion. Examination in mid-August revealed VA of 20/50 OD and finger count only OS. Bilateral optic nerve pallor was evident. The remainder of the neurological exam was normal.
Case #1

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NMO antibody titer >1:160
Case #2

• 43 yo man with no sig PMH developed R sided numbness and slurred speech while teaching a class. Taken to ED.
Case #2

- VSS, afebrile
- Systemic exam non-revealing, no rash
- Mental status: intact
- CV: significant for decreased Lt/temp in the distribution of CN V on the R and moderate dysarthria.
- Motor exam: intact.
- Sensory exam: Lt/pp decreased on R.
- Reflexes were symmetric, toes downgoing.
- Coordination was intact.
- Gait was normal including H/T/T.
Case #2
Case #2

- C spine MRI was normal.
- Lyme antibody came back weakly positive and western blot was negative.
- LP did not reveal any abnormalities. Lyme PCR was negative in the CSF.
Case #2

- Patient was treated with IV antibiotics for 3 months for CNS Lyme.
- Eventually the slurred speech and R sided numbness resolved.
Case #2

- 2 annual brain MRIs were stable
- 10 years later the patient began to have increasing gait difficulty because of LLE weakness.
- Repeat Lyme testing was negative.
- Repeat CSF showed +OCB and elevated IgG
- Repeat brain imaging showed increase in lesion burden. C spine also now showed significant disease.
Case #2
Types of MS treatments

- Treatment of relapses
- Disease-modifying Treatments
- Symptomatic treatments
Treatment of relapses

• Steroids
  – IV methylprednisolone
  – Daily for 3-5 days

• If recovery is suboptimal and function is impaired, can consider
  – Repeat course of steroids
  – Plasmapheresis
Goals of Disease-modifying Treatments

• Prevent MRI Changes:
  – Number of new lesions
  – Decrease in brain volume

• Prevent Relapses
  – With each relapse there is always a chance that recovery is incomplete

• Prevent Progressive Disease
The Evolving MS Treatment Landscape

**FDA-Approved Therapies**
- Betaseron® (IFNβ-1b)
- Avonex® (IFNβ-1a)
- Copaxone® (glatiramer acetate)
- Tysabri® (natalizumab)
- Novantrone® (mitoxantrone)
- Rebif® (IFNβ-1a)
- Extavia® (IFNβ-1b)
- Gilenya™ (fingolimod)
- Aubagio® (teriflunomide)
- Tecfidera™ (dimethyl fumarate, BG-12)
- Laquinimod
- Lemtrada™ (alemtuzumab)
- Copaxone® 40 mg TIW

**Phase III Data Released**
- Novantrone®

**Approval Date**
- 1995
- 2000
- 2005
- 2009
- 2010
- 2011
- 2012
- 2013
With all these choices, how do you decide on a treatment plan?
# Immunomodulatory Treatments

"Injectable agents"

## Nonselective Immunomodulators

<table>
<thead>
<tr>
<th></th>
<th>IFNβ-1a</th>
<th>IFNβ-1b</th>
<th>IFNβ-1a</th>
<th>Glatiramer Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Recombinant protein</td>
<td>Recombinant protein</td>
<td>Recombinant protein</td>
<td>Polypeptide mixture</td>
</tr>
<tr>
<td>Approval and indication</td>
<td>Slow accumulation of disability</td>
<td>Reduce frequency of relapses</td>
<td>Reduce frequency of relapses</td>
<td>Reduce frequency of relapses</td>
</tr>
<tr>
<td>Injection Administration</td>
<td>IM</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>Dosage</td>
<td>30 µg</td>
<td>250 µg (8 MIU)</td>
<td>22 µg 44 µg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

## Selective Immunomodulator

<table>
<thead>
<tr>
<th>Glatiramer Acetate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval and indication</td>
<td>Reduce frequency of relapses</td>
<td>Reduce frequency of relapses</td>
</tr>
<tr>
<td>Injection Administration</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>Dosage</td>
<td>20 mg</td>
<td></td>
</tr>
</tbody>
</table>
REGARD: Head to Head Comparison
IFNβ 1a (SC) vs GA

Survival Distribution Function

Time to First Relapse (days)

Hazard ratio (95% CI)=0.943 (0.74, 1.21) P=0.643

IFNβ-1a 386 335 298 271 248 231 218 172
Glatiramer Acetate 378 321 286 269 252 236 226 178

Natalizumab:
Mechanisms of Action

• **Natalizumab:** Binds at $\alpha_4$-subunit of integrins expressed on cell surface of leukocytes, preventing adhesion to vascular endothelial cells and transmigration of leukocytes across the BBB

