A Randomized Pilot Clinical Trial of the Safety of Pioglitazone in Treatment of Patients With Alzheimer Disease

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Objectives: To evaluate the safety of the peroxisome proliferator–activated receptor gamma agonist pioglitazone in nondiabetic patients with Alzheimer disease (AD) and to explore treatment effect sizes on clinical outcomes.

Design: Double-blind, placebo-controlled randomized controlled trial of 18-month duration.

Setting: Two academic medical center outpatient clinics.

Patients: Nondiabetic patients meeting research criteria for probable AD were enrolled. Twenty-five of 29 subjects completed the study; no withdrawals were attributable to adverse effects.

Intervention: Subjects received pioglitazone (Actos), titrated to 45 mg daily, or matching placebo, and 200 IU of vitamin E daily. Patients maintained treatment with cholinesterase inhibitors and could begin memantine therapy when it became available during the study.

Main Outcome Measures: The primary outcome was frequency of reported adverse effects (AEs). Secondary outcomes were measures of cognition, activities of daily living, neuropsychiatric symptoms, and global function.

Results: Peripheral edema was the principal AE occurring more frequently in subjects taking pioglitazone than placebo (28.6% vs 0%). This is consistent with the known AE profile of pioglitazone. No group differences in laboratory measures were identified. No significant treatment effect was observed on exploratory analysis of clinical efficacy.

Conclusions: Pioglitazone was generally well tolerated in this pilot study. There were no serious or unanticipated adverse events or clinical laboratory changes attributable to pioglitazone over a long-term exposure in nondiabetic patients with AD. The tolerability of pioglitazone in this population and peroxisome proliferator–activated receptor gamma effects in laboratory models of AD support further study of this drug class in earlier disease stages.

Trial Registration: clinicaltrials.gov Identifier: NCT00982202.


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subsequent double-blind, randomized, placebo-controlled study of rosiglitazone in 511 patients over 24 weeks revealed no significant improvement in the treated group overall; however, improved cognition was observed in a subset of patients who did not possess an apolipoprotein E ε4 (APOEε4) allele.3

One potential explanation of the limited efficacy of rosiglitazone is poor bioavailability to the central nervous system. Although rosiglitazone passes the blood-brain barrier, it undergoes active efflux through P-glycoprotein–dependent transport, limiting its concentration in the brain.4 Pioglitazone has demonstrated central nervous system penetration and relevant biological activity in a transgenic mouse model of AD.5 Orally administered pioglitazone enters the brains of transgenic mice expressing AD pathology6 in sufficient amounts to exert biologically relevant effects in reducing AD-related pathological burden and suppression of glial activation.7,8 Pioglitazone treatment also reversed cerebrovascular dysfunction observed in aged animals with murine models of AD.8 The combination of blood-brain barrier penetration and demonstrated activity on AD-related pathophysiology makes pioglitazone an attractive therapeutic candidate, even in light of the failure of rosiglitazone to demonstrate clinical efficacy in subjects with AD.

The specific aims of this study were to collect information on the safety and tolerability of long-term exposure to pioglitazone among nondiabetic, elderly patients with AD. Because there had been no prior experience with pioglitazone in this patient population, the study was also designed to explore treatment effect sizes to guide design of future clinical trials.

METHODS

This was a double-blind, randomized, placebo-controlled, group-comparison study of 18 months’ duration. The study was conducted at University Hospitals of Cleveland/Case Western Reserve University and The University of Virginia Health System between 2001 and 2004. The study protocol and informed consent process were approved by the authorized human subjects committee at each institution. Fifteen-milligram pioglitazone and matching placebo tablets were supplied at no charge by Takeda Pharmaceuticals North America; the manufacturer had no other role in study conduct or analysis. Secure medication management and investigator blinding was provided by the investigational pharmacy service at each institution.

SUBJECTS

Twenty-nine subjects meeting National Institute of Neurological and Communicative Disorders and Stroke–the Alzheimer’s Disease and Related Disorders Association criteria for probable AD were enrolled. Enrollment criteria included Mini-Mental State Examination7 score between 12 and 26 and Clinical Dementia Rating10 (CDR) score of 1 (mild severity) or 2 (moderate severity) at the time of treatment randomization and administration of the first dose of study medication. Potential subjects with medical conditions that would influence cognition or likelihood of study completion (including heart failure) were excluded, as were those without a reliable caregiver willing to participate and comply with protocol responsibilities. Patients with diabetes mellitus requiring treatment with oral medications or insulin were also excluded. All subjects who provided consent were randomized and received at least 1 dose of study medication. The patient flow is illustrated in the Figure.

