Tau-C. The IP products were analyzed by Western blot as well as with SDS-PAGE by using silver staining. The bands from the SDS-PAGE analysis were excised, in-gel digested with trypsin and identified by LC-MS/MS. The measured Tau-C levels by our in-house ELISA assay were 35.87 ng/mL for the AD patients and 14.7 ng/mL for the healthy controls. **Results:** The Western blot analysis detected bands at 52-64 kDa for IP products from AD patients when using our in-house antibody. No bands were detected for the IP products from the healthy controls. The SDS-PAGE analysis showed bands in the range 31-64 kDa for the IP products from AD patients. For the healthy controls bands were only detected at 64 kDa but the intensity of these was much lower when compared to the AD patients. The LC-MS/MS results of the IP products from AD patients identified the 64 kDa band from the SDS-PAGE gel as Tau-C. No significant LC-MS/MS results were obtained for the IP products from the healthy controls. **Conclusions:** Immunoprecipitation in combination with LC-MS/MS showed the presence of Tau-C in the serum of Alzheimer's patients. This shows a potential for the developed ELISA assay to be used for the diagnosis and/or prognosis of Alzheimer's disease but further analyses are needed.

WEDNESDAY, JULY 16, 2014
ORAL SESSIONS
O4-11
CLINICAL TRIALS II: ANTI-AMYLOID AND INFLAMMATION

O4-11-01 RELATIONSHIP BETWEEN CEREBROSPINAL FLUID (CSF) BIOMARKERS AND COGNITIVE PERFORMANCE OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT (MCI) AFTER LONG-TERM TREATMENT WITH CHF5074

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Background: CHF5074 is a newly identified microglial modulator previously shown to lower CSF levels of sCD40L and TNF-alpha in a 14-week, double-blind, placebo-controlled study in 96 MCI subjects. We measured CSF biomarkers, verbal memory and executive function in a subgroup of these individuals after prolonged treatment with CHF5074. **Methods:** Subjects were given the option to enter a 26-week followed by another 50-week open label extension study. Individuals received CHF5074 at the dose equal to that of their originally assigned in the double-blind study (200, 400 or 600 mg/day). Cognition was measured at Screening (Week -2), Baseline (Day -1), and at 12, 14, 26, 38, 52, 64, 76, 88 and 90 weeks. CSF biomarkers (Aβ42, tau, phospho-tau, sCD40L, TNF-alpha) were measured at Weeks 12 and 38. **Results:** Cognitive tests evaluated at Week 90 (n=42) showed statistically significant improvements compared to Baseline on Digit Symbol Substitution (+6.4±1.3 matches, $p<0.001$), Trail Making A (median -9 sec, $p<0.01$) and B (median -12 sec, $p<0.01$), Immediate Word Recall (+4.1±0.7 words, $p<0.01$) and Delayed Word Recall (+1.5±0.3 words, $p<0.01$). CSF tau levels measured at Week 38 (n=37) showed significant ($p=0.021$) dose-dependent linear trends (68.0±7.4, 57.4±5.7 and 42.7±8.0 pg/mL in the 200 mg/day, 400 mg/day and 600 mg/day groups, respectively). The mean tau values in the 600 mg/day group was significantly lower than those measured in the 200 mg/day group (-37%). Similar dose-related trends were found for phospho-tau. The other CSF biomarkers at Week 38 did not show significant difference between treatment groups. At Week 12, CSF tau levels correlated linearly with Trail Making B ($r=0.599, p<0.001$), Immediate Word Recall ($r=0.436, p=0.002$) and Delayed Word Recall ($r=0.306, p=0.035$) and predicted corresponding changes in cognitive scores at Week 90 ($r=0.523, p=0.005$, $r=0.545, p=0.003$ and $r=0.430, p=0.025$, respectively). Cognitive scores of Trail Making Test B and Delayed Word Recall at Week 90 were also predicted by tau levels measured at Week 38 ($r=0.489, p=0.009$ and $r=0.461, p=0.016$, respectively). **Conclusions:** Long-term treatment with CHF5074 (200-600 mg/day) was dose-dependently associated with a reduction in CSF tau levels in MCI subjects. CSF tau levels correlated with sustained cognitive benefit in executive function and verbal memory for up to 90 weeks.

