The Effect of HMG-CoA Reductase Inhibitors on Cognition in Patients With Alzheimer's Dementia: A Prospective Withdrawal and Rechallenge Pilot Study

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ABSTRACT

Background: Statins are well-known for their cardiovascular benefits. However, the cognitive effects of statins are not well understood. We hypothesized that individuals with preexisting dementia would be more vulnerable to statin-related cognitive effects.

Objective: The aim of this study was to evaluate the impact on cognition of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitor (statin) discontinuation and rechallenge in individuals with Alzheimer's dementia (AD) on statins at baseline.

Methods: A 12-week prospective, open-label study was conducted in a geriatric clinic setting. Eighteen older subjects underwent a 6-week withdrawal phase of statins followed by a 6-week rechallenge. The primary outcome measure was cognition, measured by the Mini-Mental State Examination (MMSE); secondary outcome measures were the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery, Activities of Daily Living (ADL) scale, Instrumental ADL (IADL) scale, and fasting cholesterol. The change in outcome measures was assessed using repeated-measures ANOVA and paired *t* tests.

Results: At the end of the intervention, there was a significant difference across time for MMSE score ($P = 0.018$), and total cholesterol ($P = 0.0002$) and a trend toward change across time for ADL ($P = 0.07$) and IADL ($P = 0.06$) scale scores. Further analyses using paired *t* tests indicated improvement in MMSE scores ($\Delta 1.9$ [3.0], $P = 0.014$) with discontinuation of statins and a decrease in MMSE scores ($\Delta 1.9$ [2.7], $P = 0.007$) after rechallenge. Total cholesterol increased with statin discontinuation ($P = 0.0003$) and decreased with rechallenge ($P = 0.0007$). The CERAD score did not show a change across time ($P = 0.31$). There was a trend toward improvement in ADL ($P = 0.07$) and IADL ($P = 0.06$) scale scores with discontinuation of statins, but no change with rechallenge.

Conclusions: This pilot study found an improvement in cognition with discontinuation of statins and worsening with rechallenge. Statins may adversely affect cognition in patients with dementia. (*Am J Geriatr Pharmacother*. 2012; 10:296–302) Published by Elsevier HS Journals, Inc.

Key words: Alzheimer's dementia, cognition, statins.

INTRODUCTION

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are commonly used in the treatment of hyperlipidemia. Statins have cardiovascular benefits in primary and secondary prevention of coronary heart disease.[1] Statins have been found to reduce the risk of all-cause mortality by 14% to 28% in different studies.[2] With aging of the U.S. population

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and the high prevalence of cardiovascular disease and dementia in this population, increasing numbers of older people, including those with dementia, are being treated with statins.

The cognitive effects of statins are not well understood. Epidemiologic studies suggested that statin use might be associated with a reduced prevalence of Alzheimer's disease (AD)[3] and other dementias.[4,5] However, prospective studies have yielded mixed results.[6–10] Subjects in the ADCLT (Alzheimer's Disease Cholesterol Lowering Treatment) trial, a double-blind, placebo-controlled, randomized trial, maintained better cognitive function (primary end point) at 6 months when taking atorvastatin compared with placebo.[11] This effect was more prominent if the serum cholesterol was high or the Mini-Mental State Examination (MMSE) score was higher at baseline or if the subjects had an apolipoprotein E4 allele. However, a recent Cochrane review that included the ADCLT trial found no beneficial effect of statins on cognitive measures.[12]

The U.S. Food and Drug Administration (FDA) recently added safety warnings to statins concerning confusion and memory loss.[13] Initial evidence of such adverse events came from case reports describing subjective and reversible worsening of cognition in individuals using statins, although none of those reports included objective cognitive measures.[14] We also reported a case series in which patients with mild cognitive impairment or dementia had a significant improvement in their MMSE score when statins were discontinued.[15] Two prospective studies showed minor declines in cognition of uncertain significance in hyperlipidemic adults treated with statins.[16,17]

Patients with AD may be more susceptible to the side effects of statins due to abnormalities in signal transduction, energy, and cholesterol metabolism in the brain.[18] We hypothesized that patients with preexisting dementia would have an improvement in cognition with discontinuation of statins and designed a prospective study to test the effect on cognition of discontinuation and rechallenge with statins.

