OUTLINE OF MS TALK

• PART 1
• EPIDEMIOLOGY
• SIGNS AND SYMPTOMS
• PATHOPHYSIOLOGY
• PART 2
• TREATMENT FORMAT
  – DMT (IMMUNOMODULATORS) EFFICACY, SAFETY, TOLERABILITY
  – DMT (IMMUNOSUPPRESORS) EFFICACY, SAFETY, TOLERABILITY
  – ALGORITHMS
  FUTURE DRUGS
EPIDEMIOLOGY OF MS

- 500,000 PEOPLE IN US WITH MS
- 3 MILLION IN WORLD (+ MANY OTHERS)
- 2/3 ONSET BETWEEN 20 & 40; AVERAGE AGE OF ONSET IS 24 YEARS
- RATIO FEMALES TO MALES IS 2 TO 1
- CAUCASIANS MORE LIKELY & NORTHERN AREAS & HIGHER IN EUROPEAN DESENT
EDSS: Assessing the course of disease

0 = Normal neurologic exam
1.0-1.5 = No impairment
2.0-2.5 = Impairment is minimal
3.0-3.5 = Impairment is mild to moderate
4.0-4.5 = Impairment is relatively severe
5.0-5.5 = Increasing limitation in ability to walk
6.0-6.5 = Walking assistance is needed
7.0-7.5 = Confined to wheelchair
8.0-8.5 = Confined to bed/chair; self-care with help
9.0-9.5 = Completely dependent
10.0 = Death due to MS

NATURAL HISTORY OF MS

• RELAPSES & REMISSIONS; VARIABLE DEGREE OF RECOVERY (25% WITH 1 POINT INCREASE OF EDSS & 50% WITH .5 INCREASE)
• MRI---FOR EVERY CLINICALLY ASSOCIATED LESION THERE ARE 5 SILENT LESIONS
• MOST GO ON TO SECONDARY PROGRESSIVE MS (SPMS); AVERAGE AFTER ONSET IS 11 TO 19 YEARS.
A relapse, or attack, is the period during which your symptoms worsen, or new symptoms occur. The 4 types of MS:

1. **RRMS** (Relapsing-remitting MS)
   - Chart showing fluctuations in disability over time.

2. **SPMS** (Secondary-progressive MS)
   - Chart showing steady increase in disability over time.

3. **PPMS** (Primary-progressive MS)
   - Chart showing steady increase in disability with occasional plateaus.

4. **PRMS** (Progressive-relapsing MS)
   - Chart showing steady increase with occasional relapses.

References:
Diagnostic criteria for clinically definite MS

• The criteria for a diagnosis of MS have evolved over time

• Poser criteria (1983)
  – 2 attacks and evidence of separate lesions

• McDonald criteria (2001, 2005, 2010)
  – Formally incorporated MRI and lesions into the established diagnostic workup that focuses on neurologic history and examination, and paraclinical laboratory examinations

• Over time, changes in diagnostic criteria have incorporated clinical advances and improvements in imaging technology to allow for earlier diagnosis and treatment

• ANY TWO IN SPACE & ANY TWO IN TIME, ANY 2 ANY NEW

MRI Scan in MS; PERIVENTRICULAR, JUXTACORTICAL, INFRATENTORIAL, GRAY MATTER, SPINAL CORD

• T2 – CSF & LESION WHITE
  – Inflammation/edema
  – Demyelination and/or gliosis
  – Axonal loss

• T1 Non-Enhanced: CSF & LESION BLACK
  – Demyelination and/or gliosis (chronic black holes)
  – Axonal loss – within and outside lesions

• T1 Enhanced: WITH CONTRAST, CSF BLACK, LESION WHITE
  – Predominantly acute inflammation, break down in BBB
Conventional MRI in MS Clinical Practice

- **T2 BOD**: Strongest correlation with progression of disability
- **T1/Gd postcontrast**: Active Inflammation
- **T1 precontrast Hypointensities**: Acute Hypointensities

- Strongest correlation with progression of disability
- Correlates with cognition
- Represents most severe tissue destruction

# Histopathologic Correlates of Black Holes: T1 Hypointensity Correlates with Axonal Loss

<table>
<thead>
<tr>
<th>Bodian axonal density</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Strongly hypointense</td>
<td>20%</td>
</tr>
<tr>
<td>2. Mildly hypointense</td>
<td>60%</td>
</tr>
<tr>
<td>3. NAWM</td>
<td>100%</td>
</tr>
</tbody>
</table>


