Novel Oligosaccharide Shows Benefits in Alzheimer's

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PHILADELPHIA, Pennsylvania — Shooting at the same target but with a different kind of arrow, Chinese researchers have shown that an oligosaccharide that binds more than one region of amyloid-β (Aβ) enhances clearance of the protein from the brain and improves cognition among patients with mild to moderate Alzheimer's disease (AD).

"Family members perceived improvements after 24 weeks [of] treatments," Shifu Xiao, MD, PhD, from Shanghai Jiao Tong University School of Medicine in China told attendees here at the 7th Clinical Trials Conference on Alzheimer's Disease (CTAD).

Most previous AD trials have used monoclonal antibodies to target Aβ and have failed to modify the course of the disease. So Dr Xiao and colleagues investigated the safety and efficacy of oligomannurarate (GV-971, Shanghai Greenvalley Pharmaceutical Company) in a multicenter, randomized, double-blind, placebo-controlled phase 2 trial involving patients with mild to moderate AD.

Monoclonal antibodies typically bind limited sites on Aβ, whereas oligomannurarate targets multiple regions and is therefore more likely to inhibit Aβ aggregation and have lower neurotoxicity, the investigators reasoned. In vitro the drug can dissociate aggregated Aβ and $A\beta_{1-42}$ mainly into monomeric nontoxic forms. It decreased Aβ plaques in the brains of transgenic mouse models of AD and improved cognitive function. It also reduced the level of acetylcholinesterase activity in the mouse model without directly affecting the enzyme.

On the basis of results of a phase 1 trial showing a dose-linear pharmacokinetic profile and no major adverse events in healthy volunteers, the researchers selected oligomannurarate doses of 600 mg/day and 900 mg/day for the phase 2 trial, which lasted 6 months. The primary endpoint was the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog/12).

Study participants were men and women aged 50 to 85 years with primary school or higher education and AD confirmed by computed tomography or MRI, with Mini-Mental State Examination (MMSE) scores of 10 to 24. They could not be receiving any other anti-AD drugs at the time of the trial.

Patients (n = 255) were randomly assigned about equally to either dose of the drug or to placebo. Similar proportions (83% to 92%) of each group completed the trial. Dropouts were for similar reasons.

Baseline demographic characteristics were similar for the three groups, with average MMSE scores of 17.31 to 18.41 and average ADAS-cog/12 scores of about 26 in the drug treatment groups and about 28 in the placebo group.

Table. Clinical Improvements at 24 Weeks

Endpoint	Placebo	Oligomannurarate, 600 mg/day	Oligomannurarate, 900 mg/day
ADAS-cog/12 mean change from baseline	–1.45	–1.39 (*P* = .886)[a]	–2.58 (*P* = .302)
CIBIC-Plus score[b]	0.35	0.18 (*P* = .110)	0.53 (*P* = .014)

[a] All *P* values vs placebo.

[b] Values estimated from graph.

Improvements in Cognition

At 12 weeks, patients receiving either dose of drug showed a trend toward improvements in ADAS-cog/12 scores compared with placebo, but by 24 weeks only the 900 mg/day group showed such a trend; this trend was not significant.

However, at 24 weeks, the 900-mg dose was associated with a significant improvement in the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus).

Treatments were safe and well tolerated. Adverse events (AEs) affected about 77% of participants in the placebo group and the 600-mg group but only 59.3% in the 900 mg group. AEs likely related to drug affected 5.9% in the placebo group, 14.3% in the 600-mg group, and 3.5% in the 900-mg group.

Serious AEs related to medication affected 1.2% of the 600-mg group and none in the other two groups. Dropouts related to any AEs were 1.2%, 6.0%, and 3.5% in the placebo, 600-mg, and 900-mg groups, respectively.

Most AEs were nervous system disorders, infections, or gastrointestinal disorders. Overall, however, any AEs were no more prevalent in the active treatment groups than in the placebo group.

Slowing in Decline of Cerebral Glucose Metabolism

"In a substudy of FDG-PET [fluorodeoxyglucose positron emission tomography], after 6 months of treatments there were significant improvements on the cerebral glucose metabolism, especially in the high dosage groups in areas of the brain," Dr Xiao found. Glucose metabolism decreased in areas of the brain affected by AD when compared with placebo.

When the researchers performed FDG-PET on subsets of patients with similar demographic and cognitive characteristics in the three groups, they found a significant decrease in metabolism in the left orbitofrontal gyrus at the 600-mg dose and in that area and in the left precuneus, right posterior cingulate gyrus, right hippocampus, and lower part of the left orbitofrontal gyrus at the 900-mg dose.

Among the 13 participants in a phase 2a pilot study receiving 600 mg or 900 mg daily for 24 weeks, evaluation of biomarkers in the cerebrospinal fluid (CSF) showed that for the 900-mg group, $A\beta_{1-42}$ increased at 24 weeks compared with baseline ($P = .009$), suggesting a clearance of amyloid from the brain into the CSF. For the 600-mg group, there was a nonsignificant trend of an increase in $A\beta_{1-40}$ and $A\beta_{1-42}$ and a decrease in total tau when compared with baseline.

On the basis of the results of this trial, investigators will take the 900 mg dose forward into a phase 3 trial.

Paul Aisen, MD, professor of neurosciences at the University of California, San Diego, commented to *Medscape Medical News* that this "very preliminary presentation of early results" suggests a possible positive effect "but needs to be replicated, as they are doing."

He mentioned that not much was said about the screening process for finding and choosing the marine-derived compound, oligomannurarate. "They apparently did screening based on [in vitro] antiaggregation potential with regard to oligomeric Aβ, which is a reasonable approach."

Dr Aisen said that as an adherent to the amyloid hypothesis of AD, he welcomes new ideas about how to attack amyloid and is glad to see new kinds of compounds being tested.

"We should be broad minded in our thinking until we're successful in developing very effective treatments, and so far we're not successful...and the more groups that are making serious attempts to develop drugs the better," he said.

The study was sponsored by Shanghai Greenvalley Pharmaceutical Company. Dr Xiao is a consultant for the Chinese divisions of Pfizer, Lilly, Novartis, GSK, Johnson & Johnson, Lundbeck, and other companies. Dr Aisen has disclosed no relevant financial relationships.

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