Team presents updated results from Phase 3 trial of IVIG for Alzheimer's disease

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Weill Cornell Medical College neurologist Dr. Norman Relkin reported new findings today from the Phase 3 clinical trial of IVIG (intravenous immunoglobulin) in mild to moderate Alzheimer's disease at the Alzheimer's Association International Conference (AAIC) in Boston, Mass. While the primary study outcomes were negative, observations from the subgroup analyses include whether there may be a dose-dependent reduction of beta amyloid in the blood and brain of IVIG-treated Alzheimer's patients who have the ApoE4 genotype.

IVIG is a mixture of antibodies derived from the blood of healthy donors. Given its ability to control infection and inflammation, IVIG has been used to treat disease for more than 30 years. It has been approved for use in treating several disorders, ranging from pediatric immune disorders to a blood cancer and Kawasaki disease, but is not approved for Alzheimer's disease.

The Gammaglobulin Alzheimer's Partnership (GAP) Study was a Phase 3, randomized, double-blind, placebo-controlled clinical trial in 390 people with mild to moderate Alzheimer's disease, conducted at 45 centers in the U.S. and Canada. Two different doses of IVIG were tested versus placebo as add-ons to approved Alzheimer's medications. The drug was administered every two weeks for 18 months. Primary study endpoints were changes on two well-established tests of cognition and daily functioning—the ADAS-Cog and ADCS-ADL.

In a topline announcement in May, the GAP researchers reported

negative results on the GAP study's primary outcomes—the ADAS-Cog and ADCS-ADL. At the same time, preliminary observations were reported on favorable changes on another cognitive test, the Modified Minimental State Examination (3MS) in two subgroups: people with Alzheimer's who carried the APOE-e4 Alzheimer's risk gene, and those who were moderately impaired. The study was not powered to show statistical significance in these pre-planned subgroup analyses.

Today at the AAIC meeting, Dr. Relkin reported for the first time on additional cognitive and biomarker tests that shed further light on the study's outcomes. The researchers found that study participants in the APOE-e4 carrier subgroup receiving IVIG 400mg/kg/2wk (n=87) had numerically superior results at 18 months relative to placebo on the Modified Mini-Mental State (3MS) Examination (n=66) and the Trails B test (n=77), two out of several measures of thinking ability made in the study. "Though 3MS and Trails B were not the primary outcome measures in the study, they are well-established cognitive measures." Dr. Relkin says.

Biomarker analyses demonstrated that antibodies from the treatment reached the central nervous system. Among the findings that Dr. Relkin reported:

- A statistically significant, dose dependent reduction in plasma beta-amyloid 42 levels (but not beta-amyloid 40) was observed in IVIG treated patients relative to placebo.
- Statistically significant, dose dependent increases in anti-oligomer and anti-fibril antibodies in the CSF or plasma occurred in IVIG-treated patients relative to placebo.
- A reduction in brain fibrillar amyloid (as measured by PET scan using florbetapir) was seen in patients who received IVIG at the 400mg/kg/2wk dose, particularly those who were APOE-e4 carriers.

- No effect in tau and phosphorylated tau levels in spinal fluid.

"It is important to say that the GAP study results do not provide grounds for prescribing IVIG in Alzheimer's disease, even with this positive signal in the APOE-e4 carriers," Dr. Relkin says. "Further confirmatory studies and regulatory approval would be needed before clinical use could be recommended."

"The primary clinical outcomes are unequivocally negative, but there are intriguing signals in the clinical and biological markers," he adds "With the understanding that we cannot draw conclusions about IVIG's effectiveness in these subgroups from these results alone, the effects of IVIG on beta-amyloid and antibody levels in the blood and brain are noteworthy. These results support that IVIG can target beta amyloid and that the antibodies it contains can reach the brains of people with Alzheimer's when administered through the bloodstream."

Despite the negative results of the Phase 3 IVIG trial, and because of the successes of IVIG in animal models of Alzheimer's and early stage trials in people, researchers continue to pursue how IVIG may work in the brain to inform ongoing Alzheimer's therapy research.

"The favorable data in subjects who carry the APOE-e4 gene also underscores the need for further research and emphasis on a precision medicine approach to Alzheimer's," Dr. Relkin says. "The APOE-e4 carrier group is easily identified by genetic testing. It may be important to more specifically target our next generation of Alzheimer's therapies with an eye towards treating identifiable subgroups of patients such as APOE-e4 carriers."

Earlier Phase Studies at Weill Cornell Showed Promise of IVIG

Dr. Relkin is associate professor of clinical neurology at Weill Cornell Medical College and study leader of the Gammaglobulin Alzheimer's Partnership (GAP) trial, conducted by Baxter International and the Alzheimer's Disease Cooperative Study (ADCS), a clinical trial consortium supported by the United States National Institute on Aging in the National Institutes of Health.

Dr. Relkin, who is also director of the Memory Disorders Program at NewYork-Presbyterian Hospital/Weill Cornell Medical Center and a researcher in Weill Cornell's Feil Family Brain and Mind Research Institute, became interested in IVIG when he and Weill Cornell colleagues Dr. Mark Weksler and Dr. Paul Szabo found evidence in 2003 of decreased levels of free antibodies against beta amyloid in the blood of patients with Alzheimer's disease. Following a report by German investigator Dr. Richard Dodel that IVIG contained increased levels of anti-amyloid antibodies, they began testing IVIG as a potential anti-amyloid immunotherapy for Alzheimer's disease.

For example, Dr. Relkin reported in 2006 that a pilot study found IVIG stabilized or improved cognitive function in Alzheimer's patients when administered over a period of a year or more. When the treatment stopped, cognitive abilities began to decline, and then stabilized once more when the treatment was offered again.

A 2007 laboratory analysis by Dr. Relkin and his colleagues demonstrated that antibodies in IVIG could not only recognize and scoop up toxic beta amyloid proteins, but also other proteins that accumulate in a wide variety of neurodegenerative diseases.

Phase2 GAP results demonstrated that patients who responded best to IVIG did not measurably decline in cognitive abilities over 18 months and had an average rate of brain shrinkage similar to elderly individuals who did not have the disease. Dr. Relkin presented these findings in

April 2010 at the annual meeting of the American Academy of Neurology.

Dr. Relkin proposed the GAP trial after the earliest phase studies he carried out showed the promise of IVIG in slowing dementia-related decline. The Phase 1 and Phase 2 trials he performed involved relatively small numbers of patients, however, making the generalizability of the findings uncertain. He proposed the GAP study as a means of assessing IVIG's safety and effectiveness in a larger number of Alzheimer's patients.

"The Phase 3 GAP study was conducted at a very high standard, setting goals that have not yet been reached by any medication for Alzheimer's disease that is approved or under investigation," Dr. Relkin says. "What we stand to learn from this research cannot be overstated. The data reinforces some of the findings from the earlier phases of the GAP study, and we need now to delve deeper into the data to help move forward toward improving the treatment of Alzheimer's disease."

Provided by Weill Cornell Medical College