Journal Club:

A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease

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This Journal Club article reviews a study from Mary Sano and colleagues,¹ in conjunction with the Alzheimer's Disease Cooperative Study (ADCS), regarding the possible utility of simvastatin in the treatment of Alzheimer disease (AD). AD affects about 5.4 million Americans, and will become increasingly prevalent in our aging society. Annual costs of the disease are estimated at \$183 billion.² Unfortunately, therapeutic agents in this disease have marginal benefit at best. The discovery of new therapies to stop or slow the disease progression would be of enormous societal benefit. Many preliminary studies have postulated a possible role of cholesterol in the pathophysiology of AD, suggesting that hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, or "statins," may protect against cognitive decline. This study demonstrates that simvastatin administration does not change cognitive outcomes in patients with AD over an 18-month period.

HYPOTHESIS AND DESIGN There are many reasons to hypothesize that cholesterol is involved with AD,² and that statin use could benefit cognitive outcomes in patients with AD. The most studied gene associated with late-onset AD is *APOE*, a cholesterol transporter. Statins have been associated with lower amounts of CNS amyloid and reduced neurofibrillary tangles in animal studies,³ and reduced CSF A β levels in humans.¹ A few small clinical trials and epidemiologic studies have suggested that lowering cholesterol could slow the clinical progression of AD.⁴

There are a number of different routes by which HMG-CoA reductase inhibitors might have a beneficial effect in AD, though the underlying mechanisms have not been well-specified. Cholesterol modulates A β production and metabolism through unclear mechanisms, and may influence the risk of cerebrovascular disease as well. In addition to interrupting cholesterol synthesis by inhibiting HMG-CoA, statins may independently decrease production

of downstream intermediate products involved in inflammation and cell signaling.⁵

Interestingly, a recent study evaluating the effect of atorvastatin on cognition in patients with mild to moderate AD found no benefit to patients receiving this medication.⁶ However, one possible explanation for the reported negative findings is that atorvastatin is unable to cross the blood-brain barrier. While the brain contains 25%–30% of the total body cholesterol, essentially all the cholesterol used in the brain is synthesized within the CNS, as the blood-brain barrier prevents direct cholesterol transport between the CNS and peripheral circulation.⁵ Therefore, a principal motivation of the current study was to assess whether a statin with reliable penetration of the blood-brain barrier, such as simvastatin, could exert a significant clinical impact.¹ To this end, the authors designed a multicenter, randomized, double-blinded, placebo-controlled study, with a goal of providing Class I evidence regarding the utility of simvastatin in slowing the clinical progression of AD.

METHODS The study was conducted by the ADCS, and involved 45 sites nationwide. The primary outcome measure was the rate of change on the Alzheimer's Disease Assessment Scale–cognitive (ADAS-cog) score. The ADAS-cog evaluates attention, memory, reasoning, language, orientation, and praxis. This score is recognized by the Food and Drug Administration (FDA) as a primary indicator of drug response for dementia, and is a common measure in trials of this kind.⁷ Additional secondary outcome measures were also taken, including the ADCS Clinical Global Impression of Change, the Mini-Mental State Examination, activities of daily living (ADLs), quality of life (QOL) measures, resource use instruments, and further supplemental tests. The researchers evaluated the outcome measures at 3, 6, 12, and 18 months after baseline.

To be enrolled in the study, patients had to have probable AD as defined by the National Institute of

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Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria proposed in 1984.⁸ Patients had to be older than 50 years, with an MMSE score between 12 and 26. While it could be argued that placing a lower limit on MMSE scores would systematically exclude the most severe Alzheimer's cases, this practice is common as severe dementia limits patients' ability to follow commands and cooperate with tests, making results unreliable. Furthermore, many believe that a potential therapeutic agent should have the most effect early in the disease course.

Because of the double-blind nature of the study, subjects were excluded if giving statins might be unsafe (e.g., a very low low-density lipoprotein [LDL]), or if the patients met Adult Treatment Panel (ATP III) guidelines requiring cholesterol-lowering treatment for patient safety. While patients taking many different medications were also excluded due to the potential for interfering with cognition or interacting with simvastatin, use of cholinesterase inhibitors and memantine was permitted. Not only did this allow the patients to continue to receive the best known therapy for their disease, it also permitted the examination of the hypothesis that these agents might act synergistically with HMG-CoA reductase inhibitors. While most baseline demographic and clinical features between the 2 groups were identical, the placebo group included significantly more Hispanic subjects and a slightly higher ADCS-ADL score.

