Atorvastatin for the Treatment of Mild to Moderate Alzheimer Disease

Preliminary Results

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Background: Laboratory evidence of cholesterol-induced production of amyloid β as a putative neurotoxin precipitating Alzheimer disease, along with epidemiological evidence, suggests that cholesterol-lowering statin drugs may favorably influence the progression of the disorder.

Objective: To determine if treatment with atorvastatin calcium affects the cognitive and/or behavioral decline in patients with mild to moderate Alzheimer disease.

Design: Pilot intention-to-treat, proof-of-concept, double-blind, placebo-controlled, randomized (1:1) trial with a 1-year exposure to once-daily atorvastatin calcium (80 mg; two 40-mg tablets) or placebo using last observation carried forward analysis of covariance as the primary method of statistical assessment.

Participants: Individuals with mild to moderate Alzheimer disease (Mini-Mental State Examination score of 12-28) were recruited. Of the 98 participants providing informed consent, 71 were eligible for randomization, 67 were randomized, and 63 subjects completed the 3-month visit and were considered evaluable.

Main Outcome Measures: The primary outcome measures were change in Alzheimer's Disease Assessment Scale–cognitive subscale and the Clinical Global Impression of Change Scale scores. The secondary outcome measures included scores on the Mini-Mental State Examination, Geriatric Depression Scale, the Neuropsychiatric Inventory Scale, and the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory. The tertiary outcome measures included total cholesterol, low-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol levels.

Results: Atorvastatin reduced circulating cholesterol levels and produced a positive signal on each of the clinical outcome measures compared with placebo. This beneficial effect reached significance for the Geriatric Depression Scale and the Alzheimer's Disease Assessment Scale–cognitive subscale at 6 months and was significant at the level of a trend for the Alzheimer's Disease Assessment Scale–cognitive subscale, Clinical Global Impression of Change Scale, and Neuropsychiatric Inventory Scale at 12 months assessed by analysis of covariance with last observation carried forward.

Conclusion: Atorvastatin treatment may be of some clinical benefit and could be established as an effective therapy for Alzheimer disease if the current findings are substantiated by a much larger multicenter trial.

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some, but not all, epidemiological studies suggest that prior statin use in treating risk of coronary artery disease may reduce the risk of AD later in life.8-10

We tested the cholesterol-lowering medication atorvastatin calcium for positive effects on cognitive and noncognitive deterioration in mild to moderate AD. This investigator-initiated clinical evaluation began in 1999 as a proof-of-concept trial evaluating atorvastatin for clinical benefit. We used tests of clinical efficacy (Clinical Global Impression of Change scale11 [CGIC]) and cognitive function (Alzheimer’s Disease Assessment Scale—cognitive subscale12 [ADAS-cog]) as primary outcomes and measures of global function (Mini-Mental State Examination [MMSE]), psychiatric symptoms (Neuropsychiatric Inventory Caregiver Distress Scale13 [NPI]), activity of daily living (Alzheimer’s Disease Cooperative Study—Activities of Daily Living Inventory14,15 [ADCS-ADL]), and depression severity (Geriatric Depression Scale16 [GDS]) as secondary outcome indexes. Tertiary outcome measures included total and fractionated cholesterol levels.

METHODS

The study was initiated as an intention-to-treat investigation using a double-blind, placebo-controlled, randomized (1:1) design testing atorvastatin calcium (80 mg/d) compared with placebo for clinical benefit in treating mild to moderate AD for a 1-year period. As an intention-to-treat study, early withdrawals were anticipated and any subject completing the 3-month visit was considered evaluable. Written informed consent was obtained from participants and the participant’s legally authorized representative or caregiver using an institutional review board–approved informed consent form.

We recruited 97 individuals with probable or possible AD (National Institute of Neurological and Communicative Disorders and Stroke—the Alzheimer’s Disease and Related Disorders Associations’ [NINCDS/ADRA] criteria)11 for this single-site study. Individuals 51 years and older with mild to moderate impairment (MMSE score, 12-28) meeting all preestablished criteria were eligible to participate in the trial. A single dose of atorvastatin calcium (80 mg/d) without dose titration was used. Because active treatment was expected to reduce circulating cholesterol levels, all investigators were blinded to both treatment group and cholesterol profiles after randomization. Only the special physician safety monitor (P.B.), who was not involved in any other aspect of the trial, viewed quarterly cholesterol levels to ensure patient safety. Blood-borne markers of liver dysfunction and altered muscle physiologic features were also monitored quarterly by the safety monitor as indicators of possible adverse events known to accompany administration of statins. Subjects were ineligible if they were already taking a cholesterol-lowering medication or being administered an investigational treatment for AD.

Atorvastatin calcium tablets (40 mg) and identical placebo tablets were supplied in bulk (single lot numbers for each, respectively) by Pfizer Pharmaceuticals, Inc (Ann Arbor, Mich). Active drug or placebo was packaged in bottles of 200 tablets for each treatment group (D.W.). Bottles of study medication (as 3-month supplies) were coded at the pharmacy.

