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Effects of Simvastatin on Cholesterol Metabolism and Alzheimer Disease Biomarkers

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Abstract

Preclinical and epidemiologic studies suggest a protective effect of statins on Alzheimer disease (AD). Experimental evidence indicates that some statins can cross the blood-brain barrier, alter brain cholesterol metabolism, and may ultimately decrease the production of amyloid- β (A β) peptide. Despite these promising leads, clinical trials have yielded inconsistent results regarding the benefits of statin treatment in AD. Seeking to detect a biological signal of statins effect on AD, we conducted a 12-week open-label trial with simvastatin 40 mg/d and then 80 mg/d in 12 patients with AD or amnesic mild cognitive impairment and hypercholesterolemia. We quantified cholesterol precursors and metabolites and AD biomarkers of A β and tau in both plasma and cerebrospinal fluid at baseline and after the 12-week treatment period. We found a modest but significant inhibition of brain cholesterol biosynthesis after simvastatin treatment, as indexed by a decrease of cerebrospinal fluid lathosterol and plasma 24S-hydroxycholesterol. Despite this effect, there were no changes in AD biomarkers. Our findings indicate that simvastatin treatment can affect brain cholesterol metabolism within 12 weeks, but did not alter molecular indices of AD pathology during this short-term treatment.

Keywords

Alzheimer disease; simvastatin; cholesterol; biomarker

Alzheimer disease (AD) is the most common neurodegenerative disease, and, in the United States (US), affects 6% to 7% of the population over age 65.¹ A study based on the 2000

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census estimated 4.5 million people were affected with AD in the US, but owing to the rapid growth of the oldest age groups, this number is expected to rise to 13.2 million people in 2050.² Any therapy capable of substantially preventing the disease or delaying its onset would not only significantly decrease its prevalence, but also alleviate the extent of associated social and economic burdens.

Hypercholesterolemia in midlife is a risk factor for development of late-onset dementia, in particular AD.^{3,4} Statins are drugs widely used in the treatment of hypercholesterolemia; they block de novo biosynthesis of cholesterol by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in the pathway. Thus, it has been postulated that statins might have a protective role against the development of AD or at least slow its progression.

In vitro and in vivo studies support a protective effect of cholesterol-lowering drugs, specifically of statins, in AD.^{5–15} However, the association between statins use and decreased risk of AD in the general population remains controversial. Early retrospective and cross-sectional epidemiologic studies reported a reduction of up to 70% in the risk of dementia and AD with the use of statins,^{16–22} whereas prospective epidemiologic studies have either failed to support that protective association,^{23–27} or confirmed it.^{28–30} Clinicopathologic studies have also yielded conflicting results.^{26,31}

The results of AD clinical trials with statins are also mixed. Two large randomized double-blind placebo-controlled clinical trials of statins in participants with vascular risk factors found no difference in the incidence of dementia or cognitive impairment, although it was considered only a secondary outcome.^{32,33} By contrast, a proof-of-concept 12-month randomized, double-blind, placebo-controlled trial of high-dose atorvastatin in mild-to-moderate AD showed significant benefits or such trends on cognitive performance and behavioral scales.³⁴ Post hoc analysis revealed that these benefits occurred only in patients with higher MMSE scores and higher plasma cholesterol levels (above 200mg/dL) at baseline, and in those who were apoE4 carriers.³⁵ In addition, retrospective studies have reported a slower rate of cognitive decline in AD patients taking statins.^{36,37}

Although a number of small clinical studies have attempted to determine the effects of statins on AD pathophysiology,^{38–52} there has been a remarkable heterogeneity in study design, target population, dose and type of statin, duration of treatment, and lipids and AD biomarkers measured. Yet some of these studies have shown that statins at therapeutic dosages can cross the blood-brain barrier, reduce brain cholesterol biosynthesis,^{38,40,41,45,49,50} and alter the levels of several AD biomarkers.^{40,41,45,47,51,52}

Here we report the results from an exploratory open-label study with high-dose simvastatin in AD patients that aimed to measure the effects of statin treatment on a comprehensive panel of sterols, stanols, and oxysterols, and AD biomarkers, in both cerebrospinal fluid (CSF) and plasma. Measurements of cholesterol precursors and metabolites in both plasma and CSF allowed us to better dissect the effects of simvastatin on cholesterol metabolism in the liver versus the brain. Simvastatin was selected as a study drug because it is a lipophilic statin, and crosses the blood-brain barrier more readily than less lipophilic statins such as pravastatin, fluvastatin, and rosuvastatin. Indeed, simvastatin is an inactive prodrug that is hydrolyzed to its active form in liver and plasma. Although the active moieties of all statins have low blood-brain barrier permeability, hydrolyzed simvastatin may in addition enter the brain through carrier-mediated transport.⁵³ To maximize the likelihood of affecting brain cholesterol metabolism, we used the highest recommended dose for patients with hypercholesterolemia, and treated for 12 weeks, which has proved to be of sufficient duration in earlier studies.^{38,49}

