Alemtuzumab (ALE) Improves Disability After Switch from Other Disease Modifying Therapies in a High Disability, Treatment-Refractory Relapsing MS Cohort

Consortium of Multiple Sclerosis Centers 2015 Abstract #3485

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Background Alemtuzumab

- Anti-CD52, humanized monoclonal IgG
  - Labeled previously CAMPATH® and now Lemtrada® (Genzyme-Sanofi)
- US indication: Relapsing MS generally third line treatment
- Older cohort given 10-20-30 mg 1st course and 10mgX3 2nd
- Now given as 5X12mg infusions and 3X12 mg after 12 months
  - As needed retreatment 3X12 mg (relapse or MRI eligible)

Background: The problem of refractory MS

- Treatment-refractory MS (TRMS)
  - e.g. recurrent relapses and worsening disability on therapy
  - Widespread therapeutic nihilism and bias against therapy of “progressive” MS
  - Worsening or poor Expanded Disability Status Scale (EDSS) scores
  - Perspective may become obsolete with the scope of treatment benefit.
- Alemtuzumab (ALE)
  - an FDA-approved, humanized anti-CD52, cytotoxic monoclonal IgG
  - selective and transient lymphopenia and subsequent immune reconstitution
  - superior EDSS and Relapse outcomes over high dose IFN-beta-1a in relapsing MS.
- An early phase I/II LALE study suggested stability in patients with progressive features, and our prior retrospective reports support long-term EDSS improvement in TRMS.
  - Given risk-benefit ratio of ALE
    - Possibly appropriate for higher disability, active patients
    - Differ from relapsing lower disability, short disease duration, age, experience
      - profile of phase II/III clinical trials.
Global Multiple Sclerosis Severity Scores (MSSS) from 9,892 European patients


• Hunter et al 2009 AAN n=43, 9M 34F relapsing (n=23) or secondary progressive (n=20)
  • mean EDSS 5.5 (median 6.0, 2.5-9), disease duration median 9.0 (3-33) years,
  • MS Severity score 6.9 ± 1.9SD (range 2.6-9.8)
  • Annualized two-year relapse rate 1.3 (median 1, range 0-3).

• Results:
  • EDSS improved mean 0.4 at median 12 months,
  • 46% unchanged, 43% of patients improved mean 1.2, and 11% worsened mean 1.0.
  • EDSS at more than 12 months after first cycle improved mean 0.7 (n=13).
  • MS Severity Scores also improved (0.50).
  • Annualized relapse rate was unaltered overall (1.2, n=41), but declined 46% in those with ≥2 relapses yearly before alemtuzumab (n=12).
  • Following 15 months(n=19), annualized relapse rate still remained similar (1.4)

1 year = minor improvement
Background Retrospective Analysis #2

Hunter et al 2011 AAN

- **Patients:** 55 serial clients, 46 female, 9 male
- **Age at ALE:** Median 47 years, range 28-67 years, median ~9 years disease duration
- **Phenotypes in cohort:** Severe relapsing, progressive relapsing, transitional progressive, secondary progressive, and MS with marked MRI activity on therapy
- **Annualized Relapse Rate during prior 2 years:** 1.5 median, 1.4 mean, range 0.5-3 (excludes those receiving regular corticosteroids)
- **EDSS at ALE:** Mean 5.5 ± 1.6, Median 6.0, range 2.5-8.5

<table>
<thead>
<tr>
<th>Months at last Follow up</th>
<th>33 median, 31 mean, range 6-46</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALE Courses:</td>
<td>3 – 30, 2 – 19, 1 – 6</td>
</tr>
<tr>
<td>EDSS Change pretreatment to follow up:</td>
<td>-0.7 ± 1.2 Mean, n = 55</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.0001, Student’s paired t test</td>
</tr>
<tr>
<td></td>
<td>Median -0.5, Range -4 to +1.0</td>
</tr>
<tr>
<td>Change in EDSS at last follow up:</td>
<td>Improved 36/55 (55%) by mean</td>
</tr>
<tr>
<td></td>
<td>-1.5 EDSS, range -4 to -0.5</td>
</tr>
<tr>
<td></td>
<td>Worsened 7/55 (13%) by mean 0.6 median 0.5, range +0.5 to +1.0</td>
</tr>
<tr>
<td></td>
<td>Stable 18/55 33%</td>
</tr>
<tr>
<td>Annualized Relapse Rate Excluding patients with baseline regular corticosteroids:</td>
<td>n = 47</td>
</tr>
<tr>
<td>EDSS at ALE:</td>
<td>Mean 5.5 ± 1.6, Median 6.0, range 2.5-8.5</td>
</tr>
</tbody>
</table>

**Hunter et al AAN 2015**

- **Treatment cohort:** Entire cohort n = 29
- **Prior Interferon-beta cohort:** n = 18
- **Prior Natalizumab cohort:** n = 7