The data were analyzed using a generalized estimating equations (GEE) method to assess rate of change on the ADAS-cog score. A GEE is commonly used in cohort studies, due to the method's ability to manage many types of unmeasured dependence between groups.⁹ A GEE may be used when there are multiple outcome measures, as was the case in this study. The primary analysis was effectively an intent-to-treat (ITT) analysis, meaning that ADAS-cog assessments were still used if a patient discontinued the study medication.^{10,11} By minimizing artifacts related to patient dropout, this approach is considered the gold standard in clinical trials. Subset analyses were also conducted on those who completed the protocol or ingested more than 80% of the prescribed medication, to ensure that any negative results were not skewed by inclusion of patients who did not complete the protocol. Missing data points were addressed using multiple imputation, a technique that estimates missing values in order to allow for better statistical comparison between groups.¹² These additional subset analyses, called "completers" and "compliers," respectively, relied on change scores, a common approach for analysis of longitudinal data.¹³

By adopting this approach, the authors ensured their data could be compared with other studies using similar change-score analyses.

RESULTS Statistical power analyses are routinely implemented in clinical trials to determine the sample size needed to ensure appropriate acceptance of a null hypothesis. This calculation centers on the selection of the type II error rate, which corresponds to the probability of not rejecting the null hypothesis when that hypothesis is actually false, and also depends on the significance criterion (usually set at $p = 0.05$) and the estimated size of the drug effect in the population. To obtain this latter estimate, the authors turned to a previous trial with similar subjects, looking at visit-to-visit variation, SD, and annual change in the ADAS-cog scores in the placebo group. Finally, the authors included a predicted dropout rate of 30% in order to determine how many research subjects would need to be included in their study.

Using this power calculation, the authors designed their study with 80% statistical power to see a 20% difference in drug vs placebo rate. This means that there is approximately a 4-to-1 tradeoff between the probability of making a type II error vs a type I error. Given the study's negative results, the increased probability of having a false-negative error (20%) compared to a false-positive error (5%) requires attention. However, the power used in this clinical trial is a standard for adequacy across most clinical trials in order to increase the meaningfulness of a rejected null hypothesis.

The study found simvastatin administration to be safe, and confirmed that the simvastatin had expected effects on cholesterol. The authors also saw a reduction in C-reactive protein, a measure of inflammation, highlighting another potential mechanism by which statins might exert their effects on neurocognitive function. Nevertheless, there was no significant difference between groups regarding the rate of cognitive decline as judged by the ADAS-cog score ($p = 0.25$, 95% confidence interval 0.0462–0.1680), or on any secondary outcome measures. Differences were also not observed in any of the other forms of analysis, including additional post hoc median-split analyses comparing low and high age groups or low and high baseline MMSE groups.

INTERPRETATION In this article, Sano and colleagues have provided strong evidence that simvastatin has no effect on cognitive outcomes in patients with AD. Strengths of this study include the following:

1. A meticulously designed, double-blind, randomized, placebo-controlled, multicenter study is the

gold standard clinical design to answer questions of this nature.

2. The study follows an encouraging trend in publicizing “negative” trial results.
3. The study authors anticipated potential problems in the statistical analyses and ran additional complementary analyses, helping to confirm that the findings are not unduly affected by variation between the groups—this is especially important because some significant differences between groups were in fact found.

Limitations of the study are as follows:

1. The maximum dose of simvastatin applied to this population was 40 mg a day. While an increased dose risks increasing the rate of medication side effects, not using the maximum dose means that a dose-dependent effect on cognition has not been completely excluded. This potential weakness may have fewer practical implications since the maximum FDA-approved dose of simvastatin has since been reduced to 40 mg from 80 mg daily.
2. As the authors mention, these results may not be applicable to those with elevated baseline cholesterol who take statins for other health reasons. Those who have an elevated LDL should receive treatment, making randomization of this group impossible. However, the authors cite additional literature that suggests that even in this patient population, there is no difference in cognitive outcome between those who take statins and those who do not.
3. While the study length of 18 months is generally considered acceptable for this type of trial, it is possible that a longer trial could have identified more significant changes. This could particularly be the case if a wider range of people—from normal cognition to more advanced disease—had been included, which is typical of the observational studies that have described a significant benefit of statins on cognitive performance.⁵
4. Theoretically, a higher proportion of Hispanics in the placebo group could complicate generalization of the results. Responses to medications can vary between ethnic groups. There are few publications that address the question of ethnic variations in response to HMG-CoA reductase inhibitors. At least one article describes some differences.¹⁴ Other articles find no such differences.^{15,16}

