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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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/ADRDA] criteria)13 for this single-site study. Individuals 51 years and older with mild to moderate impairment (MMSE score, 12-28) 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, allergy to statin medications, or screen 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 baseline 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 trials10,22 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. But all 66 individuals were taking cholesterol 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. Differences in ADAS-cog scores between the
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...
Atorvastatin produced significant benefit on the ADCS-ADL between the treatment and placebo group and improvement in the atorvastatin group (Figure 2F). Differences in performance on the ADCS-ADL between the treatment and placebo groups did not achieve significance (P > .23) (Table 2).

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 (ie, 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.

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Author Contributions: Study concept and design: Sparks and Connor. Acquisition of data: Sabbagh, Connor, Lopez, Browne, Wasser, Johnson-Traver, Lochhead, and Ziolowski. Analysis and interpretation of data: Sparks and Launer. Drafting of the manuscript: Sparks and Connor. Critical revision of the manuscript for important intellectual content: Sparks, Sabbagh, Lopez, Launer, Browne, Wasser, Johnson-Traver, Lochhead, and Ziolowski. Statistical analysis: Launer. Obtained funding: Sparks. Administrative, technical, and material support: Sparks, Sabbagh, Connor, Lopez, Browne, Wasser, Johnson-Traver, Lochhead, and Ziolowski. Study supervision: Sparks.

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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 P Value</th>
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<tbody>
<tr>
<td>CGIC11</td>
<td>.07</td>
</tr>
<tr>
<td>ADAS-cog12</td>
<td>.055</td>
</tr>
<tr>
<td>NPI13</td>
<td>.07</td>
</tr>
<tr>
<td>MMSE14</td>
<td>.25</td>
</tr>
<tr>
<td>GDS15</td>
<td>.04</td>
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<tr>
<td>ADCS-ADL16,15</td>
<td>.23</td>
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Abbreviations: ADAS-cog, Alzheimer’s Disease Assessment Scale–cognitive subscale; ADCS-ADL, Alzheimer’s Disease Cooperative Study–Activities of Daily Living Inventory; ANCOVA, analysis of covariance; CGIC, Clinical Global Impression of Change Scale; GDS, Geriatric Depression Scale; LOCF, last observation carried forward; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory Caregiver Distress Scale.

*Values are based on a 2-tailed assessment of least squares means by ANCOVA with LOCF for evaluable subjects. Atorvastatin was given as atorvastatin calcium.

References