Subjects received either 15-mg pioglitazone tablets or matched placebo beginning with 1 tablet daily. Daily dosing escalated by 1 tablet each week to 3 tablets daily to achieve a maximum dose of 45 mg of pioglitazone daily. Because of the potential for PPARγ activity by high-dose vitamin E supplementation, enrolled subjects discontinued all use of prior vitamin E supplements and were provided with 200-UI vitamin E capsules to be taken once daily. Medication compliance of more than 85% was required for continued participation and was assessed at each visit by pill counts.

Subjects could take prescribed cholinesterase inhibitor medications, provided they maintained a stable dose for 90 days prior to enrollment. Stable doses of antidepressant and antipsychotic drugs were also allowed if symptoms were adequately controlled. Memantine was approved for prescriptive use in the United States during this study. Based on subject demand, clinical equipoise, and the safety-oriented primary goal of the study, the protocol was modified to allow subjects to begin memantine therapy if prescribed. Memantine use was then incorporated as a planned covariate in the outcome analyses.

SAFETY MONITORING

Baseline health status was evaluated by physical and neurological examinations, routine blood tests, and electrocardiogram; these were repeated at study conclusion. Every 3 months, physical and neurological examinations, complete blood cell count, blood glucose level, hemoglobin A1C level, and hepatic function markers (alanine aminotransferase and aspartate aminotransferase levels) were obtained. Clinical adverse event monitoring was conducted according to Food and Drug Administration regulations. An independent safety monitoring committee systematically reviewed adverse event reporting throughout the study.

EFFICACY OUTCOMES

One goal of the study was to explore the potential magnitude of treatment effects on outcomes used in dementia clinical trials. The study was not designed to demonstrate statistically significant effects on these outcomes. Outcome measures were collected every 3 months, with planned analyses for overall change over 18 months. If statistically significant differences were identified at 18 months, additional analyses of the 3-month data...
would be conducted to determine the time course of the treatment response. Clinical outcome measures were:

1. Clinical Dementia Rating sum of boxes (CDR-SB): This is an alternate scoring system, using the same data collection process as the CDR. In contrast to its standard scoring, which provides ordinal-level data, CDR-SB provides interval-scale data, which were amenable to our planned statistical analyses.

2. Alzheimer’s Disease Assessment Scale Cognitive Score (ADAS-COG): This is a very sensitive 70-point psychometric scale for measuring cognitive function with an emphasis on memory, language, and praxis.

3. Neuropsychiatric Inventory: This was developed to assess behavioral disturbances occurring in patients with dementia. It rates severity and frequency of behavioral and psychiatric symptoms associated with dementia.

4. Alzheimer’s Disease Functional Assessment and Change Score: This scale assesses changes in instrumental and basic activities of daily living over time.

5. Nurses’ Observation Scale for Geriatric Patients: This is an easily administered scale designed to provide reliable assessments of multiple realms of function, namely memory, instrumental activities of daily living, self-care, mood, social behavior, and disturbing behavior. The instrument obtains caregiver ratings for each of 30 items on a 5-point scale according to frequency of occurrence. It provides a summary of the caregiver’s interpretation of the impact of dementia on the subject’s life.

Additionally, the Clinician’s Interview-Based Impression–Plus was evaluated at baseline and study conclusion. This is a global rating derived through an independent, comprehensive interview between the subject and caregiver by a clinician who is barred from knowledge of all psychometric test scores. Using the results from baseline for reference, the clinician interviewed the subject and caregiver at the final visit to obtain an “Impression of Change.”

ANALYSIS PLAN EFFICACY

Given the small sample size, efficacy analyses were intended to be exploratory. t Tests and χ² tests for independence were used, where appropriate, to test whether the 2 treatment groups (pioglitazone vs placebo) were similar or different in terms of age at baseline, education, sex, ethnicity (white vs minority), Mini-Mental State Examination score at baseline, presence of an APOE4 allele, and use of memantine during the study period.

The effects of pioglitazone on the clinical efficacy variables and on their rates of change over time were evaluated using multilevel models for repeated measures, except for Clinician’s Interview-Based Impression–Plus Impression of Change for which only baseline and termination scores were obtained. Multilevel analysis, a statistical technique for analyzing data with nested variability, is also commonly referred to as “hierarchical linear modeling” or “mixed models.” It corrects for a lack of independence within clusters, such as several repeated observations within the same subject.

RESULTS

SUBJECT CHARACTERISTICS

Initial enrollment was 29 (14 pioglitazone, 15 placebo) subjects; 25 subjects (12 pioglitazone, 13 placebo) completed 18 months of therapy. Early discontinuations were associated with change in caregiver status (n=2) and withdrawal of consent (n=2). The sample characteristics are reported in Table 1. Women constituted 64% of the pioglitazone group and 60% of the placebo group. Patients receiving pioglitazone were older than those in the placebo group (mean, 74.9 years vs 67.0 years; P < .05); no other demographic variable differed between groups. No statistically significant differences for education, sex, ethnicity, APOE4 status, or Mini-Mental State Examination score at baseline were identified (all P values > .05). Seven patients began memantine therapy during the study (3 pioglitazone, 4 placebo). There was no difference in the time to onset of memantine therapy between treatment groups (P > .05).

