Advances in the Management of Multiple Sclerosis: A closer look at novel therapies

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Disclosures

• National MS Society National Board member
• Fast Forward Board of Managers member
• American Academy of Neurology BrainPAC chair
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• Consulting fees from Biomarin
Objectives

• Discuss current MS therapies and pathway for drug selection
• Discuss safety concerns of MS therapies
• Discuss NEDA (no evidence of disease activity)
• Discuss emerging MS therapies and their impact on efficacy and safety

Current disease modifying therapies
MS Disease Modifying Therapies

Betaseron® (interferon beta-1b sq qod) – 1993
Avonex® (interferon beta-1a IM qweek) – 1996
Copaxone® (20 mg/ml glatiramer sq qd) – 1996
Novantrone® (mitoxantrone IV q3 months) - 2000
Rebif® (interferon beta-1a sq tiw) – 2002
Extavia® (interferon beta-1b sq qod) – 2009
Tysabri® (natalizumab IV qmonth) – 2004
Gilenya® (fingolimod po daily) – 2010
Aubagio® (teriflunomide po daily) - 2012
Tecfidera® (dimethyl fumarate po bid) - 2013
Copaxone® (40 mg/ml sq tiw) – 2014
Plegridy® (pegylated interferon beta-1a sq q2 weeks) - 2014
Lemtrada® (alemtuzumab 5 days IV, then 3 days IV after 12 months) - 2014
Glatopa™ (generic glatiramer 20 mg/ml sq qd) - 2015

How to make sense of it?

injectables  
orals  
infusions

*Route of administration* is NOT the answer!
Don’t forget the other two prongs of MS management

Treatment of acute relapses
– 1 gm. IV methylprednisolone x 3 to 5 days
– Acthar® gel 80 to 120 u daily IM/SQ x 2 – 3 weeks (intolerant of high dose steroids, steroid failure, poor IV access or preference for self-injection)

Symptomatic treatment
- Fatigue
- Cognitive dysfunction
- Pain
- Dysesthesias
- Spasticity
- Bladder dysfunction
- Bowel dysfunction
- Sexual dysfunction
- Ambulatory dysfunction
“Symptomatic management always has been and continues to be the bedrock of patient care in MS as symptoms impact quality of life for patients...prescribers must retain the right to decide on the best treatment for each individual patient. The varied and individualized course of MS mandates full access to symptomatic management as well as disease modifying therapies which, in the best judgment of the prescriber, offer optimal treatment outcomes. Medications to treat symptoms are carefully decided on an individual basis and by best practice regimens. Lack of understanding of the disease course and the challenges of MS treatment result in poor decision making practices by the insurance plans and specialty pharmacies and subsequent denial of prescribed medications. This leads to an inability to adequately serve the people living with MS, negatively affecting the patient’s quality of life.”

New safety data on current therapies
Natalizumab and Progressive Multifocal Leukoencephalopathy

- 588 cases of PML as of September 2015 (585 MS, 3 Crohn’s)
- 142,000 patients received natalizumab post-marketing as of June 2015
- Global overall incidence is 4.03/1000 patients
- 77% alive with varying levels of disability; 23% died
- Duration of therapy prior to diagnosis range from 8 to 110 doses
- 86% with > 24 doses at time of diagnosis

Biogen communication, September 2015.

Natalizumab and PML

Factors that increase risk of PML:
- Longer treatment duration (> 2 years)
- Prior treatment with immunosuppressant (e.g. mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate)
- + JCV antibody

<table>
<thead>
<tr>
<th>Estimated US incidence of PML stratified by risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-JCV ab negative</td>
</tr>
<tr>
<td>tyvlbr exposure</td>
</tr>
<tr>
<td>use</td>
</tr>
<tr>
<td>&lt;1/1000</td>
</tr>
<tr>
<td>1-24 months</td>
</tr>
<tr>
<td>25-48 months</td>
</tr>
<tr>
<td>49-72 months</td>
</tr>
</tbody>
</table>

Biogen communication, September 2015
Global cumulative natalizumab PML risk estimates by treatment duration

Management of PML risk in natalizumab patients

• Clinical vigilance is key
• Improved survival associated with
  – Early diagnosis
  – Younger age at diagnosis
  – Less functional disability prior to diagnosis
  – Lower JC viral load at diagnosis
  – More localized brain involvement by MRI at time of diagnosis
Anti-JCV antibody testing