RADIOLOGICAL ISOLATED SYNDROME

• NO SYMPTOMS—OFTEN NOT REALIZED BY PATIENT OR DISCOVERED BY CAREFUL HX

• MRI DONE FOR SOME OTHER SIGN OR SYMPTOM (ER OR OFFICE FOR HEADACHES, TRAUMA, NONSPECIFIC S & S

• MRI—USUALLY T2 LESIONS, MAYBE T1 & RARELY T1 ENHANCED; ANY 2 & ANY NEW
CLINICAL ISOLATED SYNDROME CIS

- SYMPTOM THAT MAY FIT WITH HISTORY OF MS—ONE CLINICAL EVENT BY HISTORY KNOWN
- MRI FINDINGS IN APPROPRIATE AREAS; PERIVENTRICULAR, JUXTACORTICAL, INFRATENTORIAL, GRAY MATTER OR SPINAL CORD
- ANY 2 & ANY NEW
There are many possible symptoms of MS\(^1\)

- Walking problems
- Coordination problems
- Balance problems
- Depression
- Emotional changes
- Dizziness and vertigo
- Sexual dysfunction
- Fatigue
- Pain
- Changes in cognitive function
- Vision problems
- Numbness
- Bowel/bladder dysfunction
- Spasticity

Patient Profile

- 21-year-old, right-handed female
  - Has developed painful vision loss in her left eye
  - Last year, the patient had numbness in her right leg lasting for 3 weeks
    - Confirmed by neurologist who also found increased reflexes in left arm
    - No treatment offered; numbness resolved completely
  - Diagnosed with optic neuritis
  - Abnormal MRI brain scan
Returning to our patient profile:

- Treated with steroids, symptoms resolved after 3 weeks
- Patient did well until 10 months later, when she developed vertigo, right facial numbness and tingling, and unsteady gait
  - Repeat MRI brain scan revealed a new pontine lesion; MRI cervical spine scan was normal
  - Started on Avonex® (interferon beta-1a)
- After 9 months of treatment with Avonex, patient experienced gait disturbance and right-leg paresis
  - MRI brain scan: 2 new non-enhancing right parietal subcortical lesions
  - MRI cervical spine scan revealed lesion at C4 with faint Gd+

Gd+=gadolinium enhancement.
Avonex is a registered trademark of Biogen Idec.
TREATMENT ALGORITHM

• RIS; DETERMINE CORRECT DX WITH CSF & REPEAT MRI; ? RX IF Gd+ & LOOKS LIKE MS
• CIS; AGGRESSIVE RX WITH DMT’S & CLOSE FOLLOW UP WITH MRI IN 1 YR
• RRMS; DMT’S IMMUNOMODULATORS WITH CLOSE FOLLOW UP & IF RELAPSE & MRI CHANGES (ESPECIALLY IF Gd+) OR NEW # T2 LESIONS ON MRI, CHANGE DMT
• IF RRMS & HIGH BURDEN ON MRI & OR FREQUENT & PROGRESSIVE COURSE, RX WITH NATALIZUMAB, FINGOLIMOD, OR TERIFLUNOMIDE
• USE MP OR ACTHAR IN RELAPSE
Natural History Of MS
Clinical and MRI Measures

- Measures of brain volume
- Relapses and impairment
- MRI lesion accumulation
- MRI activity

**Time to CDMS**

5 Year Results of the Integrated Data-set

![Graph showing the cumulative relative risk reduction over 5 years based on Hazard Ratio=0.63.](image)

*By proportional hazards regression adjusted for age/gender/steroids/T2-lesions/Gd-lesions*

Time to Confirmed Disease Progression*
5-year Results of the Integrated Data-set

- **Main analysis without unscheduled visits**
- **By proportional hazards regression adjusted for T2-lesion volume**


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**Confirmed EDSS Progression (%)**

- **Immediate BETASERON**
  - Year 1: 0%
  - Year 2: 10%
  - Year 3: 20%
  - Year 4: 30%
  - Year 5: 40%

- **Delayed BETASERON**
  - Year 1: 0%
  - Year 2: 10%
  - Year 3: 20%
  - Year 4: 30%
  - Year 5: 40%

**Patients at risk**

- **Placebo/BETASERON**: n= 176
  - Year 1: 150
  - Year 2: 124
  - Year 3: 105
  - Year 4: 102
  - Year 5: 61

- **Immediate BETASERON**: n= 292
  - Year 1: 223
  - Year 2: 225
  - Year 3: 206
  - Year 4: 191
  - Year 5: 120

**24% cumulative relative risk reduction based on Hazard Ratio=0.76**

*Not statistically significant*
Primary endpoint: COPAXONE® (glatiramer acetate injection) significantly delayed the second clinical event\(^2,3\)

\(\text{Hazard ratio} = 0.55\)
\(95\% \text{ CI} (0.40-0.77)\)
\(P = 0.0005\)

Placebo (%)
COPAXONE® (%)

\(45\% \text{ risk reduction}\)

PreCISe: Efficacy in clinically isolated syndrome (CIS)

