Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging July / August 2008

HIGHLIGHTS FROM ICAD 2008 – *UPDATE ON CLINICAL TRIALS*

The 11th International Conference on Alzheimer's Disease (**ICAD**) was held from July 26 to 31 at McCormick Place in Chicago IL. During the conference, 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

BIOMARKERS FOR PRECLINICAL FAMILIAL ALZHEIMER'S

Familial Alzheimer's disease (**FAD**) is known to occur earlier in life, defined as onset before the age of 65 (usually between 16 and 65 years of age) and is inherited in an autosomal dominant fashion. It also requires the patient to have first-degree relatives with a history of AD.

To understand biochemical characteristics of FAD, Dr. John M. Lingman and his colleague from UCLA Dept. of Neurology studied 21 subjects at risk for presenilin-1 (n=17) and amyloid precursor protein (n=4) mutations. Plasma from all subjects and CSF from 11 patients were obtained along with the Clinical Dementia Rating (**CDR**) scales, and plasma (Abeta40, Abeta42, and F2-isoprostane) and CSF (F2-isoprostane, t-tau, p-tau181, Abeta40, Abeta42, and Abeta42/Abeta40 ratio) levels were compared between FAS mutation carriers (MCs) and non-carriers (NCs).

They found that plasma Abeta42 levels and the ratio of Abeta42/Abeta40 were higher in pre-symptomatic MCs. Among MCs, those with CDR=0.5 had lower plasma Abeta42 levels compared to those with CDR=0. The ratio of Abeta42 to Abeta40 was also reduced in the CSF of

non-demented MCs compared to NCs. Total CSF tau and p-tau181 levels were elevated in pre-symptomatic FAD MCs. CSF levels of F2-isoprostanes were also elevated in MCs.

Ringman JM, et al. Neurology. 2008; 71(2):85-92.

APOLIPOPROTEIN E ALSO AIDS HIV

Originally recognized for their role in lipoprotein metabolism and cardiovascular disease, apolipoprotein E (ApoE) isoforms (ApoE2, ApoE3, and ApoE4) have also been implicated to play a key role in several biological processes not directly related to their lipid transport function. ApoE, for example, contributes significantly to Alzheimer's disease (**AD**).

A new study by Dr. Trevor Burt from the Division of Experimental Medicine, Department of Medicine, University of California, San Francisco and his colleagues suggests that ApoE4/E4 accelerates the HIV disease course and progression to death compared with the ApoE3/E3. However, an association between the E4/E4 genotype and HIV-associated dementia, a neurological condition with clinicopathological features similar to AD, was not detected.

Burt T, et al. PNAS. 2008; 105:8718-23.

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.

PRIMARY CARE SCREENING FOR COGNITIVE IMPAIRMENT

Dr. Kerry Donnelly from Veterans Affairs Western New York Healthcare System and his colleagues examined the diagnostic accuracy of a primary care screening procedure with the VA Integrated Service Network-2 (**VISN-2**), a 5-item questionnaire answered by family or patient, for identifying cognitive impairment in elderly veterans.

A total of 100 patients over 65 were recruited based on criteria defined by the VISN-2, and were assessed using Mini Mental State Exam (**MMSE**), Clock Drawing Test (**CDT**), Hopkins Verbal Learning Test Revised (**HVLT-R**), and Trail Making Test A and B (**TMT-A** and **-B**). The Clinical Dementia Rating Scale (**CDR**) was used as a criterion for distinguishing normal from mild cognitive impairment.

The results show that VISN-2 failed to correctly identify mildly demented cases by CDR in the entire sample while MMSE, CDT and TMT-A and -B correctly classified 80% of the sample with high specificity but variable sensitivity. TMT-B produced the best results when a cut-off of 3 minutes was used.

Donnelly K, et al. AJADD 2008; 23(3):218-26.

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.

Free Patient Brochure

Make sure your patients know that you now offer memory assessment services. We can send you complimentary copies of our educational patient brochure, "About Memory Loss", in English and Spanish. To request copies, please email us at: customerservice@mccare.com and include the address to where you would like the brochures mailed.

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