To participate, an individual 51 years or older, with a diagnosis of probable or possible AD according to NINCDS-ADRDA and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for dementia and at least a ninth-grade education, was required to provide informed consent. It was necessary for the participant to be accompanied by an appropriate caregiver who could aid in administration of medication and make assessments, be of good general health as evidenced by physical, neurological, and clinical laboratory examinations, and speak English fluently. Participants were required to score 4 or less on the modified Hachinski Ischemia Scale18 and 20 or less on the GDS.

Participants were allowed to continue the use of stable doses of medications for the treatment of nonexcluded medical conditions for 4 weeks prior to screening; this included the use of 400 IU or lower of vitamin E. Patients currently taking cholinesterase inhibitors were required to have taken a stable dose for at least 3 months. No study subject was using memantine or allowed to initiate cholinesterase inhibitor use after trial entrance and continue participation.

Individuals with a neurological or psychiatric disease other than AD, including suspected Parkinson disease or dementia with Lewy bodies,19 significant systemic illness, organ failure, myocardial infarction, cardiac or thromboembolic vascular disease, major depression according to DSM-IV criteria, or currently using anticholinergic medications, were excluded from participation. Participants with a history of head injury, significant liver disease and/or elevated transaminase levels, allergy to statins, or screening total cholesterol levels below 90 mg/dL (2.3 mmol/L) were also excluded from participation.

At screening, the baseline MMSE20 was administered to ensure eligibility; if within established criteria (score 12-28), the modified Hachinski Ischemia Scale score (≤4) and the base-line GDS score (<20)16 were established to exclude individuals with significant vascular risk factors or clinical depression, respectively. At this visit, blood was drawn for testing (experimental and safety monitoring) and the baseline ADAS-cog12 was administered (by individuals blinded to CGIC performance).

At the randomization visit, no more than 14 days after the screening visit, the baseline CGIC11 (performed by a single individual blind to all other assessment information), NPI,13 and ADCS-ADL14,15 were administered.

The ADAS-cog, MMSE, and CGIC were readministered at the 3-, 6-, 9-, and 12-month visits, and the NPI and ADCS-ADL were readministered at the 6- and 12-month visits. The GDS was readministered at the participant’s exit visit (12-month or early termination).

Fasting cholesterol (total, low-density lipoprotein, high-density lipoprotein, and very low-density lipoprotein), liver function, and creatinine phosphokinase (to monitor muscle derangements and rhabdomyolysis) tests were performed using standard, approved methods in the Clinical Laboratory Improvement Amendments–certified and accredited Clinical Chemistry Laboratory at Walter O. Boswell Hospital, Sun City, Ariz. Any individual exhibiting a greater than 3-fold increase in liver function test results or a 10-fold increase in creatinine phosphokinase level, both higher than the upper limits of normal, was considered to have experienced an adverse event requiring discontinuation of study medication without possibility of resuming trial participation.

The initial statistical evaluation was to determine if there were differences in the mean value for any index between the atorvastatin and placebo groups prior to randomization (2-tailed independent t tests) (Table 1).

Thereafter, we used a statistical approach routinely used in intention-to-treat AD trials21,22 by performing analysis of covariance considering last observation carried forward data using baseline observations as a covariant to compare differences of least
squares means between the groups (SAS Version 6.12; SAS Institute Inc, Cary, NC). Screen and quarterly visit values were evaluated for the ADAS-cog, MMSE, and cholesterol. Change in CGIC scores from baseline at quarterly visits was evaluated. Baseline and semiannual visit scores were compared for the NPI and ADCS-ADL. Screening and exit scores were compared for the GDS. Significance was based on 2-tailed evaluations.

RESULTS

SUBJECT POPULATION AND STUDY ATTRITION

We obtained 98 informed consents (Figure 1). Fifteen individuals withdrew prior to screening primarily to participate in other treatment trials. There were 12 screen failures, leaving 71 individuals eligible for randomization; 4 withdrew prior to the baseline visit. Sixty-seven individuals were blindly randomized (1:1) to receive either 80 mg of atorvastatin calcium or placebo. Sixty-three individuals were considered evaluable by completing the 3-month visit, 32 individuals receiving atorvastatin and 31 individuals receiving placebo. All but 6 individuals were taking cholinesterase inhibitors, 3 in the atorvastatin group and 3 in the placebo group. A total of 56 individuals completed the 6-month visit, 29 receiving active medication and 27 receiving placebo. Forty-six individuals completed the 9-month visit, 26 receiving atorvastatin and 22 receiving placebo. Forty-six individuals completed the 1-year study, 25 receiving atorvastatin and 21 receiving placebo.

