Short-Term Response is not Predictive of Long-Term Response to Acetylcholinesterase Inhibitors in Old Age Subjects with Alzheimer's Disease: A "Real World" Study

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Berlin, 4th October 2017
... AN AGING WORLD ...
Dementia in the oldest old: a multi-factorial and growing public health issue

Gardner Raquel C, et al. 2013 - Department of Neurology, Memory and Aging Center, University of California, San Francisco

…. despite the fact that the oldest old represent the largest and fastest growing population with dementia, the majority of dementia research focuses on the younger old. An improved understanding of dementia in this oldest population is therefore of urgent national and global importance.
Hypothetical model of the pathophysiological cascade in AD

Sperling RA et al., Alzheimers Dement. 2011
Alzheimer’s disease drug development pipeline: 2017

Jeffrey Cummings*, Garam Lee*, Travis Mortsdorf*, Aaron Ritter*, Kate Zhong*

28 Agents in Phase III

- Neurotransmitter based: 32%
- Anti-amyloid: 18%
- Anti-amyloid BACE Inhibitor: 14%
- Metabolic: 11%
- Anti-Tau: 4%
- Anti-amyloid Immunotherapy: 21%
CHOLINESTERASE INHIBITORS/MEMANTINE

Aprahamian et al, 2013
USE OF CHEIs

- Some guidelines recommend **discontinuation** of treatment in patients without an initial response, as evaluated three or six months after start of therapy.
- AD response to ChEI treatment has been shown to differ among **age ranges**.
- Younger patients (≤75 years old) have a better response in term of cognitive and functional abilities as compared with the older ones.
- Therapeutic indications can be uncertain in **very old subjects** affected by AD.

*Bullock R et al. Curr Med Res Opin 2006; Droogsma E Int Psychogeriatrics 2015*
AIM OF THE STUDY

We aimed at investigating the relationship between the initial cognitive and functional response to treatment with ChEIs and the subsequent long-term course in subjects with AD stratified by age ranges in a “real life” setting.
Materials and Methods

- Retrospective longitudinal study
- Subjects over 65 years old («young old» and «old old»)
- Responders vs Non Responders (after 3 months of treatment)
- Pearson $\chi^2$
- Student’s $t$ test
- Repeated-measure ANOVA
- $p<0.05$

- 628 old age subjects with mild or moderate AD
- Cognitive and functional assessment after 3 months and then every 6 months

- MMSE (Folstein et al., 1975)
- ADL (Katz et al., 1963)
- IADL (Lawton & Brody, 1969)
# RESULTS

Demographic and clinical characteristics of all sample (n=628) stratified by age (young-old ≤ 75 and old-old≥76 years)

<table>
<thead>
<tr>
<th></th>
<th>≤ 75 years (n=233)</th>
<th>≥76 years (n=395)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (F/M)</strong></td>
<td>159/74</td>
<td>285/110</td>
<td>0.319*</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td>5.8±3.6</td>
<td>5.0±3.3</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Family risk n (%)</strong></td>
<td>69 (29.6)</td>
<td>77 (19.4)</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td><strong>Age at onset (years)</strong></td>
<td>65.5±9.2</td>
<td>79.2±4.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Disease duration (years)</strong></td>
<td>1.7±2.8</td>
<td>1.2±1.7</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>MMSE T0</strong></td>
<td>17.9±4.4</td>
<td>19.4±4.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>ADL T0</strong></td>
<td>5.3±1.0</td>
<td>4.5±1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>IADL T0</strong></td>
<td>4.3±2.1</td>
<td>2.9±2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Follow up (months)</strong></td>
<td>47.1±26.6</td>
<td>39.3±24.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Chi-Square=1.082, ** Chi-Square=17.785
Responder: MMSE unchanged/improved after 3 months of treatment

Non responder: MMSE declined after 3 months of treatment
Repeated-measure ANOVA controlled for age, gender and education

In the long run, subjects considered as non-responders showed a lower rate of cognitive decline as compared with responders, with a mean annual decline at MMSE of 1.0 point versus 1.6 points (p<0.0001).
Repeated-measure ANOVA controlled for gender and education

In the long run, old-old subjects showed a lower rate of cognitive and functional decline as compared with young old, with a mean annual decline at MMSE of 1.0 point versus 1.32 points (p=0.004)
In the long run, old-old non responder subjects showed a lower rate of cognitive and functional declines as compared with other groups.
Logistic regression having progression of disease as dependent variable

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<th>B</th>
<th>OR</th>
<th>IC 95%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.054</td>
<td>0.948</td>
<td>0.915-0.982</td>
<td>0.003</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.643</td>
<td>0.526</td>
<td>0.279-10.992</td>
<td>0.047</td>
</tr>
<tr>
<td>Education (years)</td>
<td>-0.006</td>
<td>0.994</td>
<td>0.923-1.070</td>
<td>0.883</td>
</tr>
<tr>
<td>MMSE T0</td>
<td>0.081</td>
<td>1.084</td>
<td>1.012-1.161</td>
<td>0.021</td>
</tr>
<tr>
<td>ADL T0</td>
<td>0.110</td>
<td>1.116</td>
<td>0.864-1.441</td>
<td>0.401</td>
</tr>
<tr>
<td>IADL T0</td>
<td>-0.149</td>
<td>0.861</td>
<td>0.737-1.007</td>
<td>0.061</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>1.317</td>
<td>3.733</td>
<td>2.143-6.502</td>
<td>&lt;0.0001</td>
</tr>
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</table>
Conclusions

- Older age, independent of multiple covariates is associated with lower probability of early response to treatment.
- In the long run, those considered non responders showed a lower rate of cognitive decline as compared with initial responders.
- Slower decline in cognitive and functional status in old-old patients.
- Older age, independent of multiple covariates is associated with lower progression of disease.
Older age, independent of multiple covariates is associated with lower probability of early response to treatment. In the long run, those considered non responders showed a lower rate of cognitive decline as compared with initial responders.

Conclusions

1. Don’t stop treatment in absence of an initial response

2. Treat the old-old patients!
In collaboration with:

- Amalia Cecilia Bruni
- Nicoletta Smirne
- Alessandra Clodomiro

Perugia

Thanks for attention!

Lamezia Terme