O4-11-02 THE SAFETY AND TOLERABILITY OF ETANERCEPT IN ALZHEIMER'S DISEASE (STEADI-09): A PHASE II DOUBLE BLIND RANDOMISED PLACEBO CONTROLLED TRIAL

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Background: We have previously shown that acute and chronic systemic inflammation, associated with modest increases in peripheral levels of Tumour Necrosis Factor α (TNFα), is associated with an increased decline in cognition and an exaggeration of neuropsychiatric symptoms in subjects with Alzheimer's Disease. We hypothesised that the use of a TNF α receptor blocker (Etanercept) might, if safe and well tolerated, be worth examining for beneficial cognitive and behavioural outcomes in an AD population. **Methods:** Patients with mild to moderate AD were randomised to subcutaneous Etanercept (50mg) once weekly or to identical placebo (water) over a 6 month period with a one month wash out. Safety and tolerability of this medication was recorded with secondary exploratory outcomes of cognition (ADAS-COG; MMSE), behaviour (NPI); activities of daily living (BADLS) and clinical and carers global impressions of change measured at baseline; 3 months and 6 months. **Results:** 67 patients were screened of whom 26 failed to meet the inclusion or exclusion criteria (most exclusions were due to prior TB exposure). 41 subjects were randomised (20 Etanercept and 21 Placebo). Etanercept was well tolerated by this group with few adverse events or safety concerns. Two subjects from the Etanercept arm and six from the placebo arm failed to complete the study. Subjects in the placebo arm showed evidence of a greater rate of decline in measures of cognition, behaviour and activities of daily living compared with subjects in the Etanercept arm at 6 months who remained largely unchanged compared with baseline measures. **Conclusions:** This study shows good tolerability and safety of Etanercept in the subjects with Alzheimer's Disease. This study is also supportive of beneficial cognitive, behaviour and activities of daily living in subjects taking subcutaneous Etanercept.

O4-11-03 A PROINFLAMMATORY ENDOPHENOTYPE PREDICTS TREATMENT RESPONSE IN A MULTICENTER TRIAL OF NSAIDS IN AD

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Background: Epidemiological studies suggest that reducing inflammation through use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with decreased risk of Alzheimer 's disease (AD). However, a recent multicenter clinical trial in mild-moderate AD conducted by the Alzheimer's Disease Cooperative Study (ADCS) failed to demonstrate

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Alzheimer's & Dementia

SATURDAY, JULY 12, 2014
ALZHEIMER'S IMAGING CONSORTIUM (IC)
IC-01
LIFESTYLE AND RISK FACTORS

IC-01-01 PHYSICAL ACTIVITY MODIFIES ALZHEIMER'S BIOMARKERS IN PRECLINICAL AD: EVIDENCE FROM THE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION

