Dementia 2

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WFN15-1092

Dementia 2

Randomized, placebo-controlled, phase 1b study of anti-beta-amyloid antibody aducanumab (BIBL037) in prodromal AD/mild AD dementia: Interim results by patient subgroup


Background: Aducanumab (BIBL037) is a human mAb against aggregated Aβ peptide being investigated as a disease-modifying AD treatment.

Objective: Present interim safety, Aβ reduction, and mini-mental state examination (MMSE) and Clinical Dementia Rating sum of boxes (CDR-sb) changes by disease stage and ApoE4 status.

Methods: In this multicenter, double-blind, placebo-controlled, multiple-dose study (PRIME; NCT01677572), patients (age 50-90 years) had positive florbetapir (Amyvid) PET scan and met clinical criteria for prodromal AD or mild AD dementia. Necessary patient/IRB approvals were obtained. Patients received aducanumab or placebo once every 4 weeks for 52 weeks in 7 arms stratified by ApoE4 status. Interim analyses include results to Week 30 (all arms) and Week 54 (placebo, 1, 3, 6, 10 mg/kg aducanumab, respectively; ApoE4 non-carriers: 0%, 0%, 9%, 11%, 17%). Dose-dependent slowing of MMSE and CDR-sb decline was observed at 1 year across disease stages/ApoE4 genotypes.

Conclusions: Dose- and ApoE4-dependent ARIA was the main safety finding. Aducanumab reduced Aβ plaques and slowed MMSE/CDR-sb decline across clinical stages and ApoE4 genotypes.

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WFN15-1153

Dementia 2

Tau oligomer antibodies as potential therapeutics for parkinson’s and other synucleinopathies

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Background: Parkinson’s disease (PD) is the second most common neurodegenerative disorder and with no effective treatments or preventative measures, its prevalence is growing. PD is characterized by cognitive and movement symptoms associated with a loss of dopaminergic neurons, synaptic dysfunction, and the presence of Lewy bodies comprised of α-synuclein. Evidence shows that smaller aggregates, oligomers, may be more toxic. Moreover, we have found that oligomeric α-synuclein coexists with tau protein in disease in a possible toxic synergy, implicating tau oligomers as a therapeutic target for synucleinopathies.

Objective: Evaluate the efficacy of a tau oligomer-specific antibody (TOMA) in a synucleinopathy mouse model.

Materials and methods: We treated seven-month-old mice overexpressing A53T mutated α-synuclein intravenously with either TOMA, an antibody for all forms of tau—Tau-13, or a control IgG and wild-type mice with saline. We tested mice on a battery of behavioral tasks assessing memory and motor function. Following testing, half of the mice were sacrificed and tissue was collected for biochemical and immunological analysis. Remaining mice were aged to 12 months and tested again.

Results: A53T mice treated with TOMA were protected from cognitive and motor deficits, while treating with Tau-13 appeared to exacerbate the phenotype. We found decreased levels of toxic tau oligomers in the brains of TOMA-treated mice. Importantly, levels of dopamine were elevated in TOMA-treated mice, as well as the synaptic protein, Synapsin I.

Conclusion: Targeting tau oligomers is beneficial for a mouse model of synucleinopathy and may be a viable strategy for treating PD.

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WFN15-1177

Dementia 2

Svedem, the Swedish dementia registry – A tool for improving the quality of diagnostics, treatment and care


Background: In Sweden, there are over 100 quality registries. There was a need to initiate a dementia registry for both memory clinics and primary care units.

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Methods: The registration is on line on webpage www.svedem.se. The descriptive statistics, limitation, strenghts especially in primary care units be discussed.

Results: The database was initiated in May 2007 and covers almost all of Sweden. There were 50 000 patients registered during 2007–2014. The role of primary care units increased in that time and helped for diagnosis of new cases.

Conclusion: SveDem provides knowledge about current dementia care in Sweden and serves as a framework for ensuring the quality of diagnostics, treatment and care across the country. The special role of primary care in dementia work up is important.

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WFN15-1276
Dementia 2

The cost of dementia: The case of chile. Results of the cuideme study
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Background: Few studies have estimated the economic cost of dementia in Latin America and there is scant research on how this cost may vary across different socioeconomic status (SES) groups.

Objective: Study the economic cost of dementia in Chile, and its variation according to SES.

Patients and methods: 391 informal primary caregivers fulfilled the RUD-Lite and a SES questionnaire. The cost is decomposed into direct medical costs (medical care, drugs, exams), direct social costs (social service, daycare) and indirect costs –mostly associated to informal care. The study was approved by the Ethical and Scientific Committee - SSMO.

