Serum VEGF levels are associated with cognition and functioning in AD: Influence of the treatment with Cerebrolysin and donepezil

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Background

Vascular endothelial growth factor (VEGF) is an angiogenic growth factor showing neuroprotective, neurotrophic and cognitive effects in experimental conditions that might be relevant for the treatment of Alzheimer’s disease (AD) patients, but changes in circulating VEGF and the interactions of VEGF with clinical responses after drug treatment have not been investigated in AD.

Materials and Methods

Serum VEGF levels, cognitive and functional performance were evaluated in AD patients treated with Cerebrolysin (n=52), donepezil (n=52), or a combination of both drugs (n=53) in a 28-week double-blind, randomized clinical trial. VEGF levels were measured in serum samples by using specific ELISA kits for VEGF165 in serum samples obtained at baseline, at week-16 (end of active Cerebrolysin treatment) and at week-28 (endpoint).

Results

Overall, there were no significant treatment effects on VEGF levels (Table 1).

Table 1. Effects of Cerebrolysin, donepezil and combined therapy on VEGF serum levels in AD patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline VEGF</th>
<th>Week-16 VEGF</th>
<th>Week-28 VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrolysin</td>
<td>310±72</td>
<td>252±49</td>
<td>245±43</td>
</tr>
<tr>
<td>Donepezil</td>
<td>372±138</td>
<td>363±117</td>
<td>362±106</td>
</tr>
<tr>
<td>Combination</td>
<td>304±135</td>
<td>392±284</td>
<td>376±284</td>
</tr>
</tbody>
</table>

*p<0.05 and **p<0.01 vs Donepezil.

In moderately severe AD cases:

- The combination therapy reduced elevated VEGF levels significantly (p<0.05) at week-16 and week-28 as compared to donepezil alone (Figure 1).
- Higher baseline VEGF levels were associated to improvements in cognition (ADAS-cog+) and functioning (ADCS-ADL) (Figure 2a,b,c)
- VEGF reductions at week-28 correlated with improvements in ADAS-cog+ praxis & executive functions (Figure 2d).
- Independently of treatment, AD patients with VEGF reductions compared to those with VEGF increases at week-28 showed better improvements in cognition and functioning at endpoint (Figure 3).

Conclusions

Elevated baseline VEGF levels were associated with improved cognition-functioning in moderately-severe AD, but VEGF reductions at endpoint were found to be associated with treatment-induced cognitive-functional improvements particularly in APOE4 AD cases, and with better praxis and executive functions in advanced cases receiving Cerebrolysin plus donepezil. These findings are indicating the influence of VEGF on cognitive-functional performance and response to therapy in AD; and suggest that VEGF increases might represent a neuroprotective response in AD, especially in advanced and in APOE4 cases.