Patients of African Descent With Active RRMS Demonstrate Clinical and Radiologic Benefits With Alemtuzumab Over 5 Years

Annette Okai,1 Keith R Edwards,2 Brian Steingo,3 David H Margolin,4 Sourav Santra,5 Mitzi Williams6; on behalf of the CARE-MS I and CARE-MS II Investigators

1Multiple Sclerosis Treatment Center of Dallas, Dallas, TX, USA; 2MS Center of NE New York, Latham, NY, USA; 3Fort Lauderdale Multiple Sclerosis Center, Sunrise, FL, USA; 4Sanofi Genzyme, Cambridge, MA, USA; 5Cytel, Cambridge, MA, USA; 6Multiple Sclerosis Center of Atlanta, Atlanta, GA, USA

Presented by Annette Okai

African Ancestry Is a Risk Factor for MS Disease Progression

• Patients of African descent have more severe MS disease compared with white patients
  – More rapidly disabling disease
  – Greater MRI lesion volumes
  – Greater risk for secondary progression
  – Accelerated retinal nerve fiber layer thinning and ganglion cell/inner plexiform layer thinning
  – Possibly poorer response to disease-modifying therapies (DMTs)

CARE-MS I and II Study Background (Full Cohort)

• Phase 3 trials in active RRMS patients:
  – Treatment-naive (CARE-MS I)
  – Inadequate response to prior therapy at baseline, defined as at least one relapse (CARE-MS II)

• Alemtuzumab versus SC IFNB-1a over 2 years:
  – Significant decrease in annualized relapse rate (ARR) in both studies
  – Significantly reduced risk of 6-month confirmed disability worsening in CARE-MS II
  – MRI outcomes were significantly improved in CARE-MS I and II
    • 23% and 68% more patients with no evidence of MRI disease activity
    • 42% and 24% reduction in brain volume loss (BVL)
  – Most frequent adverse events (AEs) were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs

Disclosures

• Annette Okai: Consulting and/or speaking fees (Biogen, EMD Serono, Genentech, Mallinckrodt, Novartis, Sanofi Genzyme, and Teva)
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• David H Margolin: Compensation as an employee of Sanofi Genzyme
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• Rebif® is a registered trademark of EMD Serono Inc.
• CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis.

CARE-MS I and II Core and Extension Study Design

- Ongoing, open-label, rater-blinded extension study provides follow-up, retreatment where necessary, and reassessment of outcomes through Month 60 (Year 5)

Assessments Through 5 Years

- Relapses
  - Expanded Disability Status Scale (EDSS) score was assessed at baseline and quarterly by raters who were blinded to core study treatment assignment
    - Confirmed disability worsening: ≥1-point EDSS increase (≥1.5 point if baseline EDSS=0) confirmed over 6 months
    - Confirmed disability improvement: ≥1-point EDSS decrease from baseline over 6 months, assessed in patients with baseline EDSS ≥2.0
  - MRI was conducted at baseline and annually
    - BVL derived by brain parenchymal fraction (BPF) change
  - No evidence of disease activity (NEDA) was defined as no evidence of clinical disease activity (relapse and 6-month confirmed disability worsening) and MRI disease activity (new gadolinium-enhancing T1 and new/enlarging T2 hyperintense lesions)

General Considerations on Subgroup Analysis

- There must be careful interpretation of any subgroup analysis before making a conclusion
  - Lack of statistical significance does not imply absolute lack of treatment effect
  - Statistical significance does not imply absolutely statistically robust treatment effect
  - Relapses and disability worsening are infrequent events, so a few events may influence results
- Key statistical issues: not randomized for subgroup, not controlled for multiplicity, subgroup not powered, etc.

Patients of African Descent

- 46 patients of African descent in the pooled CARE-MS core studies (SC IFNB-1a and alemtuzumab 12-mg treatment arms)
  - 32 of 35 alemtuzumab-treated patients entered the extension study
- Baseline characteristics were comparable between treatment groups

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>SC IFNB-1a (n=35)</th>
<th>Alemtuzumab 12 mg (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>33.0 (10.12)</td>
<td>33.4 (8.21)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9 (81.8)</td>
<td>26 (74.3)</td>
</tr>
<tr>
<td>Country, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>9 (81.8)</td>
<td>28 (80.0)</td>
</tr>
<tr>
<td>Brazil</td>
<td>2 (18.2)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>UK</td>
<td>0</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Croatia</td>
<td>0</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Germany</td>
<td>0</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>EDSS score</td>
<td>2.5 (1.27)</td>
<td>2.2 (1.39)</td>
</tr>
<tr>
<td>Time since initial relapse, years</td>
<td>3.66 (2.93)</td>
<td>3.67 (2.50)</td>
</tr>
<tr>
<td>Time since most recent relapse, years</td>
<td>0.48 (0.35)</td>
<td>0.40 (0.20)</td>
</tr>
<tr>
<td>Number of relapses in year prior to randomization</td>
<td>1.45 (1.04)</td>
<td>1.66 (0.68)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise indicated.

CMSC 2016
Alemtuzumab Retreatment Rate Was Low Through 5 Years in the African Descent Subgroup (n=32)

- 88% of patients of African descent did not receive another DMT
- In the overall CARE-MS cohort, 64% did not receive alemtuzumab retreatment since Month 12 and 95% did not receive another DMT

Retreatments Since Month 12

<table>
<thead>
<tr>
<th>No. of Retreatments Following Core Study</th>
<th>Percentage of Patients (extension population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34.4</td>
</tr>
<tr>
<td>1</td>
<td>9.4</td>
</tr>
<tr>
<td>2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Reasons for Retreatment

- Relapse only: 5% of patients
- MRI only: 25% of patients
- Relapse and MRI: 70% of patients

Retreatment criteria were ≥1 protocol-defined relapse, or ≥2 new/enlarging T2 hyperintense and/or new gadolinium (Gd)-enhancing T1 brain or spinal lesions on MRI.