PATIENTS AND METHODS

Study Design, Setting, and Participants

We conducted a 12-week prospective, nonblinded study using a 6-week withdrawal phase followed by a 6-week rechallenge phase with statins that the subjects used at baseline. The Institutional Review Board at the University of Nebraska Medical Center provided approval and oversight of the protocol. All subjects signed a written assent, whereas their legal surrogates signed a written informed consent.

Subjects 60 years of age and older, receiving care through the Geriatric Medicine Clinic at the University of Nebraska Medical Center, were recruited over a 2-year period. Individuals with a history or new diagnosis of AD or stable mixed dementia with an MMSE score of $\geq$10 who were taking stable doses of statins at least for 6 weeks were approached for participation. Individuals were excluded if they had a myocardial infarction, transient ischemic attack, or stroke in the previous 6 months, serious mental illness that affected memory, active cancer diagnosis (exception of skin cancer), alcohol dependence, and secondary hyperlipidemia and if they were unable to understand the study or give assent.

Study Intervention

Primary care providers of potential subjects were informed of the study and their verbal permission was obtained to allow participation. Subjects attended 3 visits over the course of 12 weeks, visit 1 (baseline), visit 2 (at 6 weeks), and visit 3 (at 12 weeks). At each visit, primary and secondary outcome measures were recorded. At visit 1, subjects were asked to stop taking their statins. At visit 2, subjects were asked to resume taking statins at their original dose and to return for visit 3 after 6 weeks. Subjects who dropped out after the withdrawal phase were restarted on statins. Subjects and their caregivers had access to the study co-coordinator and were asked to contact the research team if any study-related side effects were experienced. Demographic and anthropometric data were recorded. Comorbid health conditions and medications and their doses were recorded based on the medical record review and examination. Functional status assessments were performed by the study primary investigator or coordinator, and the neuropsychological assessments were performed by the psychologist, primary investigator, or coordinator.

Outcome Measures

The primary outcome measure was the MMSE score, which assesses orientation, attention, immediate and short-term recall, language, and ability to follow verbal and written commands.[19] The MMSE has good test–retest reliability (0.8) when performed with serial 7s.[20] Folstein's MMSE forms were purchased from Par, Inc.

The secondary outcome measures included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery,[21] Katz Activities of Daily Living (ADL) scale,[22] and Instrumental ADL (IADL) scale,[23] and serum cholesterol. CERAD neuro-

psychological battery includes measures to test language (shortened 15-item Boston Naming Test 15, and verbal fluency test), visuospatial construction (constructional praxis), and verbal memory (word list recognition with immediate and delayed recall). The ADL scale assesses a subject's independence in performing basic tasks of daily living, whereas the IADL scale assesses independence in performing activities such as ability to prepare meals and handling finances. Higher ADL and IADL scale scores indicate better function. The serum cholesterol level was measured after fasting for a minimum of 12 hours.

Statistical Analysis

Data were analyzed using SAS version 9.1 (SAS Institute, Cary, North Carolina). All variables were normally distributed. A single-factor, repeated-measures ANOVA (RM-ANOVA) was used to determine whether there were significant time effects for the outcome measures across the 3 visits. An α level of 0.05 was used to determine significance. Post hoc analyses using paired *t* tests were performed to detect significant changes between visit 1 and visit 2 and between visit 2 and visit 3 for variables that were found significant by RM-ANOVA.