SAFETY AND TOLERABILITY

No early discontinuations were attributed to adverse events. In general, pioglitazone was well tolerated, with no pattern of effect on blood glucose levels, hemoglobin A₁c levels, or other blood chemistry or hematologic measures. No serious adverse events were associated with pioglitazone treatment. Peripheral edema was the adverse effect most clearly different between groups, affecting 4 pioglitazone-treated and no placebo-treated subjects. Edema is a commonly recognized effect of pioglitazone in clinical use and this potential adverse treatment effect was anticipated. Adverse events affecting at least 3 pioglitazone-treated subjects are reported in Table 2, all of which were of mild or moderate severity.
**Efficacy**

Observed mean scores at 6-month intervals, as well as entry and final Clinician’s Interview-Based Impression–Plus Impression of Change scores, are shown in Table 3. Regression coefficients from the multilevel analysis are illustrated in Table 4. The coefficient for pioglitazone is the estimated difference in the adjusted mean for the outcome between the pioglitazone group and the placebo group. The coefficient of pioglitazone for ADAS-COG indicates that the adjusted mean for the ADAS-COG per month is −0.746 point less in the pioglitazone group than in the placebo group. As predicted by our small sample size, no significant effect of treatment was observed on any clinical outcome measure. All measures except Neuropsychiatric Inventory total score worsened over time (\(P < .05\)), consistent with the progressive course of AD.

**Effect Size Calculations**

An exploratory goal of this study was to estimate treatment effect size for pioglitazone. Sample size analyses were conducted to determine the number of subjects needed to detect significant differences between the pioglitazone and control group on 2 outcome measures typically used for regulatory approval, ADAS-COG and CDR-SB. We used Optimal Design software (J. Spybrook, S. W. Raudenbush, R. Congdon, A. Martinez, “Optimal Design for Longitudinal and Multilevel...
Pioglitazone was well tolerated, demonstrating no unanticipated safety problems in a sample of patients with AD without diabetes mellitus through an 18-month treatment trial. No efficacy was demonstrated on clinical outcome measures. Although marketed for the treatment of type 2 diabetes, long-term pioglitazone administration did not lead to clinically significant changes in blood glucose levels in these nondiabetic individuals. Edema is a frequent complication of thiazolidinedione use in clinical populations, affecting as much as 18% of treated individuals. This rate is consistent with our observations (4 of 14 subjects, 28.6%), but much higher than prescribing information would predict, as well as higher than observed in the trial of rosiglitazone treatment in AD. The risks for peripheral edema, heart failure, and other cardiovascular morbidities will need to be closely monitored if future trials of thiazolidinedione agents are undertaken for AD. Additionally, edema may limit blinding in studies of pioglitazone.

This study was not intended to determine treatment efficacy. At the time of its design (1999-2000), no human data existed regarding the magnitude of any potential treatment effect of thiazolidinediones in AD, nor was information published on the effects of thiazolidinediones on nondiabetic older adults. The efficacy measures were selected to cover a broad range of outcomes of both clinical relevance and regulatory impact. As expected, no treatment effects were observed on the efficacy outcomes. The small and nonsignificant differences suggest that mild to moderate AD is not likely to be an appropriate population for further study of thiazolidinediones.

The reasons why PPARγ agonists exert a beneficial effect in AD models but not in clinical samples remains unclear. Disease severity may play a role. Reducing systemic insulin resistance through PPARγ modulation has a salutary effect on neuronal function and memory formation, which could contribute to the greater observed treatment effect in earlier phases of AD, like mild cognitive impairment. The amount of neuronal loss and synaptic dysfunction present by the time the full AD clinical syndrome is evident may overwhelm the functional benefits associated with treatment. It is also possible that the suppression of microglia-mediated inflammation by thiazolidinediones is insufficient to exert a clinically relevant impact in humans. Furthermore, there may be endophenotypes of AD, such as APOE4-negative individuals or those with greater insulin resistance, who might selectively benefit from this drug class. Our study was too small to evaluate the clinical meaningfulness of such variables.

Disappointing results of treatment trials based on the amyloid hypothesis, and the reasonable degree of safety identified in this trial, suggest that exploratory studies of thiazolidinediones remain warranted. Future studies of this class should focus on earlier stages of disease progression and be augmented by biomarkers, such as nuclear imaging techniques, to measure changes in microglial activation associated with treatment.

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