PARTICIPANTS AND METHODS

Participants

Participants in this prospective open-label study were recruited from the Massachusetts General Hospital Memory Disorders Unit. All patients and their caregivers provided informed written consent to participate in the study, which was approved by the Massachusetts General Hospital Institutional Review Board. Eligibility criteria included: (1) a diagnosis of probable AD according to the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria,⁵⁴ or amnesic mild cognitive impairment according to Petersen criteria⁵⁵; (2) Clinical Dementia Rating global score of 0.5 to 2.0⁵⁶; and (3) hypercholesterolemia, defined as plasma TC above 170 mg/dL, but below 240 mg/dL. This third inclusion criterion was decided because a treatment with statins would be then justified also in the absence of a diagnosis of AD. Exclusion criteria included: prior use of any lipid-lowering drug, known sensitivity to this class of drugs, diabetes mellitus, known liver disease, and any other unstable medical condition.

Data Collection

Demographic data collected at screening visit included age, gender, years of education, vascular risk factors, other medications and supplements, and age at onset of AD symptoms.

ApoE4 Phenotype

ApoE4 phenotype (present or absent) was determined by Western blot in the plasma samples with an antibody specific for the isoform 4 of the apolipoprotein E (1:1000, clone 5B5, IBL, Minneapolis, MN, Cat. no.10025). Human recombinant ApoE3 and ApoE4 (Invitrogen, Carlsbad, CA, Cat. no. P2003 and P2004) were also loaded in the gels as negative and positive controls, respectively. To confirm the presence of apolipoprotein E in the empty lanes, the same membrane was stripped and reprobed with a goat anti-human ApoE polyclonal antibody (Calbiochem, San Diego, CA, Cat. no. 178479).

Treatment

Participants began treatment with simvastatin 40 mg/d for 4 weeks and the dose was increased to 80 mg/d for the last 8 weeks. Participants were evaluated every 2 weeks during the 12-week study. Occurrence of adverse effects was ascertained at each visit, with particular emphasis on cramps and myalgias. Plasma creatine kinase levels and liver function tests (transaminases, bilirubin, alkaline phosphatase) were done at each visit. Adherence to treatment was assessed by counting pills remaining at each visit. Change in plasma total cholesterol (TC) and LDL cholesterol (LDL-c) was also used as a measure of compliance.

Primary Outcomes and Measures

Primary outcomes consisted of changes between baseline and follow-up levels (week 12) of a panel of AD bio-markers and cholesterol precursors and metabolites in both CSF and plasma.

AD biomarkers were measured by ELISA, and included plasma A β 40, and CSF A β 40, A β 42, total tau, and phospho-tau (pTau-181). ELISA kits were used according to the manufacturers instructions (A β 40 ELISA kit Cat. 292-62301 and A β 42 ELISA kit Cat. no. 298-62401 were purchased from Wako, Osaka, Japan, whereas Innotech hTau and Innotech phospho-Tau181 were from Innogenetics, Gent, Belgium). Because of the physiologic

fluctuations of CSF β -amyloid levels over hours, lumbar punctures were carried out between 8:30 and 10:30 a.m. in all the patients at baseline and also at follow-up.⁵⁷

Lipids were quantified by mass spectrometry as described earlier.³⁸ Measurements consisted of levels of dietary cholestanol and phytosterols/stanols (campesterol, campestanol, sitosterol, sitostanol, brassicasterol, stigmasterol, and avenasterol), precursors of cholesterol biosynthesis (lathosterol, lanosterol, desmosterol), and hydroxylated cholesterol metabolites (also called oxysterols, ie, 7-hydroxycholesterol, 24S-hydroxycholesterol, and 27-hydroxycholesterol).

