IVIG Reduced Brain Atrophy in Alzheimer's

VITALS

Major Finding: Treatment with a range of doses of IVIG for 18 months resulted in a mean increase of 6.7% in lateral ventricular volume, which was significantly lower than the 12.3% increase observed with placebo.

Data Source: A double-blind, randomized, placebo-controlled phase II trial of 24 patients with mild to moderate Alzheimer's disease.

Disclosures: Baxter Healthcare sponsored the study of IVIG, with additional support from the Citigroup Foundation and the National Institutes of Health. Dr. Relkin reporting no relevant disclosures besides receiving a research grant from Baxter Healthcare to study IVIG.

BY JEFF EVANS

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

TORONTO — Intravenous immunoglobulin therapy reduced brain atrophy in patients with mild to moderate Alzheimer's disease in a small phase II trial. The finding suggests that specific IgG antibody components found in the blood product might be treatment candidates for the disease.

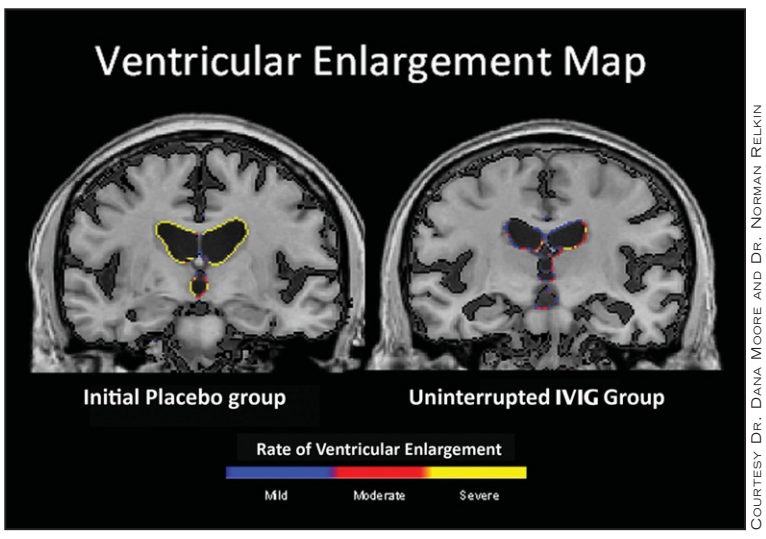
"Relative to what we have available right now [to treat Alzheimer's disease], this is a very promising outcome, and it's associated with a reduction in the rate of brain atrophy comparable with age-matched normals," Dr. Norman Relkin said during a poster presentation.

Enlargement of the cerebral lateral ventricles is known to occur as a consequence of brain atrophy in Alzheimer's disease (AD). This increase in ventricular volume is correlated with cognitive decline and increases in Alzheimer's disease neuropathology.

Dr. Relkin and his colleagues compared intravenous immunoglobulin (IVIG) therapy against placebo in a 6-month, double-blind, randomized study of 24 patients with mild to moderate AD. In a 12-month extension phase of the study, 16 patients who originally were randomized to IVIG continued to receive the same doses of IVIG, whereas 8 placebo-treated patients were re-randomized to one of four doses of IVIG. The investigators used an IVIG product produced by Baxter Healthcare called Gammagard.

IVIG exhibited a dose-dependent effect on brain atrophy in which higher doses resulted in less atrophy. Among 14 IVIG-treated patients who underwent volumetric MRI at baseline and after 18 months, the yearly increase in lateral ventricle volume measured with volumetric MRI was lowest in patients treated with 0.4 mg/kg every 2 weeks (2.4%) and highest in those treated with 0.2 mg/kg every 2 weeks (11.2%). The doses of IVIG given to patients ranged from 0.2 mg/kg every 2 weeks to 0.8 mg/kg every 4 weeks.

The volume of the lateral ventricles increased by a mean of 6.7% per year during treatment with IVIG (all doses combined), which was significantly lower than the 12.3% annual rate of increase observed in six placebo-treated patients. Only the 0.4 mg/kg dose of IVIG given every 2 weeks resulted in significantly less change in total brain volume than did treatment with placebo (–0.62% vs. –2.24%, respectively).



COURTESY DR. DANA MOORE AND DR. NORMAN RELKIN

After 18 months, the ventricular enlargement rate was greater with placebo (left) than it was with IVIG (right).

"In addition to the brain imaging, we have previously shown changes in cerebrospinal fluid and plasma amyloid levels . . . and levels of cerebral metabolism changing in response to treatment," said Dr. Relkin, director of the Memory Disorders Program at New York–Presbyterian Hospital/Weill Cornell Medical Center.

The outcome is associated with a reduction in the brain atrophy rate, comparable with age-matched normals.

