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Hippocampal volume change in the Alzheimer Disease Cholesterol-Lowering Treatment trial

■ ABSTRACT

Numerous clinical studies suggest a link between elevated cholesterol and increased risk of Alzheimer disease (AD), and the preponderance of data suggests that statin therapy may reduce the risk of AD later in life. The first clinical investigation of statin therapy in patients with AD, the AD Cholesterol-Lowering Treatment (ADCLT) trial, found that atorvastatin 80 mg/day was associated with improvements relative to placebo on some, but not all, cognitive measures after 6 months and 1 year of therapy. We report here findings from a pilot ADCLT substudy showing a nonsignificant reduction in total hippocampal volume with 1 year of atorvastatin therapy compared with placebo, driven by a highly significant reduction in right hippocampal volume with atorvastatin therapy.

Alzheimer disease (AD) is a degenerative disorder characterized by a gradual deterioration in memory. In its clinically overt stages, obvious signs of neural degeneration on magnetic resonance imaging (MRI) appear as global cerebral atrophy. Even in the earliest stages of the disease, regional cell loss can be observed, particularly in the mesial temporal lobe regions, specifically the hippocampus and entorhinal cortex.[1–3]

MRI is used primarily as a diagnostic tool to rule out conditions other than AD. However, MRI may be useful in understanding whether the underlying processes that are associated with these cognitive changes can be attributed to general or specific effects of the disease process. Volumetric changes observed with MRI in the hippocampal region have been correlated with disease progression[4,5] and predict development of AD in individuals with isolated memory impairment,[6] suggesting that neuroimaging quantification may serve as a useful measure of brain integrity in patients with AD.

New treatments for AD are emerging, and assessing their efficacy is of critical importance. The rationale for testing statin drugs as a therapy for AD was bolstered by ever-mounting preclinical animal and human data suggesting that elevated circulating cholesterol exacerbates AD-like pathology and that statin treatment, in part, reverses the effect of cholesterol. This article surveys current evidence on the association between cholesterol and AD as well as between statin use and AD risk. We conclude by focusing on results from the first clinical investigation of statin therapy in patients with AD and present new results of a substudy of this trial examining the morphologic effects of statin therapy in AD patients.

■ LINK BETWEEN CHOLESTEROL AND AD

Early epidemiologic surveys suggested an association between a high-fat/high-cholesterol diet and increased risk of AD,[7–10] and this suggestion has been supported by more recent investigations.[11,12] Cholesterol levels are increased in the blood of AD patients,[7,13–16] and increased cholesterol has been observed in the AD brain as a function of the apolipoprotein E allotype.[8,17]

Numerous clinical studies suggest a link between elevated cholesterol and increased risk of AD,[17–23] with one study reporting a threefold increase in the risk of AD with elevated serum cholesterol, even after adjusting for age and presence of the apolipoprotein E4 allele.[19] Another study indicates that persistently elevated cholesterol levels in midlife increase the risk of AD.[23] A retrospective analysis of the Framingham Study suggested, however, that there is no relationship between total cholesterol levels and risk of incident

AD.[24] A more recent report indicated that language performance in elderly subjects without dementia declined faster among those individuals with higher cholesterol levels, but this effect did not remain significant after accounting for multiple comparisons.[25] In contrast, the Three-City Study, a population-based cohort investigation of 9,294 subjects in France, demonstrated a significant increase in the risk of dementia among subjects who had hyperlipidemia (odds ratio [OR] = 1.43; 95% confidence interval [CI], 1.03 to 1.99).[12]

■ STATIN USE AND RISK OF AD

The preponderance of clinical data suggests that statin therapy may reduce the risk of AD later in life. Since the initial epidemiologic investigation assessing the effect of statin use on later risk of AD in the elderly, there have been 13 additional studies; all but two of these studies have reported benefit with cholesterol-lowering therapy.

In the two earliest epidemiologic studies, Wolozin et al demonstrated benefit with the use of lovastatin and pravastatin, but not with simvastatin or non-statin therapy,[26] and Jick et al showed benefit associated with cholesterol-lowering therapy, but not specifically with statin use.[27] Five epidemiologic studies published in 2002 suggested that prior statin use reduced the risk of dementia or AD.[28–32] Meta-analysis of these first seven retrospective studies suggested a significant reduction in the risk of later cognitive impairment with statin use (relative risk = 0.43; 95% CI, 0.31 to 0.62), but the risk reduction with lipid-lowering agents collectively (not just statins) was not statistically significant.[33]