PreCISe: A multicenter, randomized, double-blind, placebo-controlled study in patients presenting with a single, well-defined, unifocal, neurologic event highly suggestive of MS (CIS) and \(\geq 2\) T2 lesions, each \(\geq 6\) mm in diameter. Patients were randomized to receive either COPAXONE® 20 mg SC daily (n=243) or placebo (n=238). The primary endpoint was time from randomization to second clinical event.\(^3,4\)

PreCISe: T2 lesions

Secondary endpoint: COPAXONE® (glatiramer acetate injection) significantly reduced new T2 lesions\(^2,4\)

Number of new T2 lesions at LOV\(^*\)

\[
\begin{array}{c|c}
\text{Placebo} & \text{COPAXONE\(^\circledast\)} \\ 
(n=238) & (n=243) \\ 
1.8 & 0.7 \\ 
\end{array}
\]

59% reduction
\(P<0.0001\)

\(\text{LOV}\(^*\): \text{Last observed value.}\)

PreCISe: See slide 6 for full study design.

2. COPAXONE\(^\circledast\) PI.

*Last observed value.
MRI Predicts CDMS Development*

The exact relationship between MRI findings and the clinical status of patients is unknown.

Arch Neurol 1993 Aug;50(8):841-6
Early MRI Events Correlate with Disease Progression

The exact relationship between MRI findings and the clinical status of patients is unknown.

Early Relapses Affect Long-term Disability

Actuarial analysis of disability: percentage of patients not having reached DSS 6: difference between the groups significant (P<0.0001).

Brain atrophy: A long-term MRI metric

- Change in EDSS\textsuperscript{18}
  - 10-year disease duration; EDSS 2.5
  - 15-year disease duration; EDSS 4.0
    - PBVC=6.2\% (10-15 years)
  - 20-year disease duration; EDSS 6.5
    - PBVC=13.2\% (10-20 years)
    - PBVC=7\% (15-20 years)

- Cognitive impairment\textsuperscript{18}
- Fatigue\textsuperscript{19}

Brain atrophy images courtesy of R. Zivadinov. Unpublished data.

Association Between Non-adherence and Relapse

Non-experimental, retrospective analysis of pharmacy and medical claims data
(includes all licensed IFNβ drugs excluding Extavia®)

N=1606, 2006–2008
IFNβ: interferon-beta

4% of patients had MPR ≥85%, on average 72–76%

Relative risk of relapse

Medication possession ratio (MPR)
Suggested Indications of a Suboptimal Response

**Indications**

- >1 relapse per year or lack of improvement from baseline\(^1\)
- Incomplete recovery from relapses\(^1\)
- Poly-regional neurologic involvement\(^1\)
- Involvement of brainstem or spinal cord lesions\(^1\)
- Loss of neurologic function that disrupts daily activities\(^1\)
- Persistent IFN\(\beta\) or natalizumab Nabs\(^2\)
- Patient factors that influence response (non-adherence, ethnicity)\(^3-5\)

**Measures to verify changes**

- Established scores (eg, EDSS)\(^6\)
- Repeat MRI scans\(^2\)
- Rule out other causes (eg, urinary tract infection)\(^7\)
- Nab test for patients currently on IFN\(\beta\) or natalizumab therapy\(^2\)

Collective results inform the prescriber/patient decision to continue or modify DMT therapy\(^6\)

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Use of MRI in MS

- MRI findings may predict relapse rate\(^1\)*

- Surrogates of disability: MRI activity and relapse\(^2\)†
  - IFNβ treatment reduced the risk of EDSS worsening by 31%
  - 1-year MRI activity and relapses independently accounted for >60% of the treatment effect

- Further data are needed to validate MRI as a surrogate of disability\(^3\)
  - EDSS can be considered insensitive
  - Need to differentiate between surrogacy and correlation in literature

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relapse rate P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, before treatment</td>
<td></td>
</tr>
<tr>
<td>Presence of Gd+ lesions</td>
<td>0.032</td>
</tr>
<tr>
<td>Number of relapses in last 2 years</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline T2 lesions, volume</td>
<td>0.010</td>
</tr>
<tr>
<td>Black hole lesion volume</td>
<td>0.030</td>
</tr>
<tr>
<td>Within 1 year of IFNβ treatment</td>
<td></td>
</tr>
<tr>
<td>New MRI lesions</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Patients (N=857) treated with IFNβ-1b, parameters obtained before and within the first year of treatment
†Defined as EDSS increase ≥1 point over 2 years; Combination of 1-year MRI lesion activity and relapses accounted for 100% of the treatment effect on EDSS
Predictors of Poor Treatment Response

- New lesions on T2-weighted MRI after 1 year of IFNβ¹
  - Over first 2 years of IFNβ¹

- Short-term disease activity²*
  - T2-weighted lesions, Gd+ lesions
  - Relapses

*Over first 2 years of IFNβ
MRI Measures to Assess Suboptimal Response

Selected features of MRI measures used in MS and associated pathology

- **T2 weighting:**
  - New lesions: inflammation, demyelination
  - Enlarging T2 lesions: increasing inflammation, demyelination
  - Chronic lesions: non-specific (eg, demyelination, scarring, tissue destruction)