- JCV infection required for PML
- Anti-JCV ab status is not diagnostic of PML
- Anti-JCV ab negative = exposure to JCV not detected; lower risk of PML than those who are JCV ab +; potential for new JCV infection or false negative test
- rate of JCV ab seroconversion is 3-8% annually
- Don’t do < 2 weeks after plasma exchange
- ~99% sensitive

Biogen communication, September 2015

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PML in a Patient with Lymphocytopenia Treated with Dimethyl Fumarate


- 54 yo with MS, dx’ed 1996, treated with GA, received 4.5 years of DMF 240 mg tid in open label extension of DEFINE
- Developed severe lymphocytopenia (290-580 cells/cu mm) after 12 months, persisted for 3.5 years
- Developed severe gait, speech and left UE difficulties in Aug 2014, treated with steroids, plasmapheresis for presumed relapse
- Diagnosis made based on MRI and CSF JCV DNA PCR in October 2014
PML associated with fumaric acid esters used for psoriasis

- Dammeier described a patient with lymphocyte counts between 450-750/microL for prolonged time periods
- Nieuwkamp described a patient with delayed release DMF with nadir of 792 cells/mm³
- Severe lymphopenia not required; alteration of immune surveillance for prolonged time is critical for development of PML

ECTRIMS 2015, P642
Management of patients on tecfidera suspected of PML

- Check CBC before initiating therapy
- Hold Tecfidera for signs and symptoms suggestive of PML
- Follow CBC every 6 months
- Hold Tecfidera for lymphocyte counts < 500 > 6 months and follow until lymphopenia resolves

Biogen communication

PML associated with Gilenya

- > 18,000 patients received Gilenya after Tysabri use (~15 to 20%) as of April 2015
- 20 cases of PML as of August 2015
  - 17 with prior history of Tysabri use, 5 with MRI evidence before first dose of Gilenya
  - 3 without

Novartis communication
### Estimated PML Risk

<table>
<thead>
<tr>
<th>Treatment in MS Patients</th>
<th>PML Cases</th>
<th>Risk</th>
<th>PML Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilenya Without Prior Tysabri&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3&lt;sup&gt;*&lt;/sup&gt; cases per ~125,000 patients or 240,000 patient-years of Gilenya exposure</td>
<td>0.024 / 1,000 patients</td>
<td>1.25 / 100,000 patient-years</td>
</tr>
<tr>
<td>Tysabri &gt;2 years, JCV++&lt;sup&gt;2&lt;/sup&gt;</td>
<td>517&lt;sup&gt;1&lt;/sup&gt; cases per 381,000 patient-years of Tysabri exposure</td>
<td>3-13 / 1,000 patients</td>
<td>133.2 / 100,000 patient-years</td>
</tr>
<tr>
<td>Gilenya With Prior Tysabri&lt;sup&gt;3&lt;/sup&gt;</td>
<td>12 cases per 18,000 patients&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.64 / 1,000 patients</td>
<td></td>
</tr>
</tbody>
</table>

<sup>Novartis communication</sup>

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### [Platform 152 and P1102] CARE-MS Extension: Examining Durability of Effect and Long-term Safety with Alemtuzumab

**Study Design: All Alemtuzumab Patients<sup>1,2</sup>**

<table>
<thead>
<tr>
<th>Study duration</th>
<th>Core Study</th>
<th>Extension Study&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month:</td>
<td>Year 1</td>
<td>Year 2</td>
</tr>
<tr>
<td></td>
<td>N=811</td>
<td>N=810</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>N=742</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>Year 4</td>
</tr>
<tr>
<td></td>
<td>Year 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=731</td>
<td>N=771</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Year 5</td>
<td>Year 5</td>
</tr>
<tr>
<td></td>
<td>N=767</td>
<td>N=767</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

- Ongoing, open-label extension study provides follow-up, retreatment where necessary, and reassessment of outcomes through Month 60 (Year 5)
  - 95% and 93% of alemtuzumab-treated patients completing CARE-MS I and CARE-MS II, respectively, enrolled in the extension study<sup>3,4</sup>
  - Baseline characteristics of patients were similar to those of patients in the core study<sup>3,4</sup>
  - Patients qualified for retreatment based on either one clinical episode or MRI evidence for new disease activity; retreatment was available at the discretion of the treating investigator<sup>3,5</sup>