CMSC 2016

Durable Effect of Alemtuzumab on Relapses Over 5 Years in Patients of African Descent

- Cumulative ARR in the alemtuzumab-treated African descent subgroup over Years 0–5 was 0.16 (95% CI, 0.10–0.26)
- 60% of patients were free from relapse in Years 3–5

CARE-MS I and II Pooled

Mean EDSS Score Was Stable Through Year 5 in Patients of African Descent

- Mean EDSS score change from baseline to Year 5 was +0.52

CARE-MS I and II Pooled

Disability Outcomes Through Year 5 in Alemtuzumab-Treated Patients of African Descent

- 6-month confirmed disability worsening: n=32
- Patients with no evidence of 6-month confirmed disability worsening, n (%)a: 23 (71.6)
- 6-month confirmed disability improvement: n=18
- Patients achieving 6-month confirmed disability improvement, n (%)a: 9 (50.0)

aKaplan-Meier estimate

CMSC 2016
Slowing of BVL Through 5 Years in Alemtuzumab-Treated Patients of African Descent

**Percentage BVL From Baseline**

- **Median BVL Change From Baseline, % (95% CI)**
  - Alemtuzumab 12 mg
  - SC IFNB-1a 44 µg

<table>
<thead>
<tr>
<th>Year</th>
<th>Core Study</th>
<th>Extension Study</th>
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<tbody>
<tr>
<td>1</td>
<td>-0.57</td>
<td>-0.54</td>
</tr>
<tr>
<td>2</td>
<td>-1.00</td>
<td>-0.59</td>
</tr>
<tr>
<td>3</td>
<td>-1.00</td>
<td>-0.99</td>
</tr>
<tr>
<td>4</td>
<td>-1.00</td>
<td>-1.14</td>
</tr>
<tr>
<td>5</td>
<td>-0.54</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

**Median Annual Brain Volume Change**

- **Median Yearly BPF Change, % (95% CI)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Core Study</th>
<th>Extension Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.54</td>
<td>-0.03</td>
</tr>
<tr>
<td>2</td>
<td>-0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- **Year 1 Year 2 Year 3 Year 4 Year 5**
- **No. of Patients**: Core Study 11 10 9 8 7; Extension Study 35 34 33 32 31

- **53% of patients received no alemtuzumab retreatment since Month 12**

*Evaluable scans were required for patients to be included in the analysis. 30 patients remained on study through Year 5.*

CARE-MS I and II Pooled

NEDA Was Attained in Many Patients of African Descent in Years 3, 4, and 5

**No Evidence of CRAD**

- **No. of Patients**: Core Study Y1 25/35 Y2 22/34 Y3 21/33 Y4 19/31 Y5 11/26
- **No Evidence of MRI Disease Activity**
- **No. of Patients**: Core Study Y1 25/34 Y2 24/31 Y3 23/30 Y4 21/29 Y5 11/25

- **53% patients received no alemtuzumab retreatment since Month 12**

*No relapses and no evidence of disability worsening.*

CARE-MS I and II Pooled

IARs in Patients of African Descent

**Infusion-Associated Reactions**

- **Patients with IARs, %**
  - Course 1: 86
  - Course 2: 71
  - Course 3: 93
  - Course 4: 25
  - Course 5: 0

- **No. of Patients**: 35 35 15 4 1

- **There were no serious IARs in patients of African descent**

CARE-MS I and II Pooled

Safety Over 5 Years in Patients of African Descent

**Adverse Events**

- **Patients of African Descent Alemtuzumab 12 mg**
  - **Patients with AE, n**
    - Years 1–2 (n=35): Any AE 34, Serious AEs 8, Any infection 27, Serious infection 2, Thyroid AEs 3, Serious thyroid AEs 0, Immune thrombocytopenia 0, Nephropathies 1, Malignancies 0
    - Year 3 (n=33): Any AE 31, Serious AEs 2, Any infection 17, Serious infection 0, Thyroid AEs 4, Serious thyroid AEs 0, Immune thrombocytopenia 0, Nephropathies 0, Malignancies 0
    - Year 4 (n=32): Any AE 28, Serious AEs 3, Any infection 19, Serious infection 0, Thyroid AEs 2, Serious thyroid AEs 0, Immune thrombocytopenia 1, Nephropathies 0, Malignancies 0
    - Year 5 (n=30): Any AE 26, Serious AEs 2, Any infection 17, Serious infection 0, Thyroid AEs 1, Serious thyroid AEs 0, Immune thrombocytopenia 1, Nephropathies 0, Malignancies 0

- **Safety profile was similar to that for the overall cohort**

CARE-MS I and II Pooled
Conclusions

- In patients of African descent, alemtuzumab had clinical and MRI efficacy comparable with that observed in the overall CARE-MS study population.
- Efficacy was durable over 5 years.
- The majority of patients (53%) did not receive alemtuzumab treatment after Month 12.
- Immunomodulation linked to lymphocyte repopulation may contribute to durability of effect.
- Further evaluation of MS patients of African descent is warranted.

Hypothesis: Alemtuzumab Mechanism of Action May Explain Durability of Effect