- **T1 weighting:**
  - Acute hypointense lesions (black holes): edema associated with inflammation
  - Chronic hypointense lesions: tissue destruction with demyelination and axon loss

- **Gd+ enhanced T1 weighting:** disruption of the blood-brain barrier

- **Magnetization transfer:** myelin changes

- **MRS**
  - NAAP peak: axon integrity
  - Lipid peak: demyelination

- **Changes in brain atrophy:** brain atrophy that is not specific for cell type

MRS: magnetic resonance spectroscopy; NAAP: N-acetylaspartate
CSF Biomarkers of MS Activity (Oligoclonal Bands)

- B-cell activation presenting as OCB production\(^1\)
  - Predicts conversion from CIS to MS
  - Correlates with MRI activity, relapse onset, and disability progression

- Presence of OCB at disease onset predicts a more aggressive disease course (EDSS score reaching 4; \(P=0.02\))\(^2\)*

- Elevated NFL proteins are associated with conversion to more severe MS\(^3\)

*Relapsing-onset patients included relapsing-remitting and secondary progressive MS.
CSF: cerebrospinal fluid; OCB: oligoclonal bands; CIS: clinically isolated syndrome; NFL: neurofilament light
Additional Recommendations to Improve Patient Participation (INDIVIDUAL RESPONSIBILITY & EDUCATION)

- Schedule frequent office visits, particularly during the first year of treatment, to help ensure tolerance and adherence\(^1,2\)

- Improve patient–prescriber and patient–nurse interactions\(^3\):
  - Understand and identify barriers to adherence
  - Maintain communication
  - Educate resources
  - Improve QoL
  - Schedule manageable visits

- Provide a working definition of relapse during DMT therapy\(^1\)

- Help define realistic expectations (cure versus relieving symptoms)\(^4\)

Summary

- A suboptimal response to DMT may contribute to changes in relapse rate/severity, MRI activity, and disability

- Patient factors such as adherence and individual risk should be considered when assessing treatment response

- Work for individual responsibility & patient & family education

- Patients may not always display or complain of clinical symptoms but may have other markers, such as changes in MRI, indicative of disease activity

- A variety of patient and clinical factors can contribute to suboptimal response; this underlies the importance of a well-defined treatment plan with routine follow-up
Inflammatory activity and demyelination occur from the onset of MS. Repeated inflammatory injury leads to irreversible axonal damage due to formation of demyelinated plaques. Disease pathology is continuous, even during periods of apparent remission. Axonal transection is abundantly seen in active and chronic active lesions in patients as early as 2 weeks to 27 years from disease onset. Aggressive early treatment should therefore be considered.

Axons are Transected in MS Plaques

SMI-32 (non-phosphorylated neurofilament)
-demyelinated axons and swellings MBP intact axons
HISTORY OF MS DRUG RELEASE

- BETASERON—1993
- AVONEX—1996
- COPAXONE—1997
- REBIFF—2002
- NAVANTRONE—2006
- TYSABRI—2010
- ESTAVIA—2009
- GILENYA—2011
- AUBAGIO—2012
The pathophysiology of MS\(^1-4\)

MS-specific proinflammatory immune cells cross from the bloodstream into the central nervous system (CNS) secreting proinflammatory cytokines, and eventually destroy myelin and facilitate neuronal death.

Impact on the immune system in MS: Expanding our view beyond the CNS\textsuperscript{1-6}

- MS is a debilitating autoimmune disease characterized by both inflammation and axonal degeneration\textsuperscript{1}
- In order to regulate CNS damage, treatment of MS is focused on restoring immune system balance\textsuperscript{2-5}
- It is important to expand our view to consider treatment impact on the overall immune response

MS: Immune dysfunction\textsuperscript{1-4}

Presumed MOA of COPAXONE® (glatiramer acetate injection): Immunomodulation

- Induces a population of regulatory T-cell types (Th2, Treg)
- Anti-inflammatory cytokines and neurotrophic factors are released
- May prevent nerve damage and lead to remyelination*

* It is not known if these effects play an important role in the observed clinical activity of COPAXONE® in MS. T cells derived from MS patients receiving therapy with COPAXONE® have been shown to produce neurotrophic factors, including brain-derived neurotrophic factor, and to prevent nerve damage and enhance in situ remyelination and repair in animal models.