Statistical Analysis

Software SAS version 9.1.3 (SAS Institute Inc., Cary, NC) was used for statistical analysis. Comparisons between baseline and 12-week levels of lipids and AD biomarkers were calculated with analysis of variance (ANOVA) for repeated measures or paired Student *t* test when appropriate. Possible interactions of baseline demographic covariates and ApoE4 phenotype with time were tested with ANCOVA for repeated measures. Level of significance was set at a 2-tailed $\alpha = 0.05$, without adjustment for multiplicity because of the exploratory nature of the study.

RESULTS

Baseline Characteristics of Participants

Twelve patients met inclusion criteria and participated in the study (Table 1). At baseline, 10 participants had a diagnosis of probable AD, whereas 2 participants had a formal diagnosis of amnesic mild cognitive impairment, although their neurologist (J.H.G.) judged them as prodromal AD. Indeed, these 2 participants progressed to meet probable AD criteria within 1 year after their enrollment in this study. Dementia severity in participants with probable AD was mild to moderate according to clinical dementia rating and other global cognitive measures (ie, Information-Memory-Concentration subscale of the Blessed Dementia Scale⁵⁸ and Minimental State Examination⁵⁹).

All participants completed the treatment prescribed with a compliance rate greater than 90%. No adverse side-effects either from the treatment or from the lumbar punctures were reported. No abnormalities were found in liver function tests and creatine kinase levels (data not shown).

Changes in Cholesterol Metabolism

A summary of lipid measurements at baseline and 12-week visits is shown in Table 2. There were 7 paired *t* tests significant at $P < 0.05$ in the predicted direction, although only 0.025×29 tests ≈ 1 test would be expected to be significant by chance, assuming independent tests. Plasma TC and LDL-c levels were reduced after simvastatin treatment by 11% and 20%, respectively. However, CSF TC levels did not significantly decrease and there were no significant changes in plasma HDL-cholesterol or triglycerides levels.

Cholesterol Precursors

Plasma levels of the cholesterol precursors lathosterol and desmosterol decreased significantly by 33% and 10%, respectively. There was also a trend toward decrease in the plasma levels of the lanosterol (24%, Table 2). Lathosterol levels were also significantly decreased in CSF after simvastatin treatment (20%), whereas lanosterol and desmosterol CSF levels remained unchanged (Table 2).

Cholesterol Metabolites

As 24S-hydroxycholesterol (24-OHC, cerebrosterol) is a cholesterol catabolite produced almost exclusively in the brain, a reduction in plasma or CSF 24-OHC levels after treatment with statins is regarded as an indirect marker of the inhibitory effect of these drugs on brain cholesterol biosynthesis. 7-hydroxycholesterol (7-OHC) and 27-hydroxycholesterol (27-OHC) are other cholesterol hydroxylated metabolites (ie, oxysterols) that are produced mainly in the liver.⁶⁰ Plasma levels of both 7-OHC and 24-OHC were significantly decreased after simvastatin treatment (18% and 9%, respectively), whereas plasma levels of 27-OHC did not change significantly. Levels of these 3 oxysterols did not change in CSF (Table 2).

Inhibition of cholesterol biosynthesis by statins promotes the uptake of circulating LDL-c particles by the liver. Thus, aside from the inhibitory effect of simvastatin on cholesterol biosynthesis, the reduction observed in plasma 24-OHC levels might also be mediated by the decrease in plasma LDL-c levels as a result of its enhanced liver uptake. To discern between these 2 possibilities, we compared the ratios 24-OHC/LDL-c and 24-OHC/TC before and after exposure to simvastatin. We found a significant increase in the ratio 24-OHC/LDL-c as an effect of time, indicating that the reduction in plasma LDL-c exceeded the reduction in plasma 24-OHC. By contrast, we did not observe a significant change in the ratio 24-OHC/TC in plasma nor in CSF, suggesting that the decrease in 24-OHC levels is driven for the most part by the clearance of LDL-c from the blood stream into the liver (Table 3).

Dietary Stanols and Noncholesterol Sterols

Statins do not substantially affect dietary stanols or sterols absorption. Accordingly, there were no significant changes in the plasma or CSF levels of cholestanol or any of the dietary phytosterols and stanols measured (Table 2). Some researchers consider a ratio between lathosterol (the main endogenous cholesterol precursor) and campesterol (the main plant sterol in the diet) as a relative index of cholesterol biosynthesis.³⁸ This ratio was significantly decreased in both plasma and CSF after simvastatin treatment (Table 3).

