

Antidiabetic Agents Show Some Promise in Treating Alzheimer's Disease

Laurie Barclay, MD

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July 27, 2006 — Antidiabetic agents show some promise in treating Alzheimer's disease (AD), according to 3 presentations at the 10th International Conference on Alzheimer's Disease and Related Disorders (ICAD 2006) in Madrid, Spain. The 3 studies on the effect of intranasal insulin, rosiglitazone (RSG), and pioglitazone (PGZ) on nondiabetic patients with AD suggest a possible link between insulin metabolism and mechanisms underlying AD.

"Recent evidence suggests that disorders of insulin metabolism, such as insulin resistance and diabetes, increase the risk for developing AD," presenter Suzanne Craft, PhD, a professor of psychiatry and behavioral sciences at the University of Washington School of Medicine, and associate director of the Geriatric Research, Education, and Clinical Center at the Veterans Affairs Puget Sound Health Care System in Seattle, Washington, told Medscape.

Insulin resistance and diabetes are commonly associated with elevated peripheral insulin levels, which lead to reduced insulin levels and signaling in the central nervous system (CNS), Dr. Craft explained. Low cerebrospinal fluid (CSF) insulin levels have been observed in AD patients, and intravenous insulin administration, while maintaining euglycemia, improves memory, possibly by augmenting low brain levels. However, the risk of hypoglycemia with peripherally administered insulin prevents this from being a viable treatment.

"Reduced insulin signaling has been reported in neuropathological studies of patients with AD," Dr. Craft said. "Reduced insulin signaling may interfere with the normal functioning of brain insulin, which regulates glucose utilization in selected brain regions such as the hippocampus, and modulates acetylcholine levels and neuronal physiology. Insulin also regulates levels of the beta amyloid peptide in the CNS."

Intranasal Insulin Improved Daily Function

To enhance brain insulin signaling in patients with AD without raising peripheral insulin levels, Dr. Craft's group studied the effects of intranasal insulin. After intranasal administration, insulin follows extracellular pathways to the brain and largely bypasses the periphery, directly reaching the CNS within 15 minutes and avoiding the risk of hypoglycemia.

In this double-blind trial, 25 patients with early AD or amnesic mild cognitive impairment (MCI) were enrolled, of whom 12 were randomized to receive placebo and 13 to receive 20 IU intranasal insulin administered using an electronic atomizer twice daily for 21 days. Outcomes included cognitive measures and blood levels of glucose and insulin at baseline, and after 10 and 21 days of treatment.

"For a genetic subgroup of patients previously shown to be more affected by insulin resistance, memory improved [by] about 20%," Dr. Craft said. "Caregivers of these patients reported significantly improved daily function, suggesting that the effects were clinically significant. Longer-term trials of intranasal insulin appear warranted at this time."

Treatment was well-tolerated, with no serious adverse events or changes in plasma glucose or insulin levels. Compared with the placebo-treated group, the insulin-treated group showed enhanced ability to retain verbal information after a delay (memory savings; $P = .03$). Although memory savings scores were no different between the 2 groups at baseline, they were significantly higher in the insulin-treated group at day 21 (placebo group mean memory savings score, $32\% \pm 26\%$; insulin group, $53\% \pm 13\%$).

The insulin-induced increase in memory savings was less prominent in older adults, and change in memory savings was negatively correlated with age for the insulin-treated group ($r = -.97$; $P = .005$). For a subgroup of patients, insulin treatment modulated plasma beta amyloid and cortisol levels.

"The intranasal insulin treatment is very exciting, particularly since it appears that younger patients responded better than older ones," Suzanne M. de la Monte, MD, MPH, a professor of neuropathology and clinical neuroscience at Brown Medical School and Rhode Island Hospital in Providence, told Medscape. "This result is consistent with our findings of a progressive decline in brain insulin with increasing severity of disease. Presumably, older patients included in the study had the combined effects of AD plus aging-associated brain neuroendocrine deterioration."

Dr. de la Monte was not involved in these 3 studies, but she reviewed them for Medscape. She pointed out the need for larger numbers of subjects and longer periods of follow-up to make accurate clinical diagnoses as the disease progresses.