<sup>1, Havrdova E et al. ECTRIMS 2015, Platform; 2, Fox E et al. ECTRIMS 2015, P1102; 3, Cohen JA et al. Lancet 2012;380:1819-28; 4, NCT01932553</sup>
[Platform 152 and P1102] CARE-MS Extension: Retreatment Rates and Other DMT use Through Extension

CARE-MS I
Retreatment in Extension Study¹

- 68% of patients did not receive alemtuzumab treatment since Month 12

- ~2% of patients received other DMTs through year 5

CARE-MS II
Retreatment in Extension Study²

- 60% of patients did not receive alemtuzumab treatment since Month 12

- ~8% of patients received other DMTs through year 5


[Platform 152 and P1102] ARR With Alemtuzumab: 5 Year Follow-Up

CARE-MS I¹

- 68% of patients did not receive alemtuzumab treatment since Month 12

CARE-MS II²

- 60% of patients did not receive alemtuzumab treatment since Month 12

AUTHOR CONCLUSIONS:
- A low ARR was maintained from Years 3–5
- The proportion of patients free from relapse was stable or increased in Years 3, 4, and 5 compared with Years 1 and 2

[Platform 152 and P1102]: Proportion of Patients Free From 6-Month Sustained Disability Progression: 5-Year Follow-up

**AUTHOR CONCLUSIONS:** A majority of patients remained free from 6-month sustained disability progression through Year 5


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[Platform 152 and P1102]: Sustained Improvement in Pre-Existing Disability With Alemtuzumab: 5-Year Follow-up

* 92% (CARE-MS I) and 95.5% (CARE-MS II) of patients with SRD were also free from 6-month SAD over 5 years.1,3

[P1100 and P1103]: Patients Remaining Free from MRI Activity With Alemtuzumab: 5-Year Follow-up

**CARE-MS I**
- Alemtuzumab 12 mg (all patients)

**CARE-MS II**

**AUTHOR CONCLUSION:** The majority of alemtuzumab-treated patients from both studies continued to remain free of new lesions and MRI activity through Year 5 despite most patients not receiving retreatment over the previous 4 years.


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[P1100 and P1103]: No Evidence of Disease Activity With Alemtuzumab: 5-Year Follow-up

**CARE-MS I**
- Alemtuzumab 12 mg (all patients)

**CARE-MS II**

**AUTHOR CONCLUSION:** The proportion of alemtuzumab-treated patients from both studies achieving NEDA remained stable in Years 3, 4, and 5.

**[Presentation 151] Brain Volume Loss With Alemtuzumab: 5-Year Follow-up**

**CARE-MS I**
- SC IFNB-1a 44 μg
- Alemtuzumab 12 mg (all patients)
- Healthy adults

42% reduction vs SC IFNB-1a

**CARE-MS II**
- SC IFNB-1a

24% reduction vs SC IFNB-1a

*Author Conclusion:* The slowing of brain volume loss that was achieved at the end of the CARE-MS core studies was maintained over the first 3 years of the extension study.

- The mean annual rate of brain volume loss in healthy individuals is 0.1–0.3%.
- 68% of patients in CARE-MS I and 60% of patients in CARE-MS II did not receive any retreatment.


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**[Presentation 151] Median Yearly Brain Volume Loss With Alemtuzumab: 5-Year Follow-up**

**CARE-MS I**
- Year 1: -0.35
- Year 2: -0.19
- Year 3: -0.16
- Year 4: -0.20
- Year 5: -0.29

68% of patients did not receive alemtuzumab treatment since Month 12

**CARE-MS II**
- Year 1: -0.22
- Year 2: -0.19
- Year 3: -0.19
- Year 4: -0.19
- Year 5: -0.19

60% of patients did not receive alemtuzumab treatment since Month 12

**Author Conclusions:**
- Alemtuzumab slowed brain volume loss through Year 5 in active RRMS patients.
- Median annual brain volume loss in both studies was 0.2% in Years 3, 4, and 5.
- Durable slowing of brain volume loss may be explained by the unique pattern of lymphocyte depletion and repopulation following acute treatment with alemtuzumab.