Influence of ApoE4 in Cholesterol Metabolism

ApoE4 phenotype influenced neither the baseline levels nor the magnitude of changes of TC, LDL-c, HDL, triglycerides, cholesterol precursors, and dietary stanols/sterols (data not shown). Regarding cholesterol metabolites, ApoE4 carriers had higher baseline CSF levels of 24-OHC and 27-OHC than did noncarriers (24-OHC: 3.6714 ± 2.1013 ng/mL in ApoE4 carriers vs. 1.2458 ± 0.7457 ng/mL in ApoE4 noncarriers, $P = 0.02371$; 27-OHC: 2.0198 ± 0.7421 ng/mL in ApoE4 carriers vs. 1.1998 ± 0.3673 ng/mL in ApoE4 noncarriers, $P = 0.03571$, 2-tailed Student *t* test). In addition, the significant decrease in plasma 7-OHC was mainly observed in ApoE4 carriers (ApoE4 carriers: 94.9 ± 23.1 ng/mL at baseline vs. 69.4 ± 17.8 ng/mL at week 12; ApoE4 noncarriers: 83.3 ± 17.9 ng/mL at baseline vs. 80.0 ± 20.5 ng/mL at week 12, $P = 0.0028$, repeated measures ANCOVA for the interaction of ApoE4 phenotype $\times$ time).

Changes in AD Biomarkers

No significant changes were observed in the levels of AD biomarkers in CSF (A β 40, A β 42, total tau, and phospho-tau) and plasma (A β 40) after 12 weeks of treatment with simvastatin (Table 4). Covarying with age, education, disease duration, dementia severity, and ApoE4 phenotype, did not modify these results (repeated measures ANCOVA, data not shown).

DISCUSSION

We conducted a 12-week open-label trial in a sample of patients with AD and hypercholesterolemia to assess the effects of simvastatin 80 mg/d on brain cholesterol metabolism and AD biomarkers. By measuring a comprehensive panel of lipids and AD biomarkers in plasma and CSF, we found that this treatment did not modify the AD biomarkers despite affecting brain cholesterol metabolism in the predicted direction.

Effects on Cholesterol Metabolism

All together, our results show a modest inhibitory effect on cholesterol biosynthesis, which was more prominent in the liver than in the brain. The reduction of plasma TC and LDL-cholesterol levels was moderate compared with earlier large clinical trials such as the Scandinavian Simvastatin Survival Study (4S) and the Heart Protection Study. In the treatment group of the 4S, 6 weeks after a starting dose of 20 mg daily and compared with baseline levels, plasma TC was reduced on average by 28%, LDL-c by 38%, and triglycerides by 15%, whereas HDL-c cholesterol rose by 8%. However, mean baseline TC and LDL-c plasma levels were 25% to 50% higher in the 4S than in our study.⁶¹ In the Heart Protection Study, after the first year of treatment with simvastatin 40 mg/d and as compared with the changes in the placebo group, the plasma levels of TC, LDL-c, and triglycerides were reduced an average of 65, 50, and 35 mg/dL, respectively.³²

Similarly, the reduction observed in this study in the plasma levels of the cholesterol precursor lathosterol is less than that reported by Locatelli et al⁴⁹ in nondemented patients with hypercholesterolemia (73% after 6 weeks and 74% after 24 weeks of treatment with simvastatin 80 mg/d); by Vega et al³⁸ in AD patients with hypercholesterolemia (55% after 6 weeks of treatment with simvastatin 40 mg/d), and by Höglund et al⁴⁵ also in AD patients with hypercholesterolemia (66% after 12 months of treatment with simvastatin 20 mg/d).

The effect of simvastatin on brain cholesterol metabolism, although statistically significant, was also small in comparison with other studies. The decrease in CSF levels of the precursor lathosterol in our study is smaller than the decrease reported by Höglund et al⁴⁵ (33%), but greater than the reduction reported by Simons et al⁴⁰ in AD patients with normocholesterolemia (9% after 26 wk of treatment with simvastatin 80 mg/d). The reduction in plasma 24-OHC is much lower than that reported by Locatelli et al⁴⁹ (45 to 50%), by Vega et al³⁸ (24%), and by Höglund et al⁴⁵ (34%). Although Simons et al⁴⁰ observed a significant reduction in CSF 24-OHC levels, (10% reduction), our results are consistent with Höglund et al,⁴⁵ who did not find such a reduction. In our study, 2 other hydroxylated metabolites (oxysterols), 7-OHC and 27-OHC, also remained unchanged in CSF. In addition, the combination of increased 24-OHC/LDL-c ratio with unchanged 24-OHC/TC ratio suggests that the 9% reduction observed in plasma 24-OHC levels is mostly owing to the clearance of LDL-c from the blood stream, rather than to the inhibition of its production.