In 2004, Zamrini et al reported a 39% reduction in the risk of AD in statin users compared with nonusers (OR = 0.61; 95% CI, 0.42 to 0.87).[34] That same year, Li et al suggested that there was no association between statin use and a reduced incidence of probable AD using a time-dependent proportional hazards model, but if the data were analyzed (inappropriately) as a case-control study, a significant protective effect was identified.[35]

Data from the Cache County Study cohort demonstrated no significant reduction in the risk of AD with statin use but allowed for the possibility that some benefit could be provided with longer-term statin therapy.[36] In contrast, the Three-City Study of 9,294 individuals in France identified a significant reduction in the risk of AD with statin use (OR = 0.61; 95% CI, 0.41 to 0.91).[12] Rea et al reported that prior statin use did not decrease the risk of dementia or

AD, but when they included in their analysis individuals currently using a statin, there was a significant reduction in the hazard ratios for AD and for all-cause dementia.[37] The two most recent epidemiologic studies both suggest that statin therapy slows cognitive decline in AD.[38,39]

■ COGNITIVE PERFORMANCE AND STATIN USE

A retrospective cohort study that assessed intelligence and cognition at a young age and again when subjects were in their 80s indicated that statin use had a significant beneficial effect on cognitive ability.[40]

In contrast, two very large prospective studies published in 2002 suggested that statins produce no positive effect on cognition in younger individuals at risk for heart disease.[41,42] The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) found that the mean Mini-Mental State Examination (MMSE) score, which was assessed only at subjects' last on-treatment clinical visit, was comparable between the study's pravastatin and placebo groups.[41] Likewise, the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study, which used the Telephone Interview for Cognitive Status questionnaire at the end of the investigation, reported that simvastatin had no positive effect on cognitive performance compared with placebo, but this finding was obtained in the absence of baseline data.[42] Given the limited cognitive assessments performed in these two studies, no firm conclusions should be drawn.

A more recent prospective comparison of atorvastatin and placebo in younger subjects did include baseline and follow-up assessment of cognitive function, and it identified significantly superior performance in the statin-treated population on the MMSE and on tests of attention, psychomotor speed, mental flexibility, working memory, and memory retrieval.[43]

■ STATIN TREATMENT OF AD:
THE AD CHOLESTEROL-LOWERING TREATMENT TRIAL

The initial clinical investigation of statin therapy in patients with AD—the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial—involved atorvastatin.[44] Patients with mild to moderate AD were randomized to either placebo or 80 mg/day of atorvastatin for a 1-year period. Evaluable data were available for 63 patients (32 in the atorvastatin group, 31 in the placebo group). End points included the change in performance on the following measures:
- MMSE
- Alzheimer's Disease Assessment Scale–cogni-

tive subscale (ADAS-cog)
- Neuropsychiatric Inventory Caregiver Distress Scale (NPI)
- Clinical Global Impression of Change scale (CGIC)
- Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL)
- Geriatric Depression Scale (GDS).

Cognitive results

In the setting of continued cholinesterase inhibitor use, atorvastatin provided significant benefit on the ADAS-cog at 26 weeks compared with placebo (P = .003) and marginally significant benefit at 1 year (P = .055) while producing a trend for benefit on the CGIC and NPI and a statistically significant improvement on the GDS after 1 year of active treatment.[44] The observed benefit on the MMSE with atorvastatin versus placebo did not reach statistical significance, and no discernible difference was observed on the ADCS-ADL.[44] In contrast, a significant difference in the slope of deterioration on the MMSE and the GDS in the atorvastatin group versus the placebo group suggested disease modification.[45]

Blood test results

Levels of total cholesterol, low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol were significantly reduced between 3 and 12 months in the atorvastatin group compared with the placebo group;[44] levels of high-density lipoprotein cholesterol were decreased by 12 months of atorvastatin therapy,[45] but the circulating free radical load was unchanged,[45] as were levels of C-reactive protein.[46] Notably, after assuring fasting compliance, we found that triglyceride levels were significantly increased by atorvastatin treatment in AD patients **(Figure 1)**.