Dr. de la Monte summarized the controversy in this work as being 2-fold. First, now that intranasal insulin is approved for managing diabetes, "it's hard to imagine that there will not be any adverse effects on peripheral blood glucose levels or on the respiratory tract, which could receive the bulk of inhaled insulin." She noted that the AD patients in this study were not diabetic.

Second, "the conceptualization of the basic problem is strongly stated but clearly does not account for the fact that epidemiologically, the majority of patients do not have type 2 [diabetes mellitus], although their brain and CSF insulin levels are reduced." Based on direct studies of human brains, Dr. de la Monte's position is that the brain insulin deficiency in AD is largely restricted to the brain. As in metabolic syndrome X (liver insulin resistance), however, there is some overlap between AD, also referred to as type 3 diabetes, and type 2 diabetes.

"As type 2 [diabetes mellitus] increases in our population, so will the overlap with AD," Dr. de la Monte pointed out. "That said, I strongly agree that the concept of replacing brain insulin is correct, even if there is fundamental disagreement with respect to the cause of brain insulin deficiency and resistance."

Claude Messier, MD, PhD, a professor of psychology and neuroscience at the University of Ottawa in Ontario, Canada, also reviewed these 3 studies for Medscape as an independent expert, and he agreed that this study is limited by its short duration and small sample size. He suggested that insulin growth factor may be involved in mechanisms underlying the effect of intranasal insulin.

"Insulin growth factor is implicated in brain repair and remodeling, so this system could play a role in the effect observed by Craft et al," Dr. Messier told Medscape. "Intranasal insulin may not achieve large concentrations in the whole brain in general so there are some questions about how it would act on the different brain regions in humans. Data from rats indicates a good penetration in the frontal regions of the brain, particularly the olfactory system, but lesser concentrations in posterior regions of the brain."

Rosiglitazone Response May Be Determined by Presence of APOE

The second ICAD presentation described findings from a 24-week, double-blind, placebo-

controlled monotherapy trial of RSG in 511 AD patients with baseline Mini-Mental Status Examination (MMSE) score of 16 to 26 points.

"The rationale for studying RSG in AD is based upon evidence of altered glucose metabolism in AD," presenter Marina E. Zvartau-Hind, MD, PhD, director of clinical neurology at GlaxoSmithKline, told Medscape. "Preclinical evidence for peroxisome proliferator-activated receptors (PPARs) in AD, which have glucose metabolism, mitochondrial, and anti-inflammatory effects, supports theoretical mechanistic reasons to believe RSG may improve symptoms. A positive cognitive effect has also been observed in a small pilot study of RSG in [AD] patients."

Of 511 patients enrolled, 323 had results available for analysis by genetic AD markers. Overall, the intention-to-treat analysis of the whole group failed to achieve primary efficacy end points on the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) and the Clinician Interview Based Impression of Change Plus. However, a prospectively planned analysis (n = 323) of interaction between treatment and *APOE4* carriage status was significant for the ADAS-cog ($P < .014$).

"Exploratory analyses suggest that RSG response may be differentiated by a genetic biomarker (*APOE*), with *APOE*-positive subjects showing an improvement (2-3 points) and *APOE*-negative subjects showing a similar response to placebo or some decline," Dr. Zvartau-Hind said. "These findings are exploratory and require confirmation in subsequent clinical studies; no conclusions can be drawn about clinical management of patients with AD. The drug studied for use in AD is an extended-release formulation of RSG that is not yet approved and is commercially unavailable."

Dr. Messier noted that RSG has a significant anti-inflammatory action that could be a potential mechanism of action in treating AD, in addition to its effects on PPAR-gamma receptors in the brain.

"There is some potential for these treatments, particularly in *APOE4* patients that appear to be more responsive," he told Medscape. "These also could be the patients more likely to have small but distributed infarcts. However, no need to rush to the pharmacy or to the doctor to request those treatments off-label; the effect sizes are quite small in these short intervention studies."

Dr. de la Monte suggested that these preliminary data are "promising" and that the use of RSG and possibly related compounds is "very exciting.... There is already a great deal of clinical experience with this drug, and over time, more brain-specific compounds may be developed."