NEDA

• No evidence of disease activity
  - no relapse
  - no worsening of EDSS
  - lack of new/enlarging T2 lesions on MRI
  - lack of gadolinium-enhancing lesions on MRI
Criteria for NEDA to consider treatment adjustment

• MRI parameters
  – Multiple new or enlarged T2 lesions or gad-enhancing lesions

• Relapse activity
  - > 1 relapse with incomplete remission
  - > 1 severe relapse with necessity of escalating acute therapy (2 gm. IV solumedrol x 5 days)
  - > 2 objective relapses without residual symptoms at 1 year

• Disability progression
  – EDSS < 3
  – Fatigue and cognitive parameters are not considered enough

Emerging therapies in MS

Daclizumab high-yield process (DAC HYP)

• Humanized monoclonal antibody – binds to CD25 (alpha subunit of interleukin-2 receptor)
• Reversibly modulates IL-2 signaling, reducing pro-inflammatory activated T cells, expands immunoregulatory CD56\textsuperscript{bright} NK cells

DECIDE

• Randomized double blind, active-controlled phase 3 study
• 1841 RRMS patients, over 144 weeks
• DAC HYP 150 mg SQ q 4 weeks vs.. interferon beta-1a 30 mcg IM q week
DECIDE results

- ARR 0.22 vs. 0.39; 45% lower, p<0.001
- T2 lesions 4.3 vs. 9.4; 54% lower, p<0.001 at 96 weeks
- Disability progression at 12 weeks at 16% vs. 20%, p=0.16
- Serious adverse events 15% vs. 10% - infections, rash, eczema, elevations in ALT

Benefits on Brain MRI Lesion Activity with Daclizumab HYP Compared with Intramuscular Interferon Beta-1a Are Maintained Through 144 Weeks' Treatment: Results From the DECIDE Study


11th Congress of the European Committee for Treatment and Research in Multiple Sclerosis • 7-10 October, 2015 • Barcelona, Spain

P556

(B) Mean (SD) Gd+ lesions at Week 144

Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>IM IFN beta-1a (n=195)</th>
<th>DAC HYP (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66.6% reduction</td>
<td>0.78</td>
<td>0.28</td>
</tr>
</tbody>
</table>

(B) Median newly enlarging T2 hyperintense lesion volume at Week 144

Median volume, mm³

<table>
<thead>
<tr>
<th></th>
<th>IM IFN beta-1a (n=195)</th>
<th>DAC HYP (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.0</td>
<td></td>
<td>0.0</td>
</tr>
</tbody>
</table>

(C) Mean (SD) new T1 hypointense lesions at Week 144

<table>
<thead>
<tr>
<th></th>
<th>IM IFN beta-1a (n=195)</th>
<th>DAC HYP (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58.9% reduction</td>
<td>1.85</td>
<td>2.87</td>
</tr>
</tbody>
</table>

(C) Median percentage change from Baseline to Week 144 in T1 hypointense lesion volume

Median % change in volume (Baseline-Week144)

<table>
<thead>
<tr>
<th></th>
<th>IM IFN beta-1a (n=195)</th>
<th>DAC HYP (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.7</td>
<td></td>
<td>9.4</td>
</tr>
</tbody>
</table>
**[Parallel Session 10- 190] Efficacy and safety of ocrelizumab in relapsing multiple sclerosis - results of the interferon-beta-1a-controlled, double-blind, Phase III OPERA I and II studies. S.L. Hauser**

<table>
<thead>
<tr>
<th>Introduction</th>
<th>B cells are believed to contribute to the pathogenesis of multiple sclerosis (MS). Ocrelizumab (OCR) is a recombinant humanised monoclonal antibody that selectively targets CD20+ B cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>OPERA I and II are two identical Phase III, multicentre, randomised, double-blind, double-dummy, parallel-group trials aiming to assess the efficacy and safety of OCR compared with interferon (IFN)–β-1a in patients with relapsing forms of MS (RMS; OPERA I NCT01247324 and OPERA II NCT01412333)</td>
</tr>
<tr>
<td>Methods</td>
<td>Patients were randomised (1:1) to receive OCR 600 mg via intravenous infusion every 24 weeks or IFN-β-1a 44 µg subcutaneously three times per week throughout a 96-week treatment period. Eligibility criteria included an age of 18-65 years with a diagnosis of RMS (2010 revised McDonald criteria), Expanded Disability Status Scale (EDSS) score of 0-5.5 at screening and ≥ two documented clinical attacks within 2 years prior or one within 1 year prior to screening. The primary endpoint is the annualised protocol-defined relapse rate at 2 years.</td>
</tr>
</tbody>
</table>