Result: Mean monthly cost per patient is 915 USD. Direct medical costs account for 20 per cent of the cost; direct social costs are 5 per cent of the total and indirect costs is 75 per cent of total cost. The mean monthly cost is inversely related to SES. The monthly cost for the high SES is 696 USD while for the low SES it’s 1021 USD.

Conclusion: Direct medical costs increase with the SES of patients - reflecting differences in purchasing power-, indirect costs are inversely related to SES and more than compensate differences in medical costs. In lower SES groups, informal care is mostly provided by female caregivers who are inactive in the labor market. Compared to other HIC countries, the averaged cost is lower (10980 versus 32865 USD) and the distribution of informal cost is higher (70% versus 40%), consistent with the absence of universal coverage of dementia and a coherent public health response.

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WFN15-1410
Dementia 2

Systemic inflammation is linked to default mode network functional connectivity in mild alzheimer's disease and mild cognitive impairment
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Introduction: The default mode network (DMN) is early affected in AD. Inflammatory processes also play a role in pathological AD cascade, but its relationship with changes in the DMN is still unknown. We aimed to investigate the relationship between inflammatory cytokines and DMN functional connectivity (FC) in aMCI and AD patients.

Methods: 34 aMCI (positive CSF biomarker) and 30 mild AD patients were included. Images were acquired on a 3.0 T MRI scanner. DMN mask was used as a template to extract each patients FC value of the DMN subregions. We performed multiple regression tests, adding inflammatory cytokines and DMN regional FC as dependent variables and DMN regions FC values as dependent variables.

Results: In the aMCI group, medial parietal region FC correlated with age (p = 0.004, t = -3.38) and IL 10 (p = 0.03; t = -2.25, model R2 = 0.50). The frontal medial region FC correlated with age (p = 0.03; t = -2.23), IL 8 (p = 0.001; t = -3.71) and TNF-α (p = 0.01; t = 2.71, model R2 = 0.53) and the temporal region FC correlated with TNF-α (p = 0.001; t = 3.71) and age (p = 0.02, t = -2.47, model R2 = 0.51). Regarding the AD group, the medial temporal region FC correlated only with IL 6 (p = 0.008; t = -3.04, model R2 = 0.39).

Conclusions: We showed for the first time that systemic inflammation predicts FC in the DMN of aMCI and AD patients.

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WFN15-1495
Dementia 2

Subjective spatial navigation complaints are associated with regional brain atrophy and APOE in elderly with subjective memory impairment
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Background: Subjective memory complaints (SMC) may confer higher risk of developing Alzheimer’s disease (AD) known for its spatial navigation impairment. Whether subjective spatial navigation complaints (SSNC) associate with objective impairment in SMC subjects is unknown. We analyzed relationship between SSNC and brain atrophy in SMC compared to aMCI patients and controls.

Methods: After providing consent and study approval, consecutive patients with SMC (n = 61), aMCI (n = 60) and cognitively normal elderly (CN, n = 12) were recruited from memory clinic in Prague. All had neuropsychology, 1.5 T brain scan, APOE genotyping and 3T Structural Magnetic Imaging. All had neuropsychology, 1.5 T brain scan, APOE genotyping and SSNC questionnaire inquiring about spatial skills developed in house. Brain volumes and cortical thinning were calculated using Freesurfer. Spearman correlations between SSNC and imaging measures were assessed at alpha = 0.05.

Results: SMC patients scored worse on SSNC questionnaire than CN (p = .013), whereas aMCI patients did not (p = .14). aMCI patients had more atrophy in several regions including hippocampus, entorhinal, parahippocampal and precuneus cortex compared to CN
and SMC. However, in SMC, SSNC scores correlated with smaller hippocampi \((r_p = -0.36, p < 0.001)\), while in aMCI – perhaps anosognostic to spatial difficulties - did not. SMC E4 carriers scored worse on SSNC than SMC E4 noncarriers \((p = .04)\). SMC E4 carriers had cortical thinning in precuneus \((p = .013)\) and parahippocampus \((p = .034)\) compared to SMC E4 noncarriers.

**Results:** Particularly SMC E4 carriers are characterized by subjective spatial navigation difficulties associated with atrophy in regions implicated in both spatial navigation and AD. Asking a specific question may be a useful screening tool for subjects at risk of AD and may guide further referral of such patients.

**Conclusion:** CI and FI are highly correlated. The cognitive domains that better predict the FI (global and by areas) are Memory and Fluency. It should be noted that CI affects ADL globally and not separately. Moreover, CI has important implications for the capacity of the patients to perform ADL.

**Funding:** Fondecyt 1140423 & Basal Funds for Centers of Excellence, Project FB0003 - Associative Research Program – CONICYT - CHILE.

