Total plasma exchange plus replacement with 5% albumin as a new approach for the treatment of Alzheimer’s disease


Under the auspices of Grifols, Inc.
Alzheimer’s Disease Pathology

This is a term used to describe the progressive loss of structure or function of neurons, including death of neurons.

The most frequent form of neurodegenerative dementia is Alzheimer’s disease (AD).

5-10% of the subjects age >65 have AD, and is present in 45-50% of those age >85.

There will be 65.7 millions by 2030 and 115.4 by 2050 (approx. 9 -11 millions in the U.S.)

Examples of SMI-32 immunohistochemistry in layer IIIc of a CDR 0.5 case (A) and a CDR 3 case (B). Bussière et al. J Comp Neurol. 2003

Neurodegeneration

- Early stage
- Late stage

Neuropathology

- Neurofibrillary tangles
- Amyloid plaques
- Inflammation
- Lewy bodies
Examples of Experimental Therapies for Alzheimer’s Disease

Symptomatic treatments
- Cholinergic agonists (Nicotinic and Muscarinic M1 agonist)
- Anti-inflammatories
- Neurosteroids

Disease modifying treatments
- Passive and active immunizations
- Beta and Gamma Secretase inhibitors or modulators
- Insulin

Cell therapy
- Stem cell
- Gene therapy

Multiple Administration Routes

Oral/Nasal
- Cholinesterase inhibitors
- Memantine
- Rosiglitazone
- Scyllo-inositol
- Semagacestat
- Anti-inflammatories
- Insulin Nasal Spray
- Bexarotene
- Resveratrol

IV/subcutaneous
- IV-Ig
- Gantenerumab
- Bapineuzumab
- Solanezumab
- Liraglutide

Device/Surgery
- Encapsulated cell biodelivery of NGF
- Ventriculoperitoneal shunt
- Deep brain stimulation of the fornix
- Autologous fibroblasts genetically modified to express NGF into the forebrain
- Plasma exchange (albumin replacement)
Hypothesis Focuses on Reduction of Aβ by Disrupting Aβ Equilibrium Between CSF and Plasma

- The goal is to alter plasma & CSF Aβ dynamics through peripheral Aβ sequestration with albumin which has high Aβ binding affinity

- Aβ levels in plasma are a "pool" in dynamic equilibrium between peripheral and cerebral levels on the one hand and clearance on the other

- Aβ binding proteins in plasma could shift the CNS/plasma Aβ equilibrium toward the plasma and facilitate CNS Aβ clearance
Clinical Program Has Progressed from Feasibility Pilot Studies to a Phase IIb/III Trial

- **Pilot**
  - IG0502
  - Feasibility of TPE in Alzheimer’s patients

- **Pilot extension**
  - IG0502, ext.
  - Reproducibility of pilot study results

- **Phase II**
  - IG0602
  - Confirmation of pilot results in randomized, controlled study

- **Phase IIb/III**
  - AMBAR
  - IG1002; 365 subjects in Spain and US
  - Enrolling

- Adverse events were **mild** and brief in the Pilot studies.

- ADAS-cog and MMSE scores remained relatively stable during the course of the initial and extension studies.

- Preliminary results suggest that a larger trial using PE was warranted in AD patients.
## Phase II Study: Overview

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To confirm the clinical trends found in the pilot study, and to determine whether plasma exchange with 5% human albumin was able to modify the concentration of Aβ amyloid peptide in CSF in patients with AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>A multicenter, randomized (1:1), blind, controlled, parallel-group, phase II study</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>21 weeks of treatment (+ 6 months follow up)</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>42 patients with mild-moderate AD</td>
</tr>
</tbody>
</table>
| **Treatment Dosage** | 18 total plasma exchanges (TPE) with Human Albumin 5% in 3 periods:  
| Intensive period: | 2 TPE per week x 3 weeks  
| Maintenance period: | 1 TPE per week x 6 weeks  
| Maintenance period: | 1 TPE every two weeks x 12 weeks  |
| **Placebo group** | Control group: TPE were simulated (sham)                                                                                                                                                       |
| **Participant sites** | Fundació ACE (Barcelona, Spain), Hospital Gregorio Marañón (Madrid, Spain), Howard University Hospital (Washington, DC, USA), Mid Atlantic Geriatric Association (NJ, USA)  |
Treated and Placebo Arms of the Study