RESULTS

A total of 310 individuals were screened for the study, 92 of whom were taking statins. Of these, 68 subjects met inclusion and exclusion criteria and were approached for participation. Twenty-four subjects consented to participate in the study, and 18 completed the study. Six subjects dropped out of the study after the initial visit and did not go through statin withdrawal. They were not included in the final analysis. Three dropped out due to transportation problems, and 3 dropped out due to loss of interest in research participation. Barriers to recruitment included (1) difficulty obtaining consent from the subjects' caregivers or legal representatives (either no representatives could be identified or they were absent during the subjects' clinic visit); (2) subjects' desire to obtain approval from their primary care provider or cardiologist to stop the statins for the study, which was frequently not given, even for a period of 6 weeks; (3) reluctance on the part of some caregivers to consent on the subject's behalf; (4) transportation difficulties; and (5) anxiety on the part of some subjects about the required serial memory testing. No study-related adverse events were recorded in any subjects during the study.

The characteristics of the subjects are summarized in **Table I**. Twelve subjects had a diagnosis of AD, and 6 had mixed dementia with a stable vascular component.

Table I. Study subject characteristics.

Age, y, mean (SD)	76.7 (6.6)
Sex, male/female	7/11
Race, Caucasian/no.	17/18
Years of education, mean (SD)	12.4 (2.4)
MMSE score, mean (range)	22.1 (12–28)
Statin type (no. of subjects)	**Dose, mg (no. of subjects)**
Atorvastatin (8)	10 (3), 20 (2), 40 (2), 80 (1)
Simvastatin (5)	10 (1), 40 (3), 80 (1)
Fluvastatin (2)	20 (1), 40 (1)
Pravastatin (1)	20 (1)
Rosuvastatin (1)	10 (1)
Lovastatin (1)	40 (1)
Study-related adverse events	None

MMSE = Mini-Mental State Examination.

Comorbidities were common: 78% had hyperlipidemia, 72% had hypertension, 55% had depression, 50% had heart disease, 44% had chronic pain, 33% had a history of cerebrovascular disease, 28% had diabetes, and 17% had weight loss of unknown origin.

The effects of statin withdrawal and rechallenge on the outcome measures are summarized in **Table II**. There were statistically significant time effects for the primary outcome measure of the MMSE score ($P = 0.018$) and for total cholesterol ($P = 0.0002$) as measured by RM-ANOVA. Post hoc analyses using paired *t* tests indicated a significant improvement in MMSE score with 6 weeks of discontinuation of statins from visit 1 to visit 2 ($\Delta 1.9$ [3.0], $P = 0.014$). Furthermore, a significant decrease in MMSE score was noted after 6 weeks of rechallenge with statins between visit 2 and visit 3 ($\Delta 1.9$ [2.7], $P = 0.007$). **Figure 1** summarizes the change in MMSE score for each subject with statin withdrawal and rechallenge across the 3 visits. Fasting total cholesterol level increased with 6 weeks of discontinuation of statins from visit 1 to visit 2 ($\Delta 42.3$ [39.2]; $P = 0.0003$) and decreased after 6 weeks of statin rechallenge ($\Delta 40.3$ [30.9]; $P = 0.0007$) between visit 2 and visit 3. There was a trend toward significance across time for ADL ($P = 0.07$) and IADL ($P = 0.06$) scale scores. Paired *t* tests indicated a trend toward improvement of ADL scale score with discontinuation of statins ($P = 0.07$) but no significant change with statin rechallenge ($P = 0.54$). Paired *t* tests of IADL scale score indicated a trend toward improvement with statin discontinuation

Table II. Effect of statin withdrawal and rechallenge on measured outcomes.