Glatiramer acetate-induced Cytokines and Neurotrophic Factors

Blood

Glatiramer acetate (GA)

APC

GA-induced T cell

Activated (+) T cells

BBB

MMP

Th2+

Th2+

Th2+

CNS

GDNF

NT-3

NT-4

Myelin protein

GDNF

NT-3

NT-4

Myelin protein

IL-4

BDNF

TGF-β

IL-10

IGF-1

Bystander suppression

Th2

Th2

Th2

Th2
Presumed MOA of IFNβ: Immunomodulation

- Reduces proinflammatory cytokine levels
- Reduces lymphocyte trafficking into the central nervous system (CNS)

Presumed MOA of Natalizumab: Reduction of cell trafficking\textsuperscript{19}

- Inhibits the $\alpha_4$-mediated adhesion of leukocytes to vascular cell adhesion molecule-1
- Strongly reduces proinflammatory cell recruitment to the CNS

\textsuperscript{19} Tysabri\textsuperscript{®} (natalizumab) prescribing information. Biogen Idec Inc.
Presumed MOA of Fingolimod (FTY720): Immune cell sequestration²⁴,⁴⁴

- Believed to modulate sphingosine 1-phosphate receptors on lymphocytes
- Prevents lymphocytes from leaving the lymph nodes and entering the bloodstream and CNS compartment
- Still allows memory effector cells (lymphocytes) to be in plasma; lymphocytes may go to 70% of baseline

Presumed MOA of oral Cladribine: Immune cell ablation

Believed to be cytotoxic to proinflammatory immune cells
- Passively crosses immune cell membrane and accumulates inside cell
- Inhibits DNA synthesis and repair
- Reduces number of blood-cell types implicated in the pathogenesis of MS

PIVATOL TRIALS

TRIALS STARTED IN LATE 1980’S—COMPLETED IN MID 1990’S

MOST MS PATIENTS HAD DISEASE FOR 5 TO 7 YRS—HENCE DISEASE BURDEN SIGNIFICANT

DEMYELINATION & AXONAL LOSS

NATURAL HISTORY WAS ARR OF 1.7
Trends Across Clinical Trials:
Annual Relapse Rate

ARR – 2 Years

0.00 0.20 0.40 0.60 0.80 1.00

ARR = annualized relapse rate.
Recent studies: Relapse rates

ARR in patients treated with COPAXONE® (glatiramer acetate injection) 20 mg qd\(^4,13,16\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Pretreatment relapse rate</th>
<th>Results after 1 year</th>
<th>Results after 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>FORTE (n=586)</td>
<td>1.5</td>
<td>0.27</td>
<td>82%</td>
</tr>
<tr>
<td>REGARD (n=378)</td>
<td>1.01</td>
<td>0.29</td>
<td>71%</td>
</tr>
<tr>
<td>BEYOND (n=448)</td>
<td>1.6</td>
<td>0.34</td>
<td>79%</td>
</tr>
</tbody>
</table>

- During a double-blind, placebo-controlled pivotal trial, COPAXONE® reduced relapses by 29% vs placebo over 2 years (1.19 vs 1.68; \(P=0.055\)) in patients with RRMS diagnosed using Poser criteria\(^8\)

**FORTE:** Randomized, double-blind study designed to assess the efficacy, safety, and tolerability of COPAXONE® 40 mg SC daily compared with the currently approved COPAXONE® 20 mg SC daily in 1155 patients with McDonald-diagnosed RRMS. The 40-mg dose did not demonstrate increased efficacy in rate of confirmed relapses as the primary endpoint. COPAXONE® 40 mg SC is not an FDA-approved dose for the treatment of RRMS.

**REGARD:** See full study design on slide 12.

**BEYOND:** See full study design on slide 13.

\(^4\) Data on file. Teva Neuroscience, Inc.  
After discontinuing COPAXONE® (glatiramer acetate injection), withdrawn patients worsened

Patients clinically stable/improved (%)*

While on COPAXONE® prior to withdrawal†

Data from 10-year follow-up21

Withdrawn at 10-year LTFU

55%
(n=123)

28%
(n=50)

Pivotal trial and open-label follow-up: See full study design on slide 19.

COPAXONE® exposure (years; mean ± SD): 4.26 ± 3.13.

The labeling for COPAXONE® does not include an indication for slowing progression of disability.

*EDSS increase ≤0.5 points.
†One patient received 1 dose and never returned for evaluation.

Carrá: Relapse rate reduction following change in therapy\textsuperscript{7,11}

\textbf{IFNβ/COPAXONE\textsuperscript{®} (glatiramer acetate injection) n=52}

\textbf{Low-dose IFNβ/High-dose IFNβ n=31}

\textbf{COPAXONE\textsuperscript{®}/IFNβ n=16}

\textbf{IFNβ/MTX n=15}


\textbf{11. COPAXONE\textsuperscript{®} PI.}
Copaxone® (glatiramer acetate injection): PEPTIDE COPOLYMER (MIMICS MBP)
Safety information

Copaxone® is associated with
- Immediate postinjection reactions
- Injection-site reactions
- Lipoatrophy

Copaxone® is NOT associated with
- Immunosuppression/serious infections*
  —Pneumonia
  —Urinary tract infections
- PML*
- IFNβ-related flu-like symptoms
- Depression*
- Severe hepatic injury*
- NAbs
- Anaphylaxis*

*Copaxone® has no warnings or precautions for these serious adverse events.