Transendothelial Migration

Vessel Lumen

Firm Adhesion

Activated Integrin

Rolling Adhesion

Adhesion

Activated Integrin

VCAM

Selectin

Leukocyte

Inactive Integrin

Selection Counterceptor

Inflammatory Stimulus

Resting State

Endothelial Cell

Subendothelial Matrix

Inflammatory Stimulus

Chemokines

Trafficking Is a Multistep Process Requiring Many Molecules


Natalizumab
Natalizumab: AFFIRM trial

Annualized Relapse Rate

\[
\text{Annualized Relapse Rate}\quad (95\%\ CI)
\]

\[
\begin{align*}
\text{Placebo} & \quad n=315 \\
\text{Natalizumab} & \quad n=627 \\
0.81 & \quad \text{Placebo} \\
0.26 & \quad \text{Natalizumab}
\end{align*}
\]

\[
P<0.0001
\]

68%
Natalizumab: AFFIRM trial
Gadolinium-Enhancing (Gd+) Lesions

Mean Number of Gd+ Lesions

<table>
<thead>
<tr>
<th>Group</th>
<th>Number (n)</th>
<th>Mean Value</th>
<th>p-value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>315</td>
<td>1.2</td>
<td>&lt;0.0001</td>
<td>92%</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>627</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.0001
Natalizumab Adverse Event: PML

- Demyelinating CNS infection caused by JC virus
- Previously known risk factors were HIV/AIDS and immunosuppression
- Common symptoms include cognitive decline, visual symptoms and severe, focal neurologic deficit
- Often results in severe neurologic impairment or death
What is the risk of getting PML?

<table>
<thead>
<tr>
<th>Table</th>
<th>Calculated risk of natalizumab-related PML according to currently known risk factors: Duration of treatment, previous chemotherapy, and anti-JCV serology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior chemotherapy?</td>
</tr>
<tr>
<td>JC virus antibody negative</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>JC virus antibody positive</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviation: PML = progressive multifocal leukoencephalopathy.

Fingolimod (Gilenya)

Approved 2010
**Fingolimod**: First oral agent, 2010

**Mechanisms of Action**

- **Fingolimod**: Binds to 4/5 sphingosine 1-phosphate receptor subtypes
- Results in Inhibition of lymphocyte egress from lymph nodes account for effect on MS
- Reduced infiltration of cells into the CNS
- May be direct action in CNS in light of positive effects on brain atrophy
### Fingolimod: Clinical trial summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **TRANSFORMS**<sup>1</sup> | (1) Fingolimod 0.5 mg  
(2) Fingolimod 1.25 mg  
(3) IFN β-1a 30 μg | **Outcome**  
**Fingolimod**  
**Reduction (vs IFN)**  
| 0.5 mg | 1.25 mg |
| ARR     | −52% (*P* < .001)  | −38% (*P* < .001)  |
| Active T2 | −35% (*P* = .004)  | −42% (*P* < .001)  |
| GdE lesions | −55% (*P* < .001)  | −73% (*P* < .001)  |
| **FREEDOMS**<sup>2</sup> | (1) Fingolimod 0.5 mg  
(2) Fingolimod 1.25 mg  
(3) Placebo | **Outcome**  
**Fingolimod**  
**Reduction (vs PBO)**  
| 0.5 mg | 1.25 mg |
| ARR     | −54% (*P* < .001)  | −60% (*P* < .001)  |
| Enlarging T2 | −74% (*P* < .001)  | −74% (*P* < .001)  |
| GdE lesions | −82% (*P* < .001)  | −82% (*P* < .001)  |

- Results from open label phase 3 extension and 7-year phase 2 extension studies show sustained low disease activity on clinical and MRI measures in patients continuing on treatment with fingolimod<sup>3,4</sup>

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# Current Strategies for Mitigating the Potential Risks Associated With Fingolimod

<table>
<thead>
<tr>
<th>Potential AE or Risk</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
</table>
| Bradycardia/AV block         | • All pts must be observed for 6 h after initial dose for signs and symptoms of bradycardia  
                               | • If pts go off medication for prolonged time period, they must be observed when restarting therapy |
| Macular edema                | Ophthalmologic exam at baseline and 3-4 mo after treatment initiation                 |
| Infection                    | • Patients should be vaccinated for varicella zoster virus                             
                               | • Consider stopping therapy if serious infection develops                              
                               | • Avoid live attenuated vaccines for at least 2 mo after stopping therapy              |
| \(\downarrow\text{FEV}_1\) and \(\downarrow\text{DLCO}\) | Spirometric evaluation when indicated                                                 |
| LFT elevations               | Monitor regularly, as needed                                                          |
| Pregnancy risk category C    | • Counsel patients about fetal risks                                                  
                               | • Use effective contraception on treatment and for at least 2 mo after stopping therapy |

AV: atrioventricular; DLCO: diffusion capacity of the lung for carbon monoxide; \(\text{FEV}_1\): forced expiratory volume over 1 second.