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**Table 1:** Percentage of hippocampal shrinkage in the different groups with respect to the total T-ADLQ score

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Score</th>
<th>Attention &amp; Orientation</th>
<th>Memory</th>
<th>Fluency</th>
<th>Language</th>
<th>Visuospatial</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMC E4 carriers</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
</tr>
<tr>
<td>SMC E4 noncarriers</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
</tr>
<tr>
<td>aMCI - anosognostic to spatial difficulties</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
</tr>
</tbody>
</table>

**Background:** Cognitive impairment (CI) is commonly associated to functional impairment (FI) over the activities of daily living (ADL). Exploring the extent to which functional impairment is related to cognitive functioning might be interesting, particularly analyzing the relationships that might be established between decline of the performance on instrumental and basic ADL and different cognitive domains.

**Objective:** Explore the correlations and predictive relationships of CI and FI measured respectively by the Chilean Addenbrooke’s Cognitive Examination Revised (ACE-R-Ch), the Frontal Assessment Battery (FAB) and the Technology – Activities of Daily Living Questionnaire (T-ADLQ).

**Patients and methods:** 48 patients with dementia, 15 with MCI and 38 HC were assessed with the ACE-R and the FAB. The T-ADLQ was answered by the principal collateral source. Statistical analyses were performed using the SPSS Inc. v.19.

**Results:** Table 1 shows the clinical characteristics of the sample and the neuropsychological test comparison between the groups. Table 2 and 3 shows the correlation and regression analyses between the different cognitive domains measured by the ACE-R, the FAB and the 7 subscales of the T-ADLQ.

**Conclusion:** CI and FI are highly correlated. The cognitive domains that better predict the FI (global and by areas) are Memory and Fluency. It should be noted that CI affects ADL globally and not separately. Moreover, CI has important implications for the capacity of the patients to perform ADL.

**Funding:** Fondecyt 1140423 & Basal Funds for Centers of Excellence, Project FB0003 - Associative Research Program – CONICYT - CHILE.

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**Table 2:** Multiple regression analyses between ACE-R and FAB and T-ADLQ total score and subscales

<table>
<thead>
<tr>
<th>T-ADLQ</th>
<th>FAB</th>
<th>Attention &amp; Orientation</th>
<th>Memory</th>
<th>Fluency</th>
<th>Language</th>
<th>Visuospatial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global functional impairment</td>
<td>8.15</td>
<td>-0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Self-care activities</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.11</td>
<td>0.1</td>
</tr>
<tr>
<td>Frontal and executive</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.11</td>
<td>0.1</td>
</tr>
<tr>
<td>Communication</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.11</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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**Introduction:** The behavioural variant of frontotemporal dementia (bvFTD) is a clinical syndrome characterized by an early and progressive deterioration of personality, social comportment and cognition (Rascovsky et al, 2011). An early detection of behavioural impairments in FTD is crucial to an accurate Early behavioural changes such as disinhibition, apathy, loss of empathy among others are some symptoms used to diagnose probable bvFTD. However, it is unknown how those first behavioural symptoms influence and modify progression and course of the disease.

**Methods:** We evaluated the neuropsychological and clinical and neuroanatomical correlates of a sample of forty-three FTD patients organized according to its first symptoms. We also collected neuropsychological and imaging data on thirty-four healthy seniors to control the analyses observed in patients.

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**Table 3:** Multiple regression analyses between ACE-R and FAB and T-ADLQ total score and subscales

<table>
<thead>
<tr>
<th>T-ADLQ</th>
<th>FAB</th>
<th>Attention &amp; Orientation</th>
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<th>Fluency</th>
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<td>0.2</td>
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<td>0.1</td>
</tr>
<tr>
<td>Frontal and executive</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.11</td>
<td>0.1</td>
</tr>
<tr>
<td>Communication</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.11</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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**doi:** 10.1016/j.jns.2015.08.114

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**doi:** 10.1016/j.jns.2015.08.115
**Discussion:** 47% of patients debuted with apathy, 42% with disinhibition and 10% with deficits in executive functions. Patients that debuted with apathy showed worst scores in neuropsychological profile (as measured by FrSBE and Hayling test among others) compared with patients that debuted with disinhibition. Severity of apathy in apathetic-debut patients correlated with atrophy in the right dorsolateral prefrontal cortex and right insula. In contrast patients that debuted with disinhibition showed atrophy in the right mediotemporal limbic structures.

**Conclusion:** First symptom in bvFTD patients is crucial to describe the course and neuropsychological impairments. Our results show that impairments in complex social behaviors represented in the prefrontal and mesolimbic structures are also involved in course and prognosis of the bvFTD.

doi:10.1016/j.jns.2015.08.116