Enrolled Patients: 48

Screening Failures: 4
Withdraw consent: 2

Randomized: 42

Treatment Arm: 21
Withdraw consent: 2
19 included in the study
19 completed the study

Placebo Arm: 21
Withdraw consent: 3
18 included in the study
16 completed the study
# Characteristics of Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (Sham)</th>
<th>Treatment</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>18</td>
<td>37</td>
</tr>
<tr>
<td>Age</td>
<td>66.8 ± 9.0</td>
<td>67.7 ± 6.6</td>
<td>67.2 ± 6.8</td>
</tr>
<tr>
<td>Gender W/M</td>
<td>14/5</td>
<td>15/3</td>
<td>29/8</td>
</tr>
<tr>
<td>APOE-4</td>
<td>9 (47%)</td>
<td>12 (67%)</td>
<td>21 (57%)</td>
</tr>
<tr>
<td>Mean MMSE score</td>
<td>20.9 (SD: 2.7)</td>
<td>22.6 (SD: 3.1)</td>
<td>21.7 (SD: 3.0)</td>
</tr>
<tr>
<td>Mean ADAS-COG</td>
<td>23.1 (SD: 10.5)</td>
<td>18.7 (SD: 5.9)</td>
<td>20.9 (SD: 8.7)</td>
</tr>
</tbody>
</table>

Abbreviations:
MMSE, Mini-Mental State Examination
ADAS-COG, Alzheimer's Disease Assessment Scale-cognitive subscale
Central Catheter (Subclavian) in Patients Participating in the Phase II Study

Treated arm Patient

Placebo arm Patient (sham)

Catheter

Tunneled & Stitched catheter
**Aβ42 Levels in CSF During the Treatment Phase and Follow-up Period (Innotest)**

- **Axes:**
  - Y-axis: Aβ42 in pg/ml
  - X-axis: Timepoints (Baseline, Week 02, Week 08, Week 20, Week 33, Week 44)

- **Legend:**
  - Control (Orange Dashed Line)
  - Treatment (Red Solid Line)

- **Significance:**
  - Treatment vs Control: p=0.07

**Graph Analysis:**
- Baseline levels of Aβ42 are similar for both control and treatment groups.
- During the treatment phase (Week 02-20), there is a trend of decreasing Aβ42 levels in the treatment group compared to controls.
- Follow-up period (Week 33-44) shows stabilized levels for both groups, with the treatment group maintaining a slightly lower level of Aβ42 compared to controls.

The graph indicates a potential treatment effect on Aβ42 levels, with a statistically significant p-value of 0.07, suggesting a trend towards reduced Aβ42 in the treatment phase compared to controls.
T-Tau Levels in CSF During the Treatment Phase and Follow-up Period (Innotest)

Arms:
- Control
- Treatment

Week 02
Week 08
Week 20
Week 33
Week 44

Baseline

T-Tau in pg/ml

95% CI for the Mean T-Tau (Innotest) in CSF; treatment phase and follow-up period.
Plasma Aβ42 Levels During the Treatment Phase and Follow-up Period (Innotest)

Plasma Aβ42 in pg/ml

Arms:
- Control
- Treatment

Baseline Week 02 Week 08 Week 20 W33 W34

- p=0.05
- p=<0.0001
- p=0.0001
- p=0.02
- p=0.52
- p=0.86
Mini-Mental State Examination (MMSE) Score Change from Baseline