Lack of adherence to the treatment does not explain these moderate changes because compliance was above 90% in all participants at each visit. Heterogeneity regarding baseline cholesterol levels, age, and other baseline characteristics might explain to some extent the differences in brain cholesterol metabolism changes observed between earlier and this study. In keeping with earlier works, ApoE4 phenotype did not influence significantly the effect of simvastatin on cholesterol metabolism.^{45,50}

Effects on AD Biomarkers

The lack of effect on AD biomarkers in CSF and plasma in this study is largely in line with prior reports. Höglund et al⁴⁴ reported no change in plasma levels of A β 40 and A β 42. In

another study, the same researchers found no change in plasma or CSF A β 42 nor in CSF total tau, but reported significant increases in CSF phosphotau and in the soluble α -cleaved APP fragment.⁴⁵ Sjögren et al⁴³ reported a decrease in the CSF levels of both soluble α -cleaved and β -cleaved APP in AD patients treated with simvastatin 20 mg/d for 12 weeks, but no change in CSF A β 42, total tau, and phospho-tau, nor in plasma A β 42. Riekse et al⁵¹ observed a decrease in the CSF levels of phospho-tau-181 in nondemented hypercholesterolemic participants treated with 40 mg/d of simvastatin for 14 weeks, but no change in those treated with 80 mg/d of pravastatin, a nonlipophilic statin. However, CSF levels of A β 40, A β 42, soluble α -APP and β -APP, and total tau remained unchanged in both groups. Recently, Carlsson et al⁴⁸ found no significant change in CSF A β 42 and total tau in a randomized double-blind placebo-controlled trial with simvastatin 40 mg/d in asymptomatic middle-aged adults at increased risk of AD.

The absence of effect of simvastatin on AD biomarkers in our study may be attributable to insufficient inhibition of brain cholesterol metabolism down to a level that would facilitate the nonamyloidogenic processing of the APP.^{6–9} However, a cholesterol-independent but isoprenoid-dependent beneficial effect of statins on amyloid pathology has also been recently described in experimental studies. Inhibition of isoprenylation of certain proteins by statins (ie, Rab family of small GTP-ase proteins) may indirectly decrease the amyloidogenic processing of the APP,^{10,13,14} and also account for their antiinflammatory properties.^{11,12} Future clinical studies on the effects of statins in AD patients should also address the levels of isoprenoids in plasma and CSF.

Conclusions

The main strength of this study is the comprehensive panel of both lipids and AD biomarkers measured in plasma and CSF. Although changes in plasma levels of sterols and oxysterols reflect principally the drug effects on liver uptake of LDL-c (ie, the sterols transporter), CSF measures provided an opportunity for a better assessment of simvastatin effect on brain sterols. Limitations are the lack of a randomized double-blind placebocontrolled design, the short study duration, and the small sample size, although a similar duration and sample size sufficed to detect significant differences in brain cholesterol metabolism and AD biomarkers in earlier studies.^{38,43,49,51} In addition, simvastatin and its active metabolites were not quantitated in the plasma or CSF, which would otherwise enable correlation of drug levels with pharmacodynamic effects.

In conclusion, using exploratory analysis, we show modest but significant effects of high-dose simvastatin treatment on brain cholesterol metabolism in a small sample of AD patients. Within a 12-week period, no significant effects were found on AD biomarkers in plasma or CSF. Further clinical studies are needed to explore the potential for statins to beneficially modify the course of AD, suggested by epidemiologic and preclinical data.

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TABLE 1**Baseline Demographic Characteristics of the Study Participants**

Gender, n (% female)	8 (66.6)
Age at baseline, (y)	65.6 (8.6)
Education (y)	15.1 (3.8)
Age at onset of AD (y)	60.7 (8.7)
Duration of disease (y)	4.8 (1.7)
APOE4 carriers, n (%)	6 (50)
MMSE at baseline	21.7 (6.1)
BDS	9.3 (6.3)
CDR-SB	4.3 (3.3)
CDR global score:	
0.5, n (%)	7 (58.3)
1, n (%)	4 (33.3)
2, n (%)	1 (8.3)

Gender, *APOE4* carriers, and CDR global score are expressed as number (percent). Other data are presented as Mean (SD).

BDS indicates Blessed dementia scale (information-memory-concentration subscale); CDR-SB, clinical dementia rating sum of boxes; MMSE, minimental state examination.

