Original Research

Cognitive and Functional Decline in Patients With Mild Alzheimer Dementia With or Without Comorbid Diabetes

Haya Ascher-Svanum, PhD; Yun-Fei Chen, PhD; Ann Hake, MD; Kristin Kahle-Wrobleski, PhD; Dara Schuster, MD; David Kendall, MD; and Robert J Heine, MD, PhD

Eli Lilly and Company, Indianapolis, Indiana

ABSTRACT

Purpose: Although diabetes is recognized as a risk factor for the development of cognitive impairment and for accelerated progression to Alzheimer disease (AD), it is unclear whether patients with diabetes who have already progressed to AD have a different rate of cognitive and functional decline compared with that in those without diabetes. This post hoc exploratory analysis compared cognitive and functional decline over an 18-month period in patients with mild AD dementia with and without comorbid diabetes. Decline in quality of life was assessed as a secondary objective.

Methods: In a post hoc exploratory analysis, we analyzed data from the placebo groups of three 18-month, randomized, placebo-controlled trials of solanezumab and semagacestat in patients with AD. Data from patients with mild AD dementia (Mini-Mental State Examination [MMSE] score, 20–26) and comorbid diabetes at baseline were compared with data from patients with mild AD dementia without diabetes at baseline. Cognition was assessed using the 14-item AD Assessment Scale–Cognitive Subscale ($ADAS\text{-}Cog_{14}$) and the MMSE. Functioning was assessed with the AD Cooperative Study–Activities of Daily Living Inventory (instrumental subset) (ADCS-iADL). Quality of life was assessed using the European Quality of Life–5 Dimensions scale, proxy version (proxy utility score and visual analog scale score), and the Quality of Life in AD scale, self-report and proxy (caregiver) versions. Group comparisons of changes from baseline to 18 months in cognitive, functional, and quality-of-life measures employed a repeated-measures model adjusted for propensity score, study, baseline cognition score (functional or quality of life), age, sex, level of education, genotype of the apolipoprotein E gene, and concurrent use of an acetylcholinesterase inhibitor or memantine.

Findings: At baseline, patients with mild AD dementia with and without diabetes did not significantly differ on the cognitive measures, but those without diabetes were functioning at a significantly higher level. At 18 months, compared with patients without diabetes, those with diabetes showed a numerically but statistically nonsignificantly lesser cognitive decline (least squares mean between-group differences: $ADAS\text{-}Cog_{14}$ score, 1.61 [$P = 0.21$]; MMSE score, –0.40 [$P = 0.49$]) and a statistically significantly lesser functional decline (least squares mean between-group difference in ADCS-iADL score, –3.07; $P = 0.01$). The 2 groups did not differ on declines in the quality-of-life measures.

Implications: The present findings suggest that diabetes may influence the rate of functional decline among patients with mild AD dementia. These results require replication in studies that address the limitations of the present post hoc exploratory analysis and that explore the potential causes of the observed differences. (*Clin Ther.* 2015;37:1195–1205) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

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INTRODUCTION

Alzheimer disease (AD) and type 2 diabetes are chronic diseases that may share common pathologic features (eg, amyloid formation),[1–3] in addition to being linked to the aging process.[4] Diabetes is associated with the development of cognitive impairment[5–8] and with accelerated progression to dementia due to AD.[9] Some evidence suggests that AD is associated with a brain-specific type of insulin resistance and that insulin signaling may be attenuated in parts of the brain in patients with AD.[10,11] Insulin receptors are found in the memory-foundation regions of the brain,[12] and it is speculated that stimulation of insulin-receptor signaling in these brain regions with some of the glucose-lowering drugs, such as insulin, thiazolidinediones, and glucagon-like polypeptide-1 receptor agonists, may benefit patients with AD. Clinical trials of glucose-lowering drugs as alternative treatments in patients with AD have been undertaken.[13–16]

The association between mild cognitive impairment and diabetes is known.[17,18] Mild cognitive impairment represents a transitional phase between normal cognitive function and dementia, although not all people with mild cognitive impairment progress to develop dementia.[19] It is unclear whether diabetic patients who have already progressed to dementia due to AD experience a different rate of further cognitive and functional decline over time compared with that in patients with AD without diabetes. We hypothesized that the presence of comorbid diabetes is associated with a faster rate of decline in patients with AD. Therefore, we aimed to assess whether patients with mild AD dementia and comorbid diabetes show a greater magnitude of cognitive and functional decline compared with those without comorbid diabetes. The focus on patients with mild AD dementia, rather than moderate or severe AD dementia, was driven by the growing recognition that patients with mild AD dementia are more likely to benefit from disease-modifying interventions, reflecting a greater potential for change in the progression of the disease.[20,21]

The primary objective of this post hoc exploratory analysis was to compare cognitive and functional decline over 18 months between patients with mild AD dementia with and without a comorbid diabetes diagnosis. As a secondary objective, this analysis compared the decline in quality of life in patients with mild AD dementia with and without comorbid diabetes. In addition, as an exploratory objective, we repeated the analyses on data from patients with moderate AD dementia.

PATIENTS AND METHODS

Analysis Population

This post hoc exploratory analysis used data from the placebo groups of three 18-month, randomized, placebo-controlled trials of solanezumab and semagacestat in patients with AD.[22,23] The analysis population was created from the intent-to-treat populations of the placebo groups. Specifically, patients with mild AD dementia (Mini-Mental State Examination [MMSE] score, 20–26) and comorbid diabetes at baseline were compared with patients with mild AD without diabetes at baseline. The analysis was repeated on data from patients with moderate AD dementia (MMSE score, 16–19), comparing those with comorbid diabetes at baseline to those with without diabetes at baseline.

Patient Consent

The parent studies[22,23] received ethical approval from the governing institutional review boards, and patients and caregivers provided written informed consent in accordance with the Declaration of Helsinki.

Assessment of Diabetes

The presence of diabetes as a condition comorbid with AD was assessed at baseline as a part of patient-reported medical comorbidities. For the purposes of the present analyses, *comorbid diabetes* was defined as the presence of at least 1 of the following criteria: baseline random blood glucose concentration $\geq$200 mg/dL (11.1 mmol/L), patient-reported preexisting diabetes at or before baseline, and/or reported use of any glucose-lowering medication at or before baseline (a sulfonylurea [tolbutamide, glibenclamide, gliclazide, glimepiride, glipizide, glibenclamide/metformin], a biguanide [buformin, metformin], a thiazolidinedione [pioglitazone, rosiglitazone, pioglitazone/metformin, rosiglitazone/metformin], an α-glucosidase inhibitor [acarbose, miglitol, voglibose], a dipeptidyl peptidase 4 inhibitor [saxagliptin, sitagliptin, vildagliptin, sitagliptin/metformin], a meglitinide [nateglinide, repaglinide], glucagon-like