Secondary analysis and initial morphometric substudy

Secondary assessment indicated that the subjects who garnered the greatest benefit from atorvastatin therapy in terms of their 6-month ADAS-cog score were those who had higher cholesterol levels at trial entry, those who harbored the apolipoprotein E4 allele, and those who were less affected by AD at trial entry (ie, with higher entry MMSE scores).[47]

In an ADCLT substudy using new voxel-based morphometry techniques, we quantitatively assessed gray matter density in 15 ADCLT trial participants and compared it with density findings in 15 normal elderly controls.[48] Regional reductions in gray matter density were observed in the AD patients compared with the controls. Large differences in gray matter
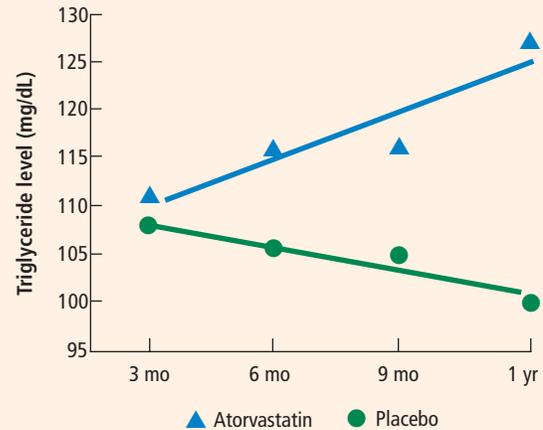
FIGURE 1. Mean circulating triglyceride levels from all evaluable subjects (N = 63) in the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. After insuring compliance for fasting blood draws, triglyceride levels were determined every quarter during the study. Atorvastatin recipients had a significant 30% increase in triglyceride levels compared with placebo controls (P < .05).

concentration were observed bilaterally in the temporal lobe. The anterior cingulate, right superior temporal, left superior frontal, and posterior cingulate regions also showed significantly decreased gray matter density in the AD patients compared with the controls. A significant relationship was observed between gray matter density and ADAS-cog error scores—ie, more severe levels of cognitive impairment correlated with reduced gray matter density.[48]

■ PILOT SUBSTUDY OF ADCLT: ASSESSING MORPHOLOGIC CHANGES WITH STATIN THERAPY

Eleven of the 15 ADCLT trial participants from the above morphometric substudy returned for MRI assessment after 1 year of treatment with either atorvastatin or placebo. We report here the comparative effects of atorvastatin and placebo on hippocampal volume and the relationship with cognitive performance.

Participants

Subjects were participating in the ADCLT trial, an investigator-initiated, double-blind, placebo-controlled study. Neuroimaging was performed at the Barrow Neurological Institute, Phoenix, AZ, for a subset of the participants in the trial (n = 11) as a pilot study to examine neural changes associated with atorvastatin therapy.

Each patient underwent screening, assignment to either atorvastatin 80 mg/day or placebo, and medical and cognitive assessment at Sun Health Research Institute, Sun City, AZ, prior to imaging at Barrow. All

TABLE 1
Patient demographics and results from pilot morphometric substudy of ADCLT

Placebo group	Age (yr)	Years of education	MMSE change score	ADAS-cog change score	Change in hippocampal volume (mm³) Left	Right	Combined
Patient 1	65	20	−2	0.5	−497	−109	−605
Patient 2	85	16	−2	1.8	−193	−307	−500
Patient 3	78	12	3	3.5	62	43	105
Patient 4	91	18	−6	7.2	−346	421	75
Patient 5	84	12	−1	−4.0	−208	457	248
Placebo group mean	80.6 ± 4.4	15.7 ± 1.6	−1.6 ± 1.4	1.9 ± 1.8	−236 ± 93	101 ± 149	−134 ± 174
Atorvastatin group							
Patient 1	83	20	1	0.0	1,650	−728	922
Patient 2	81	16	3	0.0	−250	−390	−640
Patient 3	67	16	−3	1.1	−435	−189	−624
Patient 4	79	12	1	−2.4	−407	−292	−693
Patient 5	65	18	−4	8.0	−1,289	−504	−1,793
Patient 6	72	12	−4	2.5	1	−670	−669
Atorvastatin group mean	74.5 ± 3.1	15.7 ± 1.3	−0.9 ± 1.3	1.5 ± 1.5	−121 ± 396	−462 ± 86*	−583 ± 354

* P = .008 vs placebo group

ADCLT = Alzheimer's Disease Cholesterol-Lowering Treatment trial; MMSE = Mini-Mental State Examination; ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale

patients met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria for dementia as well as NINCDS-ADRDA criteria for probable AD. Each patient was free of significant psychiatric and neurological history and had a score of 4 or less on the Hachinski Modified Ischemia Scale. All MRIs were reviewed by a neuroradiologist to ensure that there was no evidence of stroke or cortical or lacunar infarcts.

Both sites' institutional review boards approved this project, and all subjects gave written informed consent.