In the present study, if the Hispanic population had been more likely to benefit from simvastatin administration, then a lower number of Hispanic patients in the treatment group could lead to type II error. However, work by Goldberg et al.¹⁴ indicates that Hispanic patients were actually less responsive to

statins than other ethnic groups. Therefore, the scarce evidence available might actually bolster the author’s findings. Similarly, baseline LDL was also listed as a potential confounder; however, as LDL was higher in the group receiving simvastatin, one might predict that this group would be even more likely to benefit from the drug, making negative results even more striking.

These potential limitations should not detract from the fact that, as a whole, the study quality was very strong. Nonetheless, this study does not rule out potential preclinical benefits of statin use in AD, does not directly address the cognitive benefits of statins in a hyperlipidemic population, and does not address the utility of higher doses of simvastatin. Perhaps one relevant clinical “pearl” to be harvested from this study is that the likely therapeutic value of simvastatin, or any other experimental drug for that matter, on AD is unlikely to exert much of an effect once patients exhibit overt clinical symptoms. Future efforts need to be geared toward clinical trial testing in presymptomatic stages, and in such circumstances, statins might yet live to greet another AD study.

AUTHOR CONTRIBUTIONS

Dr. Pressman: concept and design. Dr. Gottfried: writing/revising the manuscript.

DISCLOSURE

P.S. Pressman serves on the *Neurology*® Resident & Fellow Section editorial team and writes the *Neurology* Guide for About.com. J.A. Gottfried receives research support from the NIH/NIDCD, receives royalties from the publication of *Neurobiology of Sensation and Reward* (CRC Press, 2011), and works at Northwestern University, which was one of the medical centers selected to participate in the research study described here. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology* 2011;77:556–563.
2. Alzheimer’s Association. 2010 Alzheimer’s disease facts and figures. *Alzheimer Dement* 2011;7:208–244.
3. Fassbender K, Simons M, Bergmann C, et al. Simvastatin strongly reduces levels of Alzheimer’s disease beta-amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. *Proc Natl Acad Sci USA* 2001;98:5856–5861.
4. Simons M, Schwarzler F, Lutjohann D, et al. Treatment with simvastatin in normocholesterolemic patients with Alzheimer’s disease: a 26-week randomized, placebo-controlled, double-blind trial. *Ann Neurol* 2002;52:346–350.
5. Reitz C. Dyslipidemia and dementia: current epidemiology, genetic evidence, and mechanisms behind the associations. *J Alzheimer Dis* 2011;28:1–19.
6. Feldman HH, Doody RS, Kivipelto M, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology* 2010;74:956–964.
7. Cano SJ, Posner HB, Moline ML, et al. The ADAS-cog in Alzheimer’s disease clinical trials: psychometric evaluation

- of the sum and its parts. *J Neurol Neurosurg Psychiatry* 2010;81:1363–1368.
8. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944.
 9. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003;157:364–375.
 10. Lachin J. Statistical considerations in the Intent-to-Treat Principle. *Control Clin Trials* 2000;21:167–189.
 11. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319:670–674.
 12. Schafer J. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8:3–15.
 13. Vickers A, Altman D. Analyzing controlled trials with baseline and follow up measurements. *BMJ* 2001;323:1123–1124.
 14. Goldberg R, Guyton J, Mazzone T, et al. Relationships between metabolic syndrome and other baseline factors and the efficacy of ezetimibe/simvastatin atorvastatin in patients with type 2 diabetes and hypercholesterolemia. *Diabetes Care* 2010;33:1021–1024.
 15. Mück W, Unger S, Kawano K, Ahr G. Inter-ethnic comparisons of the pharmacokinetics of the HMG-CoA reductase inhibitor cerivastatin. *Br J Clin Pharmacol* 1998;45:583–590.
 16. Pearson T, Denke M, McBride P, et al. Effectiveness of ezetimibe added to ongoing statin therapy in modifying lipid profiles and low-density lipoprotein cholesterol goal attainment in patients of different races and ethnicities: a substudy of the Ezetimibe add-on to statin for effectiveness trial. *Mayo Clin Proc* 2006;81:1177–1185.

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