Copaxone® is pregnancy category B
No evidence of risk in humans. Animal studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Copaxone® (glatiramer acetate injection) prescribing information. Teva Neuroscience, Inc.
High-dose Interferon-β: Safety Information

### High-dose Interferon-β® is associated with
- Injection-site reactions
- IFNβ-related flu-like symptoms
- Depression*
- Severe hepatic injury (Rebif® [IFNβ-1a] only)*
- Anaphylaxis*
- NAbs

*High-dose IFNβ has warnings or precautions for these serious adverse events.

### High-dose Interferon-β is not associated with
- Immunosuppression/serious infections
  - Pneumonia
  - Urinary tract infections
- IPIRs
- Lipoatrophy
- PML

### High-dose Interferon-β is pregnancy category C
Evidence suggests a possible risk in humans. Animal studies have demonstrated potential hazards to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Betaseron® (IFNβ-1b) prescribing information. Bayer Healthcare Pharmaceuticals Inc. Rebif® (IFNβ-1a) prescribing information. EMD Serono Inc.
Tysabri® (natalizumab): Safety Information

Tysabri® is associated with

• Progressive multifocal leukoencephalopathy (PML)*
• Immunosuppression/serious infections*
  – Pneumonia
  – Urinary tract infections
• Clinically significant hepatic injury*
• Anaphylaxis*
• Neutralizing antibodies (NAbs)*

*Tysabri® (natalizumab) has warnings or precautions for these serious adverse events.

Tysabri® is not associated with

• Depression
• Injection-site reactions
• IFNβ-related flu-like symptoms
• Immediate postinjection reactions (IPIRs)
• Lipoatrophy

Tysabri® is pregnancy category C

Evidence suggests a possible risk in humans. Animal studies have demonstrated potential hazards to the fetus, and there are no adequate and well-controlled studies in pregnant women.
NATALIZUMAB (TYSAEBRI) AFFIRM

- 942 patients, 2 to 1, infusion every 4 weeks up to 116 weeks
- ARR at 2 yrs; P 0.67 & N 0.22 (67% less)
- Gd+ lesions at 2 years; down 92%
- 42% less increased physical disability sustained for 12 weeks
- No relapses at 2 yrs; N 67% vs P 41%
- Free of Gd+ lesions; N 97% vs P 72%
- No new no enlarging T2: N 57% vs P 15%
NATALIZUMAB (TYSABRI)

- 104,300 PATIENT EXPOSURES
- PML 285 CASES; 62 DIED, SURVIVAL RATE 78%; 1/3 MILD, 1/3 M; 1/3 SEVERE
- 3 RISK FACTORS; + JCV, PRIOR IMMUNO SUPPRESSANT MEDS, > 24 MONTHS RX,
- ANTI-JCV ANTIBODY TITER @ 6 MONTHS
- PML S&S; CHANGE IN SPEECH & BEHAVIOR, MRI CHANGES(40% Gd+)
- EXCLUSION REQUIRES NEGATIVE JCV DNA IN CSF & NO PROGRESSION;
  REPEAT CSF QUANTITATIVE PCR ASSAY FOR JCV DNA
MRI & PML
Fingolimod Efficacy: ARR

TRANSFORMS

Annualized Relapse Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Annualized Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN</td>
<td>0.33</td>
</tr>
<tr>
<td>FTY 0.5mg</td>
<td>0.16</td>
</tr>
<tr>
<td>FTY 1.25mg</td>
<td>0.20</td>
</tr>
</tbody>
</table>

P<0.001 for both doses vs IFN; values represent reductions in ARR of 52% and 38% vs IFNb-1a

FREEDOMS

Annualized Relapse Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Annualized Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.40</td>
</tr>
<tr>
<td>FTY 0.5mg</td>
<td>0.18</td>
</tr>
<tr>
<td>FTY 1.25mg</td>
<td>0.16</td>
</tr>
</tbody>
</table>

P<0.001 for both doses vs placebo; values represent reductions in ARR of 54% and 60% vs PBO

FINGOLIMOD--FREEDOMS

• 1272 PATIENTS, 2 YRS, ORAL, P VS 0.5MG, 1.25MG
• DATA COMPARED TO 0.5 MG
• REDUCED ARR BY 54% FOR 0.5 MG
• RELAPSE FREE, P 46% VS F 70%, 52% REDUCTION
• # T2 LESIONS REDUCED, P 9.8 VS N 2.5, ABSOLUTE REDUCTION WAS 7.3 LESIONS
• 30% REDUCTION IS CONFIRMED PHYSICAL DISABILITY AT 3 MONTHS
FINGOLIMOD--TRANSFORMS