Cognitive assessment

A primary efficacy measure used in the parent study was the ADAS-cog,[49] and the MMSE[50] was a secondary measure. Change scores were determined by comparing values obtained at baseline, prior to randomization to treatment with either atorvastatin or placebo, and after 1 year of treatment. MMSE scores were obtained at the same session as the ADAS-cog scores. Cognitive assessments were obtained within 2 weeks prior to MRI.
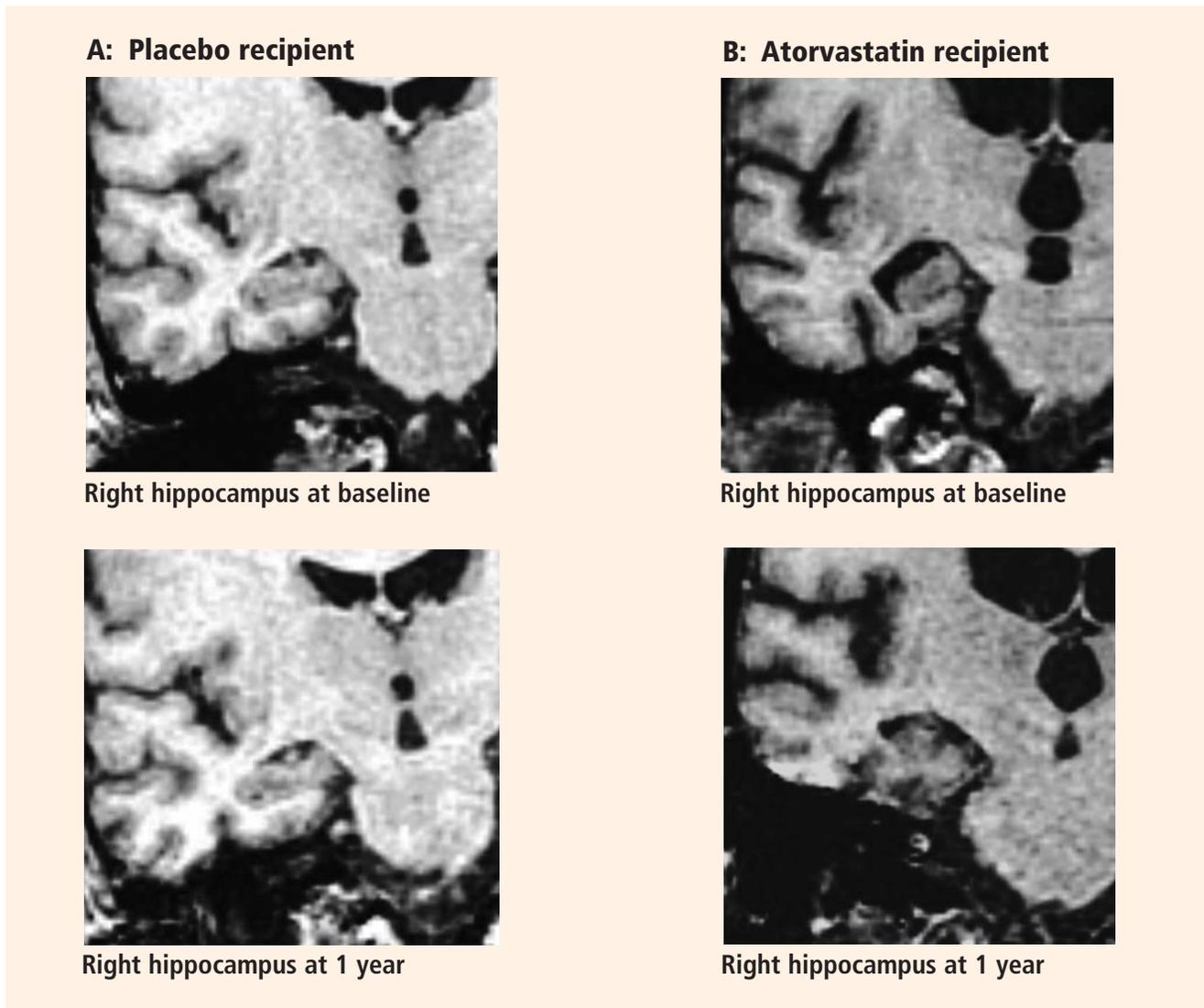
Image acquisition

All participants underwent imaging on a single 1.5-tesla GE scanner at Barrow Neurological Institute. Imaging was conducted both prior to treatment ran-

domization and again after 1 year of treatment. Images of the whole brain were collected using a coronal SPGR (spoiled gradient) T_1-weighted, three-dimensional acquisition with the following parameters:

- Number of acquisitions = 1
- Repetition time = 23 msec
- Echo time = 8 msec
- Flip angle = 35 degrees
- Bandwidth = 12.5 kHz
- Slice thickness = 1.5 mm or 1.9 mm
- 0 skip between slices
- In-plane resolution = 0.9375 × 0.9375.