**Primary endpoint:**
Significant reduction in ARR compared with IFN β -1α

![Graph showing adjusted relapse rate reduction in OPERA I and II](image)
Secondary endpoints: Significant reduction in CDP in the pre-specified pooled analysis of OPERA I and OPERA II

Time to 12-week CDP

- IFN-β-1a 44 µg (n=829)
- Ocrelizumab 600 mg (n=827)

Time to 24-week CDP

- IFN-β-1a 44 µg (n=829)
- Ocrelizumab 600 mg (n=827)

Secondary endpoint: Significant reduction in number of T1 Gd+ lesions compared with IFN β-1a

OPERA I

Mean Number of T1 Gd-enhancing Lesions per MRI Scan

IFN β-1a 44 µg (n=411)

Ocrelizumab 600 mg (n=410)

94% Reduction vs IFN β-1a p=0.0001

OPERA II

Mean Number of T1 Gd-enhancing Lesions per MRI Scan

IFN β-1a 44 µg (n=418)

Ocrelizumab 600 mg (n=417)

95% Reduction vs IFN β-1a p=0.0001
Secondary endpoint: Significant reduction in number of new and/or enlarging T2 hyperintense lesions compared with IFN β-1a

### OPERA I

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>IFN β-1a 44 μg (n=411)</th>
<th>Ocrelizumab 600 mg (n=410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean New or Enlarging T2 Hyperintense Lesions per MRI Scan</td>
<td>1.413</td>
<td>0.323</td>
</tr>
</tbody>
</table>

77% Reduction vs IFN β-1a p=0.0001

### OPERA II

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>IFN β-1a 44 μg (n=418)</th>
<th>Ocrelizumab 600 mg (n=417)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean New or Enlarging T2 Hyperintense Lesions per MRI Scan</td>
<td>1.904</td>
<td>0.325</td>
</tr>
</tbody>
</table>

83% Reduction vs IFN β-1a p=0.0001

Serious adverse events were low over 96 weeks

<table>
<thead>
<tr>
<th>Event</th>
<th>IFN β-1a 44 μg (n=824)</th>
<th>Ocrelizumab 600 mg (n=825)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients with ≥1 SAE</td>
<td>72 (8.7)</td>
<td>57 (6.9)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>24 (2.9)</td>
<td>11 (1.3)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>11 (1.3)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>10 (1.2)</td>
<td>6 (0.7)</td>
</tr>
</tbody>
</table>

During OPERA I and OPERA II, three deaths occurred
- IFN β-1a 44 μg arm: suicide, mechanical ileus
- Ocrelizumab 600 mg arm: suicide

Six malignancies were reported:
- IFN β-1a 44 μg arm: mantle cell lymphoma and squamous cell carcinoma
- Ocrelizumab 600 mg arm: renal cancer, melanoma and two breast cancers
ORATORIO

- Ocrelizumab in PPMS – placebo controlled double blind phase III study
- OCR 300 mg IV given 14 days apart every 24 weeks x 120 weeks
- 732 patients, 183 sites
- Mean age at baseline was 44.6 years
- 49.3% females, 94.1% were white
- Mean baseline EDSS score was 4.70; mean duration since MS symptom onset 6.48 years; mean duration since PPMS diagnosis was 2.82 years.
- Number of patients untreated with any MS medication in the prior 2 years was 656 (89.6%)
- At baseline, 26.4% of patients had gadolinium-enhancing (Gd+) T1 lesions; mean number of Gd+ T1 lesions was 1.0; median volume of T2 lesions was 6.96 cm3; and mean normalized brain volume was 1464.99 cm3 on MRI

ORATORIO results

• Primary endpoint - significant reduction in 12 week confirmed disability progression (24%), p=0.0321

• Secondary endpoint
  – Significant reduction in 24 week confirmed disability progression (25%), p=0.0365; significant reduction (29%) in progression rate of walking time, p=0.0404
  – Significant reduction in T2 lesion volume at 120 weeks (-3.4% vs.. 7.4%, p<0.0001)
  – Significant reduction in rate of whole brain volume loss (17.5%, p=0.0206)

X. Montalban et al. ECTRIMS 2015. Late breaking news.

Adverse events

• Similar to placebo
• Most common were mild-moderate infusion-related reactions
• Infusion reaction most severe with initial dose, then tapers

X. Montalban et al. ECTRIMS 2015. Late breaking news.
Thank you for your attention!

Questions???

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