an Ounce of Prevention

ALZHEIMER'S PREVENTION THROUGH DELAY FALL 2008

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PREVENTION HIGHLIGHT

NATIONAL MEMORY SCREENING DAY: NOVEMBER 18

November 18 is a National Memory Screening Day. It is a collaborative effort lead by the Alzheimer's Foundation of America (AFA) to promote early detection of Alzheimer's disease and related illnesses, and to encourage appropriate intervention.

AFA collaborates with organizations and healthcare professionals across the U.S. and offer free confidential memory screenings, as well as follow up resources and educational materials to those concerned about memory loss.

For further information, please visit: www.nationalmemoryscreening.org.

ALZHEIMER'S CLINICAL TRIAL UPDATE

This summer at the 11th International Conference on Alzheimer's Disease (**ICAD**), several clinical trial updates were presented.

TARENFLURBIL (FLURIZAN®)

Myriad Pharmaceutical Inc.

Tarenflurbil is a selective amyloid-beta 42 (**Abeta42**) lowering agent that modulates gamma-secretase activity to preferentially reduce production of Abeta42 in vivo and in vitro. Results from an 18-month multi-center phase III trial were presented by Dr. Robert Green from Boston University School of Medicine. The trial was conducted at 133 sites in the United States and 1684 people with mild Alzheimer's disease (**AD**) participated. While positive treatment efficacy was seen in mild AD patients in its phase II trial, phase III trial did not meet expected clinical end points on the ADAS-Cog, MMSE, ADCS-ADL and NPI. Further development on tarenflurbil was discontinued.

BAPINEUZUMAB (AAB-001)

Elan Pharmaceuticals / Wyeth Pharmaceuticals

Bapibeuzumab (AAB-001) is a fully-humanized monoclonal antibody raised against the N-terminus of Abeta, and its phase I trial has demonstrated an acceptable safety profile and tolerability in patients with mild-to-moderate AD. In an 18-months phase II trial, 234 patients were randomized to receive one of four doses of bapineuzumab (0.15 mg/kg (n=31), 0.5 mg/kg (n=33), 1.0 mg/kg (n=30) or 2.0 mg/kg (n=30)) or placebo (n=110) by intravenous infusion every 13 weeks.

Results, presented by Dr. Michael Grundman from Elan Pharmaceuticals, show that statistical significance was not obtained on the pre-specified efficacy endpoints of ADAS-cog and DAD in the total study population. However, post-hoc efficacy analyses have shown that trends in favor of bapineuzumab treated patients were observed on the ADAS-cog and NTB in the total 229 patients in a modified intent-to-treat population. Additionally, in the ApoE4 non-carrier patients, statistically significant differences from baseline to week 78 were observed in favor of bapineuzumab treated patients on both cognitive and functional efficacy endpoints while ApoE4 carrier did not show such differences. Phase III trial of bapineuzumab is currently underway.

SB-742457

GlaxoSmithKline

SB-742457, a novel 5-hydroxytryptamine 6 receptor antagonist, has been shown to enhance cognitive function in aged rats. In its 24-week phase II trial, 371 patients with mild-to-moderate AD were randomized to 5 mg/day (n=62), 15 mg/day (n=62), 35 mg/day (n=121), or placebo (n=123). Results were presented by Dr. Gareth Maher-Edwards from GlaxoSmithKline.

There was no placebo decline for CIBIC+ or ADAS-cog after 24 weeks. Linear trend analysis at week 24 LOCF for both primary endpoints suggested a dose response (CIBIC+, p=0.016; ADAS-cog, p=0.059). There was a significant improvement in CIBIC+ (global functioning) in the SB-742457 35 mg/day group compared with the placebo group (-0.31; p=0.047). The difference between SB-742457 35mg and placebo in change from baseline in ADAS-cog was not statistically significant (-1.28; p=0.135). An exploratory subgroup analysis of ADAS-cog showed greater, but not statistically significant, improvements compared to placebo in subjects with baseline MMSE <=18 (-1.73) compared to subjects with baseline MMSE >18 (-0.42).

METHYLTHIONINIUM CHLORIDE (MTC, REMBER™)

Tau Rx Therapeutics Ltd.

Methylthioninium chloride (**MTC**) has been shown to dissolve tau polymers isolated from AD brain, and to prevent tau aggregation in cell models at the nanomolar range. MTC has also shown, in tau transgenic animal models, to improve cognitive and other behavioral function, and to reverse tau pathology in the brain.