Outcome Measure	Visit 1, Mean (SD)	Visit 2, Mean (SD)	Visit 3, Mean (SD)	Time Effect, P*	Post Hoc Analyses: Change: Visit 1 to Visit 2, P†	Post Hoc Analyses: Change Visit 2 to Visit 3, P†
MMSE score	22.1 (4.5)	24.0 (4.2)	22.1 (5.3)	0.018‡	0.014‡	0.007‡
CERAD§	53.2 (12.0)	55.7 (12.7)	55.3 (11.3)	0.31	0.22	0.70
Language	23.6 (5.6)	23.1 (4.9)	24.9 (4.7)	0.17	0.63	0.01‡
Visuospatial construction	8.3 (1.9)	8.5 (2.1)	8.3 (1.7)	0.89	0.70	0.67
Verbal memory	21.3 (7.6)	24.2 (7.7)	22.0 (8.2)	0.14	0.04‡	0.08
ADL	21.5 (2.6)	22.5 (1.6)	22.6 (1.4)	0.07	0.07	0.54
IADL	13.3 (5.2)	15.2 (6.7)	15.0 (6.7)	0.06	0.06	0.67
Total cholesterol	185.2 (51.9)	227.6 (56.2)	187.3 (46.3)	0.0002‡	0.0003‡	0.0007‡

ADL = activities of daily living; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; IADL = instrumental activities of daily living; MMSE = Mini-Mental State Examination.
*Assessed with repeated-measures ANOVA.
†Assessed post hoc using paired *t* test.
‡Statistically significant.
§CERAD score was obtained by adding scores of language, visuospatial construction, and verbal memory.

of ($P = 0.06$) but no significant change with rechallenge ($P = 0.67$).

The total CERAD neuropsychological battery score (combined scores of language, construction praxis, and verbal memory) did not show a statistically significant change across time ($P = 0.31$). When measures of language ($P = 0.17$), construction praxis ($P = 0.89$), and verbal memory ($P = 0.14$) were compared individually, no significant differences were found across time. However, verbal memory showed a statistically significant improvement with statin withdrawal ($P = 0.04$) and a trend toward a decline with statin rechallenge ($P = 0.08$). Language showed a statistically significant improvement with statin rechallenge ($P = 0.01$).

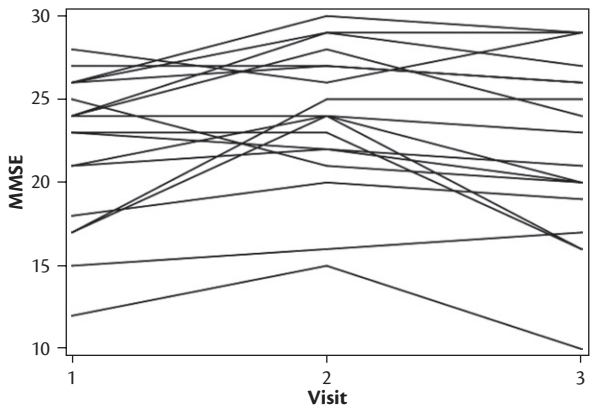

Figure 1. Change in Mini-Mental State Examination (MMSE) score with statin withdrawal and rechallenge.

DISCUSSION

In this pilot study, subjects with preexisting dementia acted as their own controls, allowing us to study the temporal association of cognitive changes with statin withdrawal and rechallenge. Patients with dementia were chosen because they might be more susceptible to cognitive side effects due to preexisting defects in cholesterol metabolism.[18] The mean MMSE total patient score improved with withdrawal of statins and decreased when the same statin was reinitiated on rechallenge. This suggests a detrimental effect of statins on cognition in patients with preexisting dementia. There are several mechanisms that might explain how statins could worsen cognition. Statins cross the blood–brain barrier (BBB), depending on their solubility in lipids (lipophilic) or water (hydrophilic). Lipophilic statins such as simvastatin and lovastatin cross the BBB and lower the cholesterol in the brain to a critical level, causing neuronal injury.[24,25] The impact on cognition is also hypothesized to be related to the dose of the lipophilic statins such that a larger dose of a lipophilic statin would have greater impact on cognition.[26] Furthermore, lipophilic statins have been shown to be proinflammatory in human monocytes in vitro and mice leukocytes in vivo,

another mechanism through which cognition could be worsened in patients with AD.[27] We were unable to differentiate the cognitive effects between lipophilic (n = 6) and hydrophilic statins (n = 12) due to the small sample size.