Teriflunomide (Aubagio)

Approved, September 2012
Teriflunomide Mechanism of Action

- Teriflunomide is the active metabolite of the rheumatoid arthritis drug leflunomide
- Reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase
- DHODH provides the rate-limiting step in pyrimidine synthesis
- When lymphocytes are blasting, pyrimidines provided by the salvage pathway are not sufficient → selective targeting of blasting rather than resting lymphocytes

- Likely other targets involved in inflammation such as the JAK/STAT pathway, COX-2, EGFR, iNOS, others

Teriflunomide Phase III Study (TEMSO): Primary Endpoint

*Statistically significant compared to placebo
ARR = annualized relapse rate; RRR = relative risk reduction vs placebo

TEMSO: Disability Progression

7 mg vs Placebo: 23.7% reduction ($P=0.08$)
14 mg vs Placebo: 29.8% reduction ($P=0.03$)

Teriflunomide
Adverse Effects

• No treatment-related fatalities in either phase III trial
• Hair thinning
• Gastrointestinal (nausea, diarrhea)
• Elevation in aminotransferases –
  – LFTs checked monthly x6
• Neutropenia
• PPD or Quantiferon Gold check prior to initiation
• Pregnancy Category X (note for male and female pts
Dimethyl Fumarate

Tecfidera

Approved, March 2013
Dimethylfumarate (BG-12) 
Mechanism of Action

- Dimethylfumarate rapidly metabolized to active metabolite, monomethylfumarate (MMF)
- MMF releases the transcription factor Nrf-2 from its usual binding to Keap-1
- Nrf-2 inhibits translocation of NF-κB into the nucleus
- Ultimately leads to a decrease in inflammatory cytokines, chemokines, and adhesion molecules
- Induces a Th1 to Th2 shift
- Decreases circulating T cells
- Possible neuroprotective effects


DEFINE: Cumulative Probability of Relapse (1 Endpoint)

Hazard Ratio:
BG-12 BID vs placebo = 0.51 ($P < 0.0001$)
BG-12 TID vs placebo = 0.50 ($P < 0.0001$)

Hazard Ratio:
BG-12 BID vs placebo = 0.51 ($P < 0.0001$)
BG-12 TID vs placebo = 0.50 ($P < 0.0001$)

Number of Patients at Risk:
- Placebo: 406, 358, 321, 282, 243, 224, 205, 190
- BG-12 BID: 410, 353, 324, 303, 288, 287, 255, 243
- BG-12 TID: 416, 348, 322, 301, 288, 270, 251, 244

Patients were censored if they withdrew from study or switched to alternative MS medication without a relapse.

Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]
DEFINE: Annualized Relapse Rates

Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]
DEFINE: Time to 12-Week Confirmed Disability Progression

Hazard Ratio:
BG-12 BID vs placebo = 0.62 (P = 0.0050)
BG-12 TID vs placebo = 0.66 (P = 0.0128)

Number of Patients at Risk:
Placebo   408  375  345  319  291  285  242  224
BG-12 BID 409  359  333  328  304  290  278  267
BG-12 TID 416  360  346  325  324  291  276  265

Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]
DEFINE: MRI Outcomes - 2 Years

**Gd-enhancing lesions**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Number of GD+ Lesions</th>
<th>Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 165)</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG-12 BID (n = 152)</td>
<td>0.1</td>
<td>90%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BG-12 TID (n = 152)</td>
<td>0.5</td>
<td>73%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**New or newly enlarging T2 lesions**

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Mean Number of New or Newly Enlarging T2 Lesions</th>
<th>Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 165)</td>
<td>17.0</td>
<td>90%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BG-12 BID (n = 152)</td>
<td>2.6</td>
<td>85%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BG-12 TID (n = 152)</td>
<td>4.4</td>
<td>74%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Arnold DL, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [P831]
CONFIRM: Safety

- Flushing and gastrointestinal symptoms were common AEs reported more frequently in BG-12 groups vs placebo
  - Incidence of flushing and gastrointestinal symptoms decreased substantially after the first month of BG-12
- AEs reported more frequently with GA were injection-related
- The incidence of serious infections was low and similar across groups (1–2%)
  - No opportunistic infections reported in any treatment arm
- No malignancies reported in patients receiving BG-12

When to refer to an MS Center?

• First attack with possible features of other diseases on the differential
  – Infections, rheumatologic or mixed connective tissue diseases (Sarcoid, Behçet’s, SLE, etc)
• MRI appearance that is uncharacteristic
  – Long spinal cord lesions like NMO/Devic’s
• Recurrent relapses on treatment
  – New treatment strategies
  – Off-label treatment for progressive MS
• Unmet psychosocial needs
  – MS-trained Psychiatrists/Psychologists, Nurse Practitioners, PT/OT, Social work
Thank You!