Pioglitazone: No Difference vs Placebo but Effect Size Promising

The third study presented at the meeting was a randomized, double-blind, placebo-controlled, pilot study designed to evaluate the safety of PGZ in nondiabetic patients with AD during an 18-month treatment course. PGZ is a thiazolidinedione approved to treat type 2 diabetes, and it is a potent and specific agonist of PPAR-gamma. In animal models of AD, PPAR-gamma agonists have been shown to lower beta amyloid peptide levels, reduce plaque deposition, and suppress microglial-mediated inflammation.

"This was designed as a safety study to determine whether nondiabetic patients with AD were able to take PGZ over a protracted period," presenter David Geldmacher, MD, an associate professor of neurology at the University of Virginia Health System in Charlottesville, told Medscape. "We also wanted to determine the effect size, because this agent had never been used before in AD. So we had no idea if it would be effective, and if so, to what extent."

After providing informed consent, 29 subjects who met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD were randomized to receive PGZ 45 mg daily (n = 14) or placebo (n =

15). All subjects also received vitamin E, 200 units daily, and remained on stable doses of cholinesterase inhibitors, with memantine therapy also permitted when it became available. Mean age was 70.9 years, and mean MMSE score was 21.0.

Of 25 subjects who completed the 18-month study, 12 were assigned to PGZ and 13 to placebo. Edema was the main, clinically significant adverse effect, occurring in 28.6% of the PGZ group and in none in the placebo group. There were no differences between the 2 groups in laboratory-measured hypoglycemia, nor in measures of cognition, function, or behavior.

"This was a small pilot study, so we were unable to demonstrate statistical significance," Dr. Geldmacher said. "However, the effect size was promising and comparable to that of other agents, suggesting that further study is indicated."

When asked about the implications of findings from these studies for AD mechanisms and treatment, Dr. Messier said that drawing any firm conclusion would still be premature. Despite the strong evidence that diabetes and glucose intolerance increase the likelihood of AD, one explanation may be increased occurrence of small infarcts giving rise to vascular dementia.

"Although there have been some claims that AD is the type 3 diabetes, with a disturbance of insulin function in the brain, there is still very little support for this idea," Dr. Messier said. "That includes an immense lack of understanding of the role of insulin in the brain — quite an obstacle for any strong hypothesis. Right now, available treatments are quite limited [for AD patients overall], but there is a small percentage that appears to respond better to some pharmacological treatments."

However, Dr. de la Monte is cautiously optimistic. She pointed out that many investigators agree that AD is a metabolic and neuroendocrine disease, although many still debate the role of amyloid.

"The findings in these studies clearly support the growing paradigm shift regarding the pathogenesis of AD, ie, that AD is caused by insulin resistance and insulin deficiency in the brain," Dr. de la Monte said. "Certainly other factors and disease processes such as vascular disease, neuro-inflammation, and oxidative stress can accelerate or contribute to the neurodegeneration cascade. However, just as occurs in type 1 and type 2 diabetes, oxidative stress, inflammation, and vascular disease are secondary consequences of insulin deficiency and/or resistance, and therefore integrally related to the disease processes."

Objective Assays and Biomarkers Needed

In terms of additional research, Dr. de la Monte recommended development of objective assays and biomarkers of brain insulin deficiency and resistance; and positron emission tomography studies or other objective assays of brain function before and after treatment, to see if improvement in brain metabolism correlates with changes in cognition.

"There may be a need to utilize both therapeutic approaches, because in AD, there is both brain insulin deficiency and brain insulin resistance," Dr. de la Monte said. "RSG works on the insulin resistance arm, whereas intranasal insulin treatment could replete the missing growth factor in the brain. Both approaches may ultimately provide the best therapy. Since the RSG treatment is known to be safe, there may even be a good argument for its compassionate use in patients with early disease who are not or cannot be enrolled in clinical trials."

For the intranasal insulin study, Dr. Craft reports no relevant financial relationships. **Kurve Technology provided electronic atomizers free of charge**; 2 coauthors have patents on intranasal delivery device or AD treatment. For the RSG study, Dr. Zvartau-Hind and coauthors are employees of GlaxoSmithKline. The PGZ study was funded by the National Institute for Aging and by Takeda Pharmaceuticals North America; Decatur provided study medication and placebo;

and some of the authors report various financial relationships with Takeda. Dr. Geldmacher has received consulting fees from Decatur and Takeda Pharmaceuticals and has a financial interest in a patent for the use of this agent in AD. Drs. de la Monte and Messier report no relevant financial relationships.

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