PRERANDOMIZATION COMPARISON OF GROUP DIFFERENCES

There was no significant difference in the mean entrance values for any demographic, clinical, or chemical index between individuals later randomized into the atorvastatin and placebo groups (Table 1), although performance on the NPI in the placebo group was somewhat more impaired at the start of the trial. There was no difference in the entrance Hachinski Ischemia Scale score (mean ± SD, atorvastatin = 2.44 ± 0.25; placebo = 2.52 ± 0.23) between the 2 groups.

BLOOD TESTING RESULTS

Consistent with results in individuals with normal cognition, atorvastatin treatment produced significant decreases in total cholesterol (Figure 2A), low-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol levels (not shown) among the individuals with mild to moderate AD compared with placebo (P<.01). These significant decreases relative to placebo (P<.002) in total cholesterol (40%), low-density lipoprotein cholesterol (54%), and very low-density lipoprotein cholesterol (30%) levels were detected at the 3-month visit and persisted to 12 months.

PRIMARY CLINICAL OUTCOME MEASURES

Both the atorvastatin and placebo groups showed deterioration on the ADAS-cog at 3 months; the placebo population continued to deteriorate approximately 1 point per quarter thereafter (Figure 2B). Performance on the ADAS-cog in the atorvastatin population was approximately 3.5 points superior to the placebo group at 6 months and 12 months. Difference in ADAS-cog scores between the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Group (n = 31)</th>
<th>Atorvastatin Calcium Group (n = 32)</th>
<th>P Value</th>
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<tr>
<td>Age, y</td>
<td>78.9 ± 1.2</td>
<td>78.15 ± 1.3</td>
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<td>Female, %</td>
<td>35.5</td>
<td>37.5</td>
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<tr>
<td>Education, y</td>
<td>14.03 ± 0.53</td>
<td>13.41 ± 0.47</td>
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<td>Apo E4 allele, %</td>
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<td>ADAS-cog</td>
<td>19.90 ± 1.73</td>
<td>20.60 ± 1.73</td>
<td>.71</td>
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<td>MMSE20</td>
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<td>NPI13</td>
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<td>GDS19</td>
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<td>ADCS-ADL14,15</td>
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<td>Blood marker</td>
<td>Total cholesterol, mg/dL</td>
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<td>LDL cholesterol, mg/dL</td>
<td>121.22 ± 6.19</td>
<td>124.47 ± 5.92</td>
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<td>VLDL cholesterol, mg/dL</td>
<td>26.65 ± 2.26</td>
<td>27.84 ± 2.13</td>
<td>.81</td>
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</table>

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; Apo E, apolipoprotein E; GDS, Geriatric Depression Scale; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory Caregiver Distress Scale; VLDL, very low-density lipoprotein.

SI conversion factors: To convert total cholesterol to millimoles per liter, multiply by 0.0259; LDL cholesterol to millimoles per liter, 0.02586.

*Values are expressed as mean ± SEM (based on eventual randomization grouping) unless otherwise indicated.
groups was significant at 6 months ($P < .003$) and all but significant at 12 months ($P = .055$) (Table 2). A trend for a difference on the CGIC between the atorvastatin and placebo groups was achieved at both 9 ($P = .058$) (Figure 2C) and 12 months ($P = .07$) (Table 2).

SECONDARY CLINICAL OUTCOME MEASURES

Although performance on the MMSE in the atorvastatin group showed limited improvement after the 3-month visit (Figure 2D), the difference between the groups was
We have found that daily administration of 80 mg of atorvastatin calcium significantly reduces circulating cholesterol levels and may have a positive effect on the progressive deterioration of cognitive function and behavior anticipated in mild to moderate AD. As a pilot proof-of-concept study, significant differences were not expected, but benefits identified tend to support the trial’s rationale based on the hypothesis that excess brain cholesterol-promoting amyloid β production and subsequently the symptoms of AD come from the blood because of increased circulating levels. Although the data may seem to support a cholesterol-lowering mechanism, we must acknowledge that other physiologic effects of atorvastatin (i.e., anti-inflammatory, vascular, or pleiotropic) could contribute to or produce the apparent beneficial effect.

Finally, although the results clearly hold promise, this was a pilot proof-of-concept trial with a small number of participants. We believe that we provide evidence for proof of concept, and establishment of similar benefit of atorvastatin in a multicenter trial investigating the effect in a much larger population may provide proof of therapy. Two such studies are ongoing.

Acknowledgment: We thank the Institute for the Study of Aging and the Estee Lauder Charitable Trust for making this study possible by providing initial funding. We thank Pfizer Inc for provision of additional funding and study medication.

**Table 2. Significance of Difference After 12 Months of Atorvastatin Treatment Compared With Placebo for Each Clinical Instrument**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>ANCOVA-LOCF</th>
<th>P Value</th>
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<tr>
<td>CGIC&lt;sup&gt;11&lt;/sup&gt;</td>
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**REFERENCES**