- p-values indicate statistical significance of treatment effect

### Change from Baseline MMSE Score

**Arms:**
- Control
- Treatment

**Treatment Phase:**
- Baseline
- Week 10
- Week 20

**Follow-up:**
- Week 33
- Week 44

**Improvement**

**Worsening**
Boston Naming Test (BNT) Score Change from Baseline

- p-values indicate statistical significance of treatment-by-visit effect

- Improvement
  - p=0.36
  - p=0.33
  - p=0.27

- Worsening

Arms:
- Control
- Treatment

Change from Baseline BNT Score

Baseline | Week 03 | Week 10 | Week 20 | Week 33 | Week 44
----------|--------|--------|--------|--------|--------

Treatment Phase: p=0.36
Follow-up: p=0.08, p=0.04
Semantic Verbal Fluency (SVF) Score Change from Baseline

- p-values indicate statistical significance of treatment-by-visit effect

Arms:
- Control
- Treatment

Baseline | Week 03 | Week 10 | Week 20 | Week 33 | Week 44

Treatment Phase

Follow-up

- p=0.03
- p=0.02
Rey Auditory Verbal Learning Test (RAVLT) Score Change from Baseline

- p-values indicate statistical significance of treatment effect

Arms:
- Control
- Treatment

Treatment Phase
- Week 03
- Week 10
- Week 20
- Week 33
- Week 44

Follow-up

p=0.049
Alzheimer’s Disease Cooperative Study – Activities of daily Living (ADCS-ADL): Score Change from Baseline

- p-values indicate statistical significance of treatment effect

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Score Change from Baseline</th>
<th>Improvement</th>
<th>Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>p=0.049</td>
<td></td>
<td>p=0.12</td>
</tr>
<tr>
<td>Week 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Arms:
- Control
- Treatment

p=0.07
## Selected Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (Sham)</th>
<th>Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>3 (21.4%)</td>
<td>7 (38.9%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (14.3%)</td>
<td>7 (38.9%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (7.1%)</td>
<td>0 (0)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>2 (14.3%)</td>
<td>2 (11.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (14.3%)</td>
<td>1 (5.6%)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>4 (28.6%)</td>
<td>10 (55.6%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Devise-related infections</td>
<td>1 (7.1%)</td>
<td>5 (27.8%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (7.1%)</td>
<td>2 (11.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0 (0)</td>
<td>1 (5.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>CNS disorders</strong></td>
<td>2 (14.3%)</td>
<td>4 (22.2%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Grand mal seizures</td>
<td>1 (7.1%)</td>
<td>0 (0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Partial complex seizures</td>
<td>0 (0)</td>
<td>1 (5.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Psychiatric symptoms</strong></td>
<td>5 (35.7%)</td>
<td>9 (50%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Aggression</td>
<td>1 (7.1%)</td>
<td>1 (5.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (7.1%)</td>
<td>0 (0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (14.3%)</td>
<td>4 (22.2%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Depression</td>
<td>0 (0)</td>
<td>1 (5.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Other medical devise complications</strong></td>
<td>2 (14.3%)</td>
<td>3 (16.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>0 (0)</td>
<td>2 (11.1%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Site Hemorrhage</td>
<td>0 (0)</td>
<td>1 (5.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Site Inflammation</td>
<td>1 (7.1%)</td>
<td>0 (0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Deceased</td>
<td>0 (0)</td>
<td>1 (5.6%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Conclusions

- TPE showed no statistical effect on plasma or CSF biomarkers, although plasma Aβ-42 levels in the treated group remained below those observed in the placebo group.

- There was a trend in global cognitive measures in favor of TPE treatment, but it did not reach statistical significance.

- Exploratory analyses showed an improvement in language and memory tests that persisted after the TPE treatment was discontinued.

- There was a worsening of ADLs in the TPE treated group, which subsided after the treatment phase was discontinued.

- The persistent improvement of specific cognitive measures after treatment discontinuation supports longer trials with TPE for AD patients, although there is a worsening of ADLs during the treatment phase.
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