An exploratory, dose-range finding, parallel design, double-blind, randomized, placebo-controlled trial of MTC monotherapy was conducted in 332 subjects meeting DSM-IV and NINCDS-ADRDA for probable AD in UK and Singapore. Dr. Claude M. Wischik from the University of Aberdeen in United Kingdom reported the results. In the pre-specified analyses at 24 weeks, MTC produced a significant improvement compared to placebo on the ADAS-Cog in patients with moderate AD at dose 60 mg tid. While there was no placebo

decline in patients with mild AD for the first 24 weeks preventing efficacy analyses, treatment efficacy was seen in a SPECT study. Over all, MTC stabilized the progression of AD over 50 weeks in both mild and moderate AD. The overall effect size was -6.8 ADAS-Cog units. This is the first study to show tau aggregation inhibitor therapy is a viable disease-modifying treatment for mild-to-moderate AD.

RESEARCH UPDATES

ALZHEIMER'S: CURRENT ATTITUDES, PERCEPTIONS AND KNOWLEDGE

A new survey revealed disparities between beliefs and behavior in pursuing Alzheimer's screening and diagnosis. The results demonstrate the urgent need for increased education and awareness of disease symptoms and benefits of early diagnosis and treatment.

The online survey of 1,040 U.S. adults over 55 years old was conducted by Harris Interactive and commissioned by the Alzheimer's Disease Screening Discussion Group (ADSDG), a consortium of multi-disciplinary experts in Alzheimer's disease (AD) and senior health.

In the survey, almost 95% agree that they would encourage a loved one to seek early diagnosis upon suspecting signs of AD. However, of 34% who thought their loved one had the disease, only one-quarter prompted that person to take an AD screening and less than 40% encouraged them to seek conversation with doctors. The survey also found that more than 90% could not accurately distinguish early disease symptoms from late disease symptoms or symptoms unrelated to AD although 78% believe that they could notice the signs of AD in themselves or a loved one. Moreover, almost one-third are not aware that there are AD medications currently available and about 85% of those who are aware about the medications do not understand how treatment works.

Alzheimer's Disease Screening Discussion Group (www.seethesigns.com), 2008.

PHYSICAL ACTIVITY AND COGNITION IN OLDER ADULTS AT RISK FOR AD

A randomized controlled trial of a 24-week physical activity intervention was conducted between 2004 and 2007 to determine whether the intervention can reduce the rate of cognitive decline among older adults at risk for Alzheimer's disease.

A total of 170 people over 50 years old with self-reported memory problems were randomized and 138 participants completed the 18-month assessment. All participants did not meet criteria for dementia at baseline. Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity. The intervention group improved 0.26 points on the ADAS-Cog at the end of the intervention, while the usual care group deteriorated 1.04 points. The absolute difference on the outcome measure between the intervention and control groups was -1.3 points at the end of the intervention. At 18 months, the intervention group improved 0.73 points on the ADAS-Cog while the usual care group improved 0.04 points. Word list delayed recall and Clinical Dementia Rating Scale sum of boxes improved modestly whereas cognitive

assessments such as word list total recall, digit symbol coding, and verbal fluency did not change significantly.

This study was conducted in metropolitan Perth, Western Australia, and by Dr. Nicola Lautenschlager and his colleagues from Academic Unit for Psychiatry of Old Age, University of Melbourne.

Lautenschlager NT, et al. JAMA 2008; 300(9):1027-37.

PHYSICAL FRAILTY IN ELDERY ASSOCIATED WITH AD PATHOLOGY

Researchers from Rush Alzheimer's Disease Center, Ruth University Medical Center, Chicago, IL, studied brain autopsies from 165 cases from the Rush Memory and Aging Project, and examined association between physical frailty in older persons and common age-related brain pathology including Alzheimer's disease (AD), cerebral infarcts and Lewy body disease.

Physical frailty was measured annually in those 165 cases based on grip strength, time to walk 8 feet, body composition and fatigues. Multiple regression analyses were used to examine the relation of postmortem (mean age at death = 88.1 with SD=5.7) neuropathologic findings to frailty proximate to death, controlling for age, gender and education.

The level of AD pathology was associated with frailty proximate to death regardless of a presence of dementia, accounting for 4% variance of physical frailty, while neither cerebral infarcts nor Lewy body disease pathology was associated with frailty.

Buchman AS, et al. Neurology 2008; 71(7): 499-504.