<table>
<thead>
<tr>
<th>Monthly Change (Mean ± SD):</th>
<th>n = 29</th>
<th>n = 18</th>
<th>n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 63, Range 9-60</td>
<td>63 ± 20 months</td>
<td>47 ± 20 months</td>
<td></td>
</tr>
<tr>
<td>EDSS Baseline (Mean ± SD):</td>
<td>5.1 ± 1.3</td>
<td>4.7 ± 1.0</td>
<td>6.7 ± 1.0</td>
</tr>
<tr>
<td>Median 6.5, Range 2.0 - 7.5</td>
<td>5.8, Range 2.0 - 7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS Change baseline to best follow up (Mean ± SD):</td>
<td>-0.8 ± 1.1 (improved)</td>
<td>-1.0 ± 1.1 (improved)</td>
<td>-0.6 ± 1.3 (improved)</td>
</tr>
<tr>
<td>Median -1.0, Range -3.0 to +1.0</td>
<td>Median -1.0, Range -3.0 to +1.0</td>
<td>Median -1.0, Range -3.0 to +1.0</td>
<td></td>
</tr>
<tr>
<td>MS Severity Score (Mean ± SD):</td>
<td>6.6 ± 2.1</td>
<td>6.5 ± 2.1</td>
<td>8.0 ± 1.9</td>
</tr>
<tr>
<td>Median 6.0, Range 4.6-8.8</td>
<td>Median 6.7, Range 4.8-8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last Change in MS Severity (Mean ± SD):</td>
<td>-1.6 ± 1.6 (improved)</td>
<td>-2.3 ± 1.8 (improved)</td>
<td>-1.6 ± 1.8 (improved)</td>
</tr>
<tr>
<td>(deciles Mean ± SD):</td>
<td>Median -2.3, Range -1.2 to +1.3</td>
<td>Median -2.3, Range -1.2 to +1.3</td>
<td>Median -1.0, Range -1.2 to +0.0</td>
</tr>
<tr>
<td>Annualized Relapse Rate 2 yrs pre ALE (Mean ± SD):</td>
<td>1.6 ± 0.7</td>
<td>1.6 ± 0.8</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>Median 1.5, Range 0.5-3.5</td>
<td>Median 1.5, Range 0.5-3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARR Month 1-36 post ALE Mean ± SD:</td>
<td>-0.7% ± 33%</td>
<td>-0.9% ± 30%</td>
<td>-1.3% ± 51%</td>
</tr>
<tr>
<td>n = 26</td>
<td>n = 17</td>
<td>n = 7</td>
<td></td>
</tr>
</tbody>
</table>
Background Retrospective Analysis #3 contd.

- Hunter et al AAN 2015

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Best change EDSS Below Median Mean ± SD</th>
<th>Best change EDSS Above Median Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age first ALE</td>
<td>&lt;53 yo: -1.0 ± 1.2</td>
<td>≥53 yo: -1.0 ± 1.1</td>
</tr>
<tr>
<td>Clinical Phenotype</td>
<td>RR: -0.9 ± 0.9</td>
<td>SP: -0.7 ± 1.4</td>
</tr>
<tr>
<td>Disease duration</td>
<td>&lt;8.0 yrs: -1.0 ± 1.1</td>
<td>≥8.0 yrs: -0.7 ± 1.2</td>
</tr>
<tr>
<td>Baseline EDSS</td>
<td>&lt;5.5: -0.4 ± 0.8</td>
<td>≥5.5: -1.1 ± 1.2</td>
</tr>
<tr>
<td>MSSS</td>
<td>&lt;6.9: -0.5 ± 1.1</td>
<td>≥6.9: -1.1 ± 1.2</td>
</tr>
</tbody>
</table>

Open label Refractory MS Therapy with ALE

- **Phase I retrospective and prospective:** NCT01624714: clinicaltrials.gov
  - Combination trial design
  - Retrospective data collection (EDSS/relapse/safety)
  - Prospective MSFC, EDSS, OCT, EDSS, Relapse, Safety

- **ALE-experienced Inclusion criteria**
  - Off-label treated, refractory MS clinic cohort
  - Prior treatment experience with approved disease modifying agents
  - >1 courses of prior ALE therapy

- **ALE-naive Inclusion criteria**
  - Documented relapses on therapy prior two years
  - Prior treatment experience with disease modifying agents
  - EDSS 3-7

- **Exclusion:** pregnancy, neoplasm, infection, uncontrolled autoimmunity

**Improvement despite poor prognostic factors**

**Benchmark Responses to ALE after other immunotherapy**
Method - Interim first year analysis

Phase I prospective analysis of EDSS and MSSS change following ALE.

Inclusion criteria: prior immunotherapy failure, and relapse within two years, regardless of apparent progressive features.

60 ALE-treated TRMS subjects followed prospectively:
- 30 ALE-naïve analyzed prospectively for a short-term cohort
- 30 ALE-experienced analyzed retrospectively and prospectively for a long-term cohort

Primary outcomes: Change in EDSS, MSSS following ALE.