- 1292 PATIENTS, 1 YR, ORAL INTERFERON BETA-1a IM, 0.5MG, 1.25MG
- DATA COMPARED TO 0.5MG
- ARR, P 0.33 VS F 0.16, 52% REDUCTION
- RELAPSE FREE, P 70% VS F 83%, 19% REDUCTION
- T2 LESIONS REDUCED, P 2.6 VS F 1.6,
FINGOLIMOD (GILENYA) PRECAUTIONS

• CARDIAC—LOW HEART RATE (MONITOR FOR 6 HOURS), LOW BP; LUNGS---SOB; LIVER; ELEVATED ENZYMES, EKG BASE LINE, THEN DAY OF AND AT 6 HOURS (QTc INTERVAL)

• MACULAR EDEMA—1 IN 500, VISUAL LOSS; MONITOR BEFORE & AT 3 MONTHS; HIGHER RISK IN DIABETICS & UVEITIS

• INFECTIONS---2 DEATHS IN HIGHER DOSE (1.25); NEED HX OF CP OR GET VZV VACCINATION & WAIT ONE MONTH.

• WBC LOWER; AFTER DC NORMAL IN 1 TO 2 MONTHS

• CATEGORY C FOR PREGNANCY

• AE---HA, FLU LIKE S & S, BRONCHITIS, BACK PAIN, DIARRHEA

• DEATHS; 30 REASON UNCERTAIN
TERIFLUNOMIDE (AUBAGIO)--TEMSO

• FDA APPROVED ON 9/12/12, AVAILABLE 10/1/12
• 1088 PT IN STUDY, ORAL, P VS 7MG & 14MG (MORE ROBUST EFFICACY WITH 14MG, SIMILAR AE’S)
• ANNUALIZED RELAPSE RATE (ARR)
  • AT 2YR: P 0.54 VS 0.37 FOR 7MG & 14MG, REDUCED BY 31%
  • AT 5 YR EXTENSION: 0.234 FOR 7MG AND 0.206 FOR 14MG
• 3-MONTH SUSTAINED DISABILITY PROGRESSION:
  • AT 2YR: P 27.3% VS 20.2% FOR 14MG, REDUCED BY 30%

O’Conner P. et. al. NEJM 2011; 365-1293-303
TERIFLUNOMIDE (AUBAGIO) - TEMSO

• TOTAL LESION VOLUME (T1 HYPOINTENSE PLUS T2 HYERINTENSE):
  • 69% RELATIVE RISK REDUCTION BY 14MG VS PLACEBO

• T1 GD-ENHANCING LESIONS:
  • 80% RELATIVE RISK REDUCTION BY 14MG VS PLACEBO

O’Conner P. et. al. NEJM 2011; 365-1293-303
TERIFLUNOMIDE (AUBAGIO) - TEMSO

• SIMILAR AE’S, SERIOUS AE’S, AND AE’S LEADING TO RX DISCONTINUATION FOR PLACEBO VS TERIFLUNOMIDE

• PREGNANCY CATEGORY X: BASED ON ANIMAL DATA
  • PREGNANCY REGISTRY: 12 LIVE BIRTHS ON TERI, ALL HEALTHY WITH NO STRUCTURAL OR FUNCTIONAL DEFECTS

• COMMON AE’S:
  • DIARRHEA: P 9%, 15% 7MG, 18% 14MG (1 PT D/C IN EACH T ARM)
  • NAUSEA: P 7%, 9% 7MG, 14% 14MG (1 PT D/C IN 7MG)
  • INCREASED ALT: P 7%, 12% 7MG, 14% 14MG
    • ALT>3X ULN SIMILAR FOR P VS T; SIMILAR D/C RATE
  • HAIR THINING: P 3% VS 10-13% T (WITH 1% D/C ON T). PEAK 3-6MO. CAN RECOVER SPONTANEOUSLY EVEN WHILE ON RX, 94% RECOVER WITH OUT SEQUELAE, 2% RECOVER WITH SEQUELAE

O’Conner P. et. al. NEJM 2011; 365-1293-303
TERIFLUNOMIDE (AUBAGIO) - TENERE

• 324 PTS, INFβ-1A (REBIF 44MCG TIW) VS TERIFLUNOMIDE 7MG & 14MG

• PRIMARY ENDPOINT (TIME TO FAILURE = CONFIRMED RELAPSE OR PERMENANT RX D/C)
  • 37.8% FOR 14MG VS 42.3% FOR REBIF (NS)

• ARR: 0.26 FOR 14MG VS 0.22 FOR REBIF (NS)

