Study Type: POEM

Purpose: Does vitamin E or donepezil delay the clinical diagnosis of AD in subjects with amnestic form of mild cognitive impairment?

Study Duration: 3 year trial

Trial Design: double-blinded, placebo-controlled, intention-to-treat, multicenter (69 sites in USA and Canada)

Drug: 2000 units of vitamin E + placebo donepezil vs 10 mg donepezil + placebo vitamin E vs placebo vitamin E and donepezil - all groups got an MVI

Patients: 769 patients, mean age ~73, ~45% female, ~55% with APOE allele, MMSE = 27, ADAS cog = 11, CDR score = 1.8, global GDS = 2.7, ADL’s = 46

Inclusion: amnestic form of mild cognitive impairment, MMSE of 24 to 30, age 55 to 90

Exclusion: published on-line

Outcome Scores:
Primary end point: diagnosis of probable AD defined by specific clinical criteria
Secondary measures: MMSE, ADAS-cog, global CDR, ADCS Mild Cognitive Impairment ADL Scale, other neuropsychological test

1. Are the results valid?
   * randomized? yes
   * double-blinded? yes
   * were groups similar? yes
   * allocation concealment? yes
   * all patients accounted for? yes

2. What were the results:
   Primary Outcomes
   * 214 patients progressed to dementia with 212 being classified as probable AD. The overall rate of progression was 16%.
   * Neither treatment, as compared to placebo, was different in the rate of progression to AD.
   * Progression to AD was lower in the donepezil group than the placebo group for first year only (p = .04, ARR = 8.4%, NNT = 12). This did not persist at 36 months.
   * Those with the APOE allele were more likely to progress to AD and respond to donepezil.

   Secondary Outcomes
   * MMSE scores decreased by ~2.5 points in either group at 36 months
   * few differences in scores between vitamin E and placebo
   * scores were better in donepezil group, but clinical benefit is not assessed, the scores were not statistically significant

Adverse Event

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Donepezil</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>ARI</th>
<th>NNH Donepezil vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>16.7%</td>
<td>10.2%</td>
<td>6.6%</td>
<td>10.1%</td>
<td>10</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>16.3%</td>
<td>1.2%</td>
<td>1.9%</td>
<td>14.4%</td>
<td>7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10.8%</td>
<td>3.1%</td>
<td>1.9%</td>
<td>8.9%</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.4%</td>
<td>1.2%</td>
<td>1.9%</td>
<td>6.5%</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>6.8%</td>
<td>0.4%</td>
<td>1.6%</td>
<td>5.2%</td>
<td>19</td>
</tr>
<tr>
<td>Arthritis</td>
<td>5.2%</td>
<td>2.0%</td>
<td>1.6%</td>
<td>3.6%</td>
<td>28</td>
</tr>
</tbody>
</table>

3. Will the results help me?
   * Point differences between drug- and placebo-treated patients on quantitative scales do not necessarily indicate that these effects are clinically relevant.

Conclusion: Vitamin E does not slow progression of mild cognitive impairment to AD. Donepezil provides an early benefit to 1 out of 12 patients during the first year. This benefit is gone by 3 years. Those with the APOE allele had the best benefit from donepezil.