Hippocampal volumetrics

All imaging analysis was performed within the Analysis of Functional Neuroimages (AFNI) package.[51] We traced the outline of the hippocampus using the three-dimensional SPGR images. The hippocampi were visualized in all three planes, landmarked in the coronal and sagittal planes, and drawn in the coronal plane. We employed the guidelines of Insausti et al[52] and Machulda et al[53] to define the hippocampal boundaries. First we defined the anterior boundary by observing the white matter band and/or the cerebrospinal fluid space between the amygdala and hip-

A: Placebo recipient

Right hippocampus at baseline

Right hippocampus at 1 year

B: Atorvastatin recipient

Right hippocampus at baseline

Right hippocampus at 1 year

FIGURE 2. Differential effects of placebo and atorvastatin therapy on size of the right hippocampus in a pilot substudy of the Alzheimer's Disease Cholesterol-Lowering Treatment trial of patients with mild to moderate Alzheimer disease. In placebo patient 3 from Table 1 (panel A), the right hippocampus is slightly larger after 1 year of treatment with placebo relative to baseline. In contrast, in atorvastatin patient 2 from Table 1 (panel B), the right hippocampus is much smaller after 1 year of treatment with atorvastatin.

pocampus in the sagittal plane. The posterior aspect of the posterior region was initially landmarked in the sagittal plane by locating the posterior edge of the hippocampus and then checking in the coronal plane to ensure that the fornices were completely visualized. Volumes were calculated by importing the extracted hippocampi into MATLAB to measure the volumes.

Statistical analyses

Mean differences between the atorvastatin and placebo groups were evaluated using two-tailed Student *t* tests. Correlation between changes in cognitive measures and changes in the hippocampal volume for the total population and for the treatment groups was determined using Pearson's *r* coefficient. Significance was defined as a *P* value less than .05; a *P* value between .05 and .10 was deemed a trend.

Results

There was no difference in age or in years of education between the atorvastatin and the placebo groups (Table 1).

In contrast to other studies,[54–58] we found in this pilot study that right hippocampal volume was slightly less than left hippocampal volume (2,015 ± 141 mm^3 vs 2,135 ± 183 mm^3).

Mean changes in performance on the ADAS-cog and MMSE were less pronounced in the atorvastatin group than in the placebo group, but not significantly so **(Table 1)**. However, there was a trend toward superiority in the atorvastatin group on performance on the free word-recall subscale of the ADAS-cog.

The reduction in total hippocampal volume was greater in the atorvastatin group than in the placebo group **(Table 1)**, but the difference was not statistically significant. This effect seems to have been driven by the highly significant reduction in right hippocampal volume in the atorvastatin group relative to the placebo group (P =.008), as illustrated in **Figure 2**.

No significant correlations were found between change in cognitive performance and change in hippocampal volume.

◾ DISCUSSION

The preponderance of evidence clearly indicates that hippocampal volume is reduced in patients with AD compared with individuals with normal cognitive ability for their age. There is also evidence indicating that as cognitive performance deteriorates in AD patients, there are concurrent further reductions in hippocampal volume.[54] Many studies reported that there was no significant volume difference between the right and left hippocampi, but most suggested that the left hippocampus was slightly smaller than the right.[54–58] We identified no significant difference in volume between the sides, but we did find that the right hippocampus was smaller than the left in a very limited population of subjects with mild to moderate AD.

The major finding of this pilot study flies in the face of conventional wisdom in that there seems to be significant shrinkage of the right hippocampus with atorvastatin therapy compared with placebo in a randomized AD treatment trial that demonstrated clinical benefit with atorvastatin therapy.[44] A similar finding was reported from the beta-amyloid immunization (AN1792) treatment trial in AD.[59] In that study the active immunization was associated with significant clinical benefit, reduced beta-amyloid load, and reduced hippocampal volume.[59] The authors suggested that removal of beta-amyloid and/or other protein constituents from the tissue might have caused a "fluid shift" out of the tissue, resulting in shrinkage.

Based on our previous finding of reduced brain tissue density in AD patients compared with age-matched normal controls,[48] an alternative explanation can be proposed. Neuronal loss in the hippocampus may be accompanied by increased fluid balance (reduced density) in an attempt to retain the previous volume at the expense of function. Accordingly, as the hippocampus shrinks, it approaches a more normal density for the remaining neuronal complement, and cognitive function improves.

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