Groups were stratified by:
- (i) median lunar months follow up (MFU) duration:
  - long-term (LT) 82 MFU (27-104, n=30) or
  - short-term (ST) 10 MFU (6-25, n=30), and
- (ii) DMD immediately before and within the prior 2 year epoch before ALE:
  - interferon-beta or glatiramer acetate (IFNGA)
  - fingolimod (FTY)
  - natalizumab (NAT).

ALE Experienced Cohort ca. 2006-2012

- Treated outside of trials with CAMPATH
- Several prior retrospective analyses, baseline data is retrospective
- Long-term, treatment responders – seek further treatment
- Prior treatment principally interferon-beta and short term natalizumab
  - combination with steroids or immunosuppressives
**ALE Naïve Cohort – ca. 2012-2014**

- “Modern era MS patients”
- Substantial prior fingolimod and longterm natalizumab

**Prospective Outcome by Follow up Cohort**

<table>
<thead>
<tr>
<th>COHORT</th>
<th>Age At ALE</th>
<th>Follow up Months (range)</th>
<th>BASELINE EDSS Mean±SD (range)</th>
<th>Change EDSS Mean±SD (range)</th>
<th>BASELINE MSSS Mean±SD (range)</th>
<th>Change MSSS Mean±SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LONG TERM</td>
<td>48 ± 9 (33-63)</td>
<td>82 (27-104)</td>
<td>5.5 ± 1.3 (2.0-7.5)</td>
<td>-1.0 ± 1.4 (-4.0 to +2.0)</td>
<td>6.49 ± 2.09 (1.70-9.63)</td>
<td>-2.34 ± 1.95 (-6.84 to +0.89)</td>
</tr>
<tr>
<td>SHORT TERM</td>
<td>49 ± 10 (33-68)</td>
<td>10 (6-25)</td>
<td>5.0 ± 1.3 (2.5-7.0)</td>
<td>-0.4 ± 1.4 (-4.5 to +1.5)</td>
<td>6.09 ± 2.16 (1.28-9.90)</td>
<td>-0.54 ± 0.97 (-2.82 to +1.16)</td>
</tr>
</tbody>
</table>

Similar to First Retrospective Cohort
# Prospective Outcome by Immediate prior DMD

<table>
<thead>
<tr>
<th>COHORT</th>
<th>Follow up Months (range)</th>
<th>Change EDSS Mean±SD (range)</th>
<th>Change MSSS Mean±SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-GA</td>
<td>82 (12-104)</td>
<td>-0.9 ± 1.4 (-4.0 to +2.0)</td>
<td>-2.24 ± 1.97 (-6.84 to +1.02)</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>10 (6-25)</td>
<td>-0.4 ± 1.0 (-2.0 to +1.0)</td>
<td>-0.53 ± 1.06 (-2.82 to +1.16)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>49 (6-99)</td>
<td>-0.5 ± 1.5 (-3 to +1.5)</td>
<td>-1.24 ± 2.05 (-5.0 to +0.89)</td>
</tr>
</tbody>
</table>

N.B. These groups are exclusive

# Outcome by DMD within prior two years

<table>
<thead>
<tr>
<th>COHORT</th>
<th>Follow up Months (range)</th>
<th>Change EDSS Mean±SD (range)</th>
<th>Change MSSS Mean±SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-GA</td>
<td>61 (6-103)</td>
<td>-0.8 ± 1.4 (-4.0 to +2.0)</td>
<td>-2.24 ± 1.97 (-6.84 to +1.02)</td>
</tr>
<tr>
<td>Fingolimod/FTY n=14</td>
<td>14 (6-36)</td>
<td>-0.4 ± 1.0 (-2.0 to +1.0)</td>
<td>-0.61 ± 1.06 (-2.17 to +1.16)</td>
</tr>
<tr>
<td>Natalizumab n=29</td>
<td>29 (6-99)</td>
<td>-0.2 ± 1.5 (-3.0 to +2.0)</td>
<td>-0.59 ± 1.36 (-5.0 to +1.16)</td>
</tr>
<tr>
<td>Transition from Nat. to FTY to ALE n=10</td>
<td>12</td>
<td>-0.4 ± 1.2 (-2.0 to +1.0)</td>
<td>-0.57 ± 1.07 (-2.17 to 1.16)</td>
</tr>
</tbody>
</table>

N.B. These groups are not exclusive.
Conclusions

• Length of follow up important in assessing ALE response
• Short term (<1 year) improvements smaller
• ALE equals immunotherapeutic rescue for most TRMS patients
  • group-wise EDSS and MSSS stability or improvement,
    • notwithstanding other recent, effective, and even aggressive, prior therapies.
• Further analysis required to ascertain effects of prior therapy
• Improvement favors treatment of high disability TRMS
• Benchmarks outcomes following ALE for TRMS after standard immunotherapy
• Possible ongoing long-term sustained disability improvement 5-8 years, regardless of prior immunotherapy

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