DR. RELKIN

The reduction in brain atrophy was significantly correlated with improvement in clinical outcomes at 18 months on the Clinical Global Impression of Change and the cognitive subscale of the Alzheimer's Disease Assessment Scale. Patients' baseline characteristics were not correlated with volumetric MRI outcomes.

"This is a 'kitchen sink' approach, so the next step is to find what is in [IVIG] that is causing the therapeutic effect. . . . We know that it has a fairly good complement of antiamyloid antibodies. Those are prime candidates, but we don't know for sure yet that those are ones responsible for a therapeutic effect," Dr. Relkin said in an interview.

In addition to an ongoing, multicenter, phase III study of IVIG in 360 patients with mild to moderate AD, Dr. Relkin and his colleagues are testing subsets of antibodies within IVIG in cell culture–based studies and preclinical animal models to see which components are therapeutically relevant. "We are not encouraging people to use [IVIG] off-label for Alzheimer's disease, even though it has been safe and well tolerated in these small studies," he said. "It has never been studied in the Alzheimer's population before."

Baxter Healthcare sponsored the phase I and II studies of IVIG, with additional support from the Citigroup Foundation and the National Institutes of Health. The phase III trial is cosponsored by Baxter and the NIH. Dr. Relkin reported no relevant disclosures besides receiving a research grant from Baxter Healthcare to study IVIG. ■

Data on Inappropriate Sexual Behavior in Elderly Fall Short

BY ROXANNA GUILFORD-BLAKE

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR GERIATRIC PSYCHIATRY

SAVANNAH, GA. — Little research exists on inappropriate sexual behavior in patients with dementia. The behaviors, while distressing and disruptive, are poorly defined, and data on the neurobiology, prevalence, assessment, and treatment are lacking.

An estimated 7%-25% of patients with dementia exhibit such behavior, Dr. Alicia A. Romeo reported. Males are far more likely than females to engage in inappropriate sexual behavior, but the types of behaviors do not vary by sex.

Few studies have looked at prevalence rates for sexually inappropriate behaviors in dementia, and discussion among symposium members and the audience indicated that such behaviors often go unreported, noted Dr. Romeo, a psychiatrist in the Geropsychiatry Program at the Boston VA Healthcare System and an instructor at Harvard Medical School, Boston.

The few data that do exist suggest that nonpharmacologic and pharmacologic treatments can work. Behavioral modification can be "very effective," she said. For example, ensuring adequate social activity is crucial. Adjustment of social cues given to these patients makes a significant difference. For instance, when nursing assistants wear white coats, it signals they are medical professionals.

Nonpharmacologic therapy also can involve supportive psychotherapy for the family and caregivers, and additional staff training—including a "suitable" sex education program. With no Food and Drug Administration–approved medication for treatment for such behaviors, what little research there is addresses off-label use. And with no double-blind placebo-controlled trials, researchers can only look at case reports to identify possible medical therapies.

Medications found to be useful in the treatment of inappropriate sexual behaviors in patients with dementia include anticonvulsants; antidementia agents; antidepressants such as trazodone; cimetidine, a histamine H_2 receptor antagonist; and pindolol, a beta-blocker, she reported.

Three case reports suggest that antipsychotics might be an option, but she advised against using them, citing the side effects. (The FDA issued an advisory and black box warning in 2005 about the risk of atypical antipsychotics in elderly patients with dementia. Three years later, the agency revised labeling for conventional antipsychotics with wording stating that "elderly patients with dementia-related psychosis who are treated with antipsychotic drugs have an increased risk of death ["All Antipsychotics Get Warnings About Elderly," July 2008, p. 9].) Clinicians should first consult with the family and document everything.

Use medications only when other methods fail, and use them in combination with other treatments, she advised. The choice of treatments depends upon the urgency of the situation, the types of behaviors manifested, and the patient's underlying medical conditions.

Dr. Romeo offered an algorithm to help make treatment decisions. It was developed by the session's chair, Dr. Rajesh R. Tampi of Yale University, New Haven, Conn., who has coauthored articles on the subject (J. Geriatr. Psychiatry Neurol. 2005;18:155-62 and Am. J. Alzheimers Dis. Other Demen. 2008;234:344-54).

Four brain systems have been implicated in the neurobiology, Dr. Romeo said. The frontal system dysfunction typically involves disinhibition. Temporolimbic system and hypothalamic disorders are associated with hypersexual behavior. Striatum dysfunction is associated with obsession.

Future research should focus on effective treatments as well as early detection and prevention, she said. But defining what constitutes inappropriate behavior can be tricky, and ethical issues can arise over what's appropriate and inappropriate.

Improved interaction between the clinician and caregivers, including nurses, will help in early detection and treatment of these behaviors," Dr. Tampi said in an interview. Neither Dr. Romeo nor Dr. Tampi reported any conflicts. ■