• TREATMENT D/C DUE TO AE:
  • 10.9% FOR 14MG VS 21.8% FOR REBIF

• ALT INCREASED: 10.9% FOR 14MG VS 30.7% REBIF

BG-12 (DIMETHYL FUMARATE) DEFINE 2 YR VS P; NOT APPROVED BY FDA YET

- 1237 PATIENTS, ORAL, 240MG 2 X’S (BID) OR 3 X’S (TID) A DAY
- ARR REDUCED FOR 2X’S WAS BY 53%, FOR 3X’S WAS BY 48%
- REDUCED RISK OF RELAPSE FOR 2X’S WAS 49%, FOR 3X’S WAS 50%
- Gd+ LESIONS REDUCED FOR 2X’S WAS 90%, FOR 3X’S WAS 73%
- T2 NEW OR ENLARGING LESIONS REDUCED FOR 2X’S WAS 85%, FOR 3X’S WAS 74%
- T1 NEW HYPOTENSE REDUCED FOR 2X’S WAS 72%, 3X’S WAS 63%
- REDUCED DISABILITY PROGRESSION FOR 2X’S BY 38%, FOR 3X’S WAS 34%; FREE OF Gd+ LESIONS
- AE—FLUSHING, HEADACHE, DIARRHEA, FATIGUE, NAUSEA, NASOHPARYNGITIS (NO INCREASED INFECTIONS)
- PREGNANCY CATEGORY?
BG-12 (DIMETHYL FUMARATE) CONFIRM—2 YEAR TO P & WITH GA

- ARR REDUCED FOR 2 X’S WAS 44%, 3X’S WAS 51%, & GA WAS 29%
- % OF PATIENTS THAT RELAPSED FOR 2X’S WAS 34%, 3X’S WAS 45% & GA WAS 29%
- REDUCED DISABILITY PROGRESSION FOR 2X’S WAS 21%, 3X’S WAS 24% & FOR GA WAS 7%
- T2 NEW OR ENLARGING REDUCED FOR 2X’S WAS 71%, FOR 3X’S WAS 73 % & GA WAS 54%
- T1 NEW HYPOINTENSE REDUCED FOR 2X’S WAS 57%, 3X’S WAS 73% & FOR GA WAS 41%
BG-12 DIMETHYL FUMARATE (MECHANISM OF ACTION?)

- ORAL
- ACTIVATES THE Nrf2 PATHWAY WHICH Reduces the impact of inflammatory cell on CNS
- INDUCES DIRECT CYTOPROTECTIVE RESPONSES IN CELLS & BALANCES THE PROINFLAMMATORY & OXIDATIVE STATE
TREATMENT ALGORITHM

- RIS; DETERMINE CORRECT DX WITH CSF & REPEAT MRI; ? RX IF Gd+ & LOOKS LIKE MS
- CIS; AGGRESSIVE DMA’S & CLOSE FOLLOW UP WITH MRI IN 1 YR
- RRMS; DMA’S IMMUNOMODULATORS WITH CLOSE FOLLOW UP & IF RELAPSE & MRI CHANGES (ESPECIALLY IF Gd+) OR NEW ?# T2 LESIONS ON MRI, CHANGE DMT
- IF RRMS & HIGH BURDEN ON MRI & OR FREQUENT & PROGRESSIVE COURSE, RX WITH NATALIZUMAB OR FINGOLIMOD, OR TRIFLUNOMIDE
- USE MP OR ACTH/AR AS INDICATED
RESCUE RX FOR ACUTE RELAPSE

• M P 1000MG IV FOR 3 TO 5 DAYS
• ORAL PREDNISONE—60 TO 100MGS FOR 5 TO 7 DAYS
  — 30 TO 40% OF RXED RELAPSE CASES ARE NOT IMPROVED WITH THE ABOVE RESCUE RX.
• ACTHAR—GEL; 80 TO 120 UNITS SUBQ OR IM SELF ADMINISTERED DAILY FOR 2 TO 3 WEEKS OR LESS—BINDS TO MELANOCORTIN RECEPTORS IN BRAIN—SUPPRESSES CYTOKINES
FUTURE DRUGS PHASE 3 TRIALS

- ALEMTUZUMAL—MONOCLONAL ANTIBODY; TARGETS CD52 ANTIGEN AND B & T CELLS
  - CNS INFECTIONS, INFUSION REACTIONS
- LAQUINIMOD—ORAL, SHIFTS TH1 CELLS TO TH2
  - AE—GBS, RA
- MORE MONOCLONAL ANTIBODIES
- STEM CELLS
- OTHER AVAILABLE DRUGS; AMPURA (10MG BID); NEUDEXTA (10 MG BID FOR PBA); ACEI
- EXERCISE; MAY SLOW PROGRESSION OF MS
OUTLINE OF MS TALK

- PART 1
  - EPIDEMIOLOGY
  - SIGNS AND SYMPTOMS
  - PATHOPHYSIOLOGY
- PART 2
- TREATMENT FORMAT
  - DMT (IMMUNOMODULATORS) EFFICACY, SAFETY, TOLERABILITY
  - DMT (IMMUNOSUPPRESSORS) EFFICACY, SAFETY, TOLERABILITY
  - ALGORITHMS
- FUTURE DRUGS