Other studies found detrimental effects of statins on cognition. Deficits in attention and psychomotor speed were reported with use of lovastatin without an associated decline in cognition.[16] In another double-blind, placebo-controlled trial, a small decline in neuropsychological performance was noted in the simvastatin group compared with a placebo group.[17] Wagstaff et al[14] reviewed 60 case reports (36 simvastatin, 23 atorvastatin, and 1 pravastatin) of self-reported memory loss associated with statins. No specific memory tests were reported in these patients. However, 50% of patients described cognitive adverse effects within 2 months of initiation of statin therapy, and 56% reported improvement in cognition when the statin was discontinued. Only 4 subjects were rechallenged with statins and their memory loss recurred.[14] Evans et al[28] conducted a survey of 171 subjects who reported statin-related cognitive adverse events. Of the 143 who discontinued statins due to cognitive adverse events, 128 reported improvement in cognition, sometimes within days; hence, the adverse effect was determined to be probably or definitely related to statin therapy.[28] Thus, it is possible that some individuals may be susceptible to significant cognitive adverse effects of statins and that a larger group may experience at least subtle cognitive changes when carefully tested. It is important for clinicians to recognize that the presence of dementia may further increase a patient's susceptibility to statin-induced cognitive decline.

We deliberately chose 6 weeks as the duration each for discontinuation and rechallenge of statins to allay concerns about losing the cardiovascular benefits of statins. We had concerns about the learned effect of administering the MMSE at shorter intervals of time. If there was a learned effect, the third visit would have shown further improvement instead of the decline. The fact that MMSE scores had decreased at the third visit makes the findings of our pilot study more robust. There was a trend toward significance of the measures of functional status in this cohort, which suggests that there might be some impact of statins on the functional status. If so, that impact may take much longer than 6 weeks to show an effect. The expected effect of statin use on cholesterol levels was entirely expected and helps to document subject adherence with the protocol.

The strengths of our study include its prospective design with withdrawal and rechallenge. The limitations of our study include the fact that the study was not randomized, included no control group, was not blinded, may have had a nonrepresentative sample of subjects because of the small sample size, and was conducted over a short duration. Additionally, we did not have information on how long the patients had been taking statins before entering the study. A larger sample size would allow us to conduct secondary analyses using subgroups or other methods to control for the type of statin used, medical comorbidities, baseline variability in MMSE score, or other factors. In this study, we included patients with both AD and mixed dementia in whom statins could have a differential impact on cognition and functional status. There is also lack of sensitivity of the assessment measures and that a more sensitive assessment measure with greater specificity (which might be used in future studies of this type) would be the Montreal Cognitive Assessment[29] instead of the MMSE.

A possible recommendation based on this study and the recent FDA caution regarding cognitive side effects is to consider holding statins in patients with dementia for 4 to 6 weeks and performing a repeat measure of cognitive performance. Because these agents are meant to provide long-term benefit, a short time off these agents should be safe for most patients.

Future studies need to delineate the cognitive effects of statins based on subject characteristics, disease markers, stage of dementia, and individual properties of the statins. Subject characteristics of interest are the age (young old [65-85 years] vs the old old [>85 years]), functional status (community dwelling vs institutionalized), and gender differences. Disease markers of interest include the amyloid burden, cerebrospinal fluid β-amyloid load, and the apolipoprotein E4 status. Cognitive effects of statins in mild to moderate dementia versus severe dementia may be very different and need to be studied. Of the properties of statins, lipophilicity may have the most influence on the cognitive effects; therefore, studies need to separate the cognitive effects of statins based on their lipophilicity and hydrophilicity.

CONCLUSIONS

Statins can produce adverse effects on cognition in individuals with dementia. In this study of older individuals with mild to moderate dementia, cognition improved with discontinuation of statins and worsened with rechallenge. Studies with a larger sample size and a longer

duration need to be performed to further evaluate the effects of different classes of statins on cognition and function in patients with preexisting dementia. A prudent approach on an individual basis would be to discuss the risks and benefits of statins with the patient with dementia and caregiver(s) and give them an option of a trial off the statin to determine the effect on cognition and function.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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