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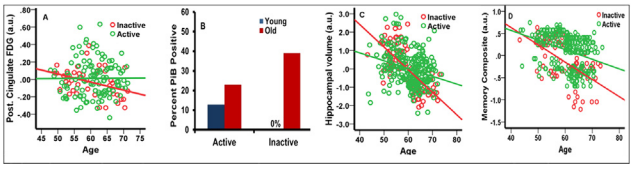
Background: Without effective therapies, the number of persons living with Alzheimer's disease (AD) is projected to increase exponentially owing to the rapid growth in the elderly segment of the United States' population. To thwart this public health epidemic that AD is poised to become, there is a critical need to uncover preventative approaches capable of curbing the progression of the underlying disease process and thereby delaying the onset of overt symptoms. This study examined whether engagement in physical activity might favorably alter the age-dependent evolution of AD-related brain and cognitive changes in a cohort of at-risk, late-middle-aged adults. **Methods:** Three hundred and seventeen enrollees in the Wisconsin Registry for Alzheimer's Prevention (age= 60.29±6.29 years, 68% women, 40% APOE4 carriers, and 74% with family history of AD) underwent T1 MRI; and a subset also underwent PiB-PET (n=186) and FDG-PET (n=152) imaging. Their responses on a self-report measure of current physical activity were used to compute MET-hours/week scores. These scores were then used to classify the participants as either Physically Active or Physically Inactive based on American Heart Association guidelines. The participants also completed a comprehensive neuropsychological battery that assessed 6 domains: Immediate Memory, Verbal Learning & Memory, Working Memory, Speed & Flexibility, Visuospatial Ability, and Verbal Ability. Regression analyses were used to test whether the known effect of age on AD biomarkers and cognition was modified by physical activity, after controlling for relevant covariates. **Results:** There were significant age–physical activity interactions for hippocampal volume (p=.025), amyloid burden (p=.015), and glucose metabolism (p=.015) such that, with advancing age, Physically Active individuals had reduced hippocampal degeneration, slower accumulation of amyloid, and attenuated glucose hypometabolism compared with the Physically Inactive. Similar age–physical activity interactions were also observed on cognitive domains of Immediate Memory, Visuospatial Ability, and Verbal Ability. **Conclusions:** In a middle-aged, at-risk cohort, engagement in physical activity is associated with an attenuation of the deleterious influence of age on key AD biomarkers. Randomized controlled trials in such risk-enriched cohorts, with longitudinal follow up, would help clarify the extent to which midlife participation in structured physical exercise protects against the development of AD and related disorders in later life.



Age-associated glucose hypometabolism (a), amyloid deposition (b), hippocampal shrinkage (c), and memory decline (d) are attenuated in physically-active subjects but pronounced in inactive subjects. P values for interaction are .025, .015, .015, .042 respectively.

IC-01-02 AMYLOID ACCUMULATION IN EARLY AND MIDDLE ADULTHOOD: THE IMPACT OF LIFE EXPERIENCE

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Background: Increasing evidence indicates that lifestyle factors such as high levels of education and lifetime cognitive activity predict lower levels of amyloid deposition in healthy older adults, suggesting these experiences may confer protection against accumulation. Little is known, however about amyloid in young and middle age. We assessed whether there were reliable increases in amyloid deposition in 266 healthy adults from 30 to 89, and primarily focused on identifying variables that predicted amyloid accumulation in those aged 30 to 59. **Methods:** Data were analyzed from a sample of 266 healthy adults, aged 30-89 from the Dallas Lifespan Brain Study who received PET with florbetapir. Eight bilateral ROIs were normalized to cerebellar hemispheres to estimate the mean cortical standardized uptake value ratio (SUVR). Twenty eight subjects with elevated amyloid were isolated using an iterative outlier method. Using GLM, age, education, lifetime cognition, and APOE 4 carrier status were used to predict mean cortical SUVR in separate samples of non-elevated middle aged adults 30-59 (n=81), non-elevated older adults aged 60-89 (n=157) and all older adults including those with elevated amyloid (n = 176). **Results:** We found that age, APOE 4 status and lifestyle variables had the strongest effects on non-elevated amyloid in middle age. Most notably, higher age (p<.001) and low lifetime cognition in 4 carriers (p=.001) predicted higher SUVR in the middle-aged group. In older adults without elevated SUVR, only trend significant effects of lifetime cognition (p=.06) and a lifetime cognition x Education interaction (p=.056) were detected. If elevated SUVR subjects were included, age, APOE, education and lifetime cognition all interactively predicted SUVR, most notably with increasing amyloid across age for older adults with low but not high lifetime cognition (p<.001). **Conclusions:** Meaningful amounts of amyloid begin to accrue in middle-aged adults and accumulation is modified by both genetics and experiences, despite no evidence for accumulation at "preclinical" amyloid levels. These results suggest that amyloid systematically increases in vulnerable individuals beginning in young adulthood and that early experiences could modify accumulation and play a key role in delaying dementia onset.