THE IMPORTANCE OF DAYTIME MOVEMENTS IN ELDERY

Dr. Deborah E. Barnes and her colleagues from University of California San Francisco studied the relationship between daytime movements and cognitive functions. 2736 older women (mean age of 83±4) without evidence of dementia participated in the study; 10% were African American.

Daytime movement was assessed using actigraphy, which involved wearing a watch-like device that objectively quantified accelerometer motion over a mean of 3.0±0.8 days. Cognitive function was measured using the Trail-Making Test, Part B (Trails B) and the Mini-Mental State Examination (MMSE). Cognitive impairment was defined as performing 1.5 standard deviations (SDs) worse than the mean on a given test.

Results show that, after adjustment for age, race, and education, the highest movement quartiles had better mean cognitive test scores (20±0.3 seconds faster on Trails B and 0.3±0.2 points higher on MMSE, both P<.001) than those in the lowest quartile, and were less likely to be cognitively impaired (odds ratio (OR)=0.61, 95% confidence interval (CI)=0.41–0.92 for Trails B; OR=0.68, 95% CI=0.44–1.07 for MMSE). These results were independent of self-reported walking, medical comorbidities, physical function, and other health-related behaviors.

Barnes DE, et al. JAGS 2008; 56(9): 1658-64.

DEMENTIA DIAGNOSIS AND BREAST CANCER SURVIVORS WHO USE CHEMOTHERAPY

To determine patterns of dementia diagnosis seen after chemotherapy treatment, Dr. Julia E. Heck and her colleagues from Departments of Epidemiology and Health and Behavior Studies, Columbia University, New York, examined the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database, ICD-9 diagnoses of dementia occurring in the years after breast cancer diagnosis.

From the SEER program, which collects information from population-based tumor registries in seven metropolitan areas (San Francisco and Oakland, Detroit, Atlanta, Seattle, Los Angeles County, San Jose and Monterey Counties, and the greater California area) and eight states (Connecticut, Iowa, New Mexico, Utah, Hawaii, Kentucky, New Jersey, and Louisiana), 18,360 women diagnosed with Stage II, III, or IV breast cancer were identified.

The results show that there were significant differences at baseline between individuals who received and did not receive chemotherapy. In the first few years after breast cancer diagnosis, dementia was more common in women who had not had chemotherapy, probably reflecting group differences at baseline. In the longer term, diagnoses of dementia were more common in women who had chemotherapy treatment (hazard ratio=1.20, 95% confidence interval=1.08–1.33).

This study suggests the possibility of severe cognitive changes associated with chemotherapy, particularly over the long term.

Heck JE, et al. JAGS. 2008; 56(9): 1687-92.

CARDIORESPIRATORY FITNESS REDUCE BRAIN ATROPHY IN ALZHEIMER'S

Dr. Jeffrey M. Burns and his colleagues from University of Kansas School of Medicine examined a relation between cardiorespiratory fitness and brain atrophy and cognition in early-stage Alzheimer's disease (**AD**). They found that increased cardiorespiratory fitness is association with reduced brain atrophy in AD.

Patients with early-stage AD (n=57) and normal group (n=64) had MRI and standard clinical and psychometric assessments. Peak oxygen consumption (VO2-peak), the standard measure of cardiorespiratory fitness, was assessed during a graded treadmill test. VO2-peak was modestly reduced in early-stage AD patients, and was associated with whole brain and white matter volume after controlling for age. VO2-peak was also associated with performance on delayed memory and digit symbol tests in early AD, but not after controlling for age. The normal group had no relationship between fitness and brain atrophy although fitness was associated with global cognitive function and performance.

Burns JM, et al. Neurology. 2008; 71(3):211-6.

REPLAY OF TEMPORAL PATTERNS IN HIPPOCAMPUS WEAKENS WITH AGE

The hippocampus is thought to coordinate memory consolidation by reactivating traces from behavioral experience when the brain is not actively processing new input. Dr. Jason L. Gerrard from Arizona Research Laboratories Division of Neural Systems, Memory and Aging, University of Arizona and his colleague compared CA1 sequence activity pattern replay in young and old rats during rest periods after behavior.

They found that the young rats exhibited significant sequence reactivation while it was markedly impaired in the aged ones. When the spatial memory scores were compared with the degree of sequence reactivation, significant correlation was observed. This finding suggests that weak replay of temporal patterns has behavioral consequences, and supports the idea that reactivation processes are essential to memory consolidation.

Gerrard JL, et al. J Neurosci. 2008: 28(31):7883-90.