TABLE 2
Lipids Measured in Plasma and CSF at Baseline and After 12 Week of Treatment With Simvastatin

	Plasma			CSF		
	Baseline	12-week	P	Baseline	12-week	P
Total cholesterol (mg/dL)	212.0 (18.3)	189.2 (42.0)	0.0274	0.459 (0.145)	0.455 (0.131)	0.6935
LDL-cholesterol (mg/dL)	126.1 (16.8)	101.4 (35.7)	0.0102	ND	ND	—
HDL-cholesterol (mg/dL)	64.7 (18.9)	64.3 (20.0)	0.9008	ND	ND	—
Triglycerides (mg/dL)	106.3 (58.0)	117.7 (83.3)	0.3000	ND	ND	—
Lathosterol (mg/dL)	0.221 (0.153)	0.148 (0.153)	0.0077	0.201 (0.066)	0.162 (0.065)	0.0368
Lanosterol (μg/dL)	23.4 (9.3)	17.9 (5.3)	0.1062	0.033 (0.017)	0.027 (0.008)	0.3277
Desmosterol (mg/dL)	0.194 (0.028)	0.175 (0.037)	0.0103	1.334 (0.159)	1.346 (0.174)	0.7476
7-hydroxy-cholesterol (ng/mL)	89.7 (19.8)	74.2 (18.9)	0.0053	0.168 (0.079)	0.199 (0.085)	0.3180
24S-hydroxycholesterol (ng/mL)	52.3 (11.8)	47.8 (12.5)	0.0368	2.459 (1.966)	2.485 (1.805)	0.8225
27-hydroxycholesterol (ng/mL)	199.8 (35.1)	187.9 (39.8)	0.1811	1.609 (0.704)	1.712 (0.787)	0.2869
Cholestanol (mg/dL)	0.367 (0.114)	0.338 (0.086)	0.0716	1.440 (0.529)	1.438 (0.462)	0.9489
Campesterol (mg/dL)	0.352 (0.279)	0.381 (0.259)	0.3367	0.639 (0.429)	0.696 (0.398)	0.0864
Sitosterol (μg/dL)	0.274 (0.259)	0.289 (0.232)	0.7260	0.897 (0.473)	1.010 (0.392)	0.1417
Brassicasterol (μg/dL)	16.943 (18.123)	19.593 (17.933)	0.2343	0.066 (0.035)	0.076 (0.033)	0.0668
Stigmasterol (μg/dL)	12.889 (6.535)	12.849 (5.226)	0.6823	ND	ND	—
Avenosterol (μg/dL)	1.595 (1.915)	1.627 (1.543)	0.8881	ND	ND	—
Campestanol (μg/dL)	5.403 (1.807)	5.578 (1.754)	0.5029	ND	ND	—
Sitostanol (μg/dL)	5.485 (2.559)	5.463 (1.899)	0.6008	ND	ND	—

Results are expressed as mean (SD). Two-tailed paired student *t* test.

ND indicates not done.

TABLE 3

Descriptive Ratios of Changes in Cholesterol Metabolism

	Plasma			CSF		
	Baseline	12-week	P	Baseline	12-week	P
Lathosterol/campesterol	1.101 (1.730)	0.805 (1.348)	0.0551	0.404 (0.255)	0.316 (0.261)	0.0243
24S-hydroxycholesterol/TC	0.249 (0.061)	0.267 (0.081)	0.1820	4.849 (2.815)	4.972 (2.679)	0.5698
24S-hydroxycholesterol/LDL-c	0.417 (0.093)	0.535 (0.231)	0.0232	ND	ND	—

Results are expressed as mean (SD). Two-tailed paired student *t* test.
LDL-c indicates low density lipoprotein-cholesterol; ND, not done; TC, total cholesterol.

TABLE 4

Simvastatin did not Affect AD Biomarkers in Plasma and CSF

	Baseline	12-week	<i>P</i>
Plasma A β 40 (pmol/L)	81.4 (22.0)	85.3 (17.3)	0.3700
CSF A β 40 (pmol/L)	1573.1 (501.4)	1542.8 (531.0)	0.3016
CSF A β 42 (pmol/L)	61.2 (29.9)	59.1 (26.2)	0.2624
CSF total tau (pg/mL)	690.2 (312.2)	699.0 (322.4)	0.6072
CSF phospho-tau (181) (pg/mL)	87.1 (57.4)	90.0 (60.9)	0.1705

Results are expressed as mean (SD). Two-tailed paired Student *t* test.