Published in final edited form as:

Alzheimers Dement. 2008 May ; 4(3): 174–175. doi:10.1016/j.jalz.2008.03.003.

Commentary on “The Atorvastatin/Donepezil in Alzheimer’s Disease Study (LEADe): Design and baseline characteristics”

Marwan N. Sabbagh, MD¹

¹The Cleo Roberts Center for Clinical Research, Sun Health Research Institute, Sun City AZ 85351

Keywords

cholesterol; lipid profile; Alzheimer’s; atorvastatin

Jones et al present in this journal edition the design and baseline characteristics of the LEADe study for the LEADe study group¹. The LEADe study is an international, multi-center, randomized, double-blind, placebo controlled study in conjunction with donepezil as a treatment for Alzheimer’s disease. The rationale of this clinical trial stems from the growing belief that lipid lowering drugs including statins could lessen the risk of dementia and perhaps alter the rate of progression of Alzheimer’s disease. Several epidemiological studies have suggested the protective roles of statins^{2–6}, but a number of cohort studies have not found a clear association between statins and reduced risk of dementia^{7–9}. There are plausible biological reasons why it is appropriate to test lipid-lowering drugs including statins as treatments for Alzheimer’s disease. Statins have been shown to have some influence on the pathogenesis of Alzheimer’s disease. They have also been shown to have anti-inflammatory, anti-oxidant, and neuro-protective properties¹⁰. Collectively these observations provide the impetus to pursue randomized clinical trials of atorvastatin and other statins as treatments for Alzheimer’s disease.

From the baseline LEADe data, several observations should be identified. First, the total cholesterol is recorded to be slightly elevated at 224 mg/dl. The LDL was reported to be elevated at 143 mg/dl and the HDL was reported to be normal at 64mg/dl. The triglycerides were slightly elevated as well. Previously, we have reported a similar pattern in a smaller cohort of individuals¹¹ that is not influenced by apolipoprotein E genotype¹². Given this observation has been now reproduced in the large multi-center LEADe clinical trial, this pattern of mildly-elevated total cholesterol, LDL and triglycerides represents the lipid profile of Alzheimer’s disease and heretofore should be referred to as such..

Part of the impetus for pursuing a multi-center clinical trial comes from the findings of the Alzheimer’s Disease Cholesterol-Lowering Treatment Trial (ADCLT), a single-center, double-blind, placebo-controlled trial investigating the effect of atorvastatin as a treatment of Alzheimer’s disease¹³. The ADCLT was a positive pilot study indicating that atorvastatin provided benefit on the course of mild to moderate Alzheimer’s disease in subjects receiving background therapy of cholinesterase inhibitor. This study did show some trends toward

Send Reprint Requests to: Marwan Sabbagh MD, FAAN, Cleo Roberts Center for Clinical Research, Sun Health Research Institute, 10515 W. Santa Fe Dr, Sun City, AZ 85351, Phone: (623) 876-5328, FAX: (623) 875-6504, Marwan.Sabbagh@sunhealth.org.

Publisher’s Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

cognitive benefit on the ADAS-Cog in the treated group compared to the placebo group. The trends in that pilot study were tantalizing and beg to identify the mechanism of action for the observed effect. Secondary analyses of the ADCLT have been performed to explore this.

In the ADCLT, the group treated with 80mg of atorvastatin had significant reductions in total cholesterol. Additionally LDL and VLDL were reduced as well. However, there are no effects SOD or GPX¹⁴. Additionally there was no reduction in A β 40 or 42 and no effects of ceruloplasmin in that study¹⁵. The preliminary data suggests that the mechanism of action was not driven by effects other than the reduction of cholesterol.

The secondary analysis of the ADCLT also reveals that the effect of atorvastatin was not seen in all groups of individuals. Specifically, subjects with higher cholesterol (greater than 200 mg/dl) had significantly positive effects on ADAS-Cog compared to placebo, and subjects with lower cholesterol had no effect. Similarly, the gross magnitude of effect was seen in APOE-4 positive carriers compared to non-E4 carriers¹⁶. These data suggest that the subjects likely to benefit could be identified in advance with better effects hypothetically predicted to be in subjects that are E-4 carriers and subjects with higher cholesterol.

Because of the post-hoc analysis of the ADCLT, interpretation of the primary end points of LEADe and other statin trials may reflect case selection stratified by baseline cholesterol levels rather than mechanisms of actions of individual products. This is very important since both simvastatin and atorvastatin are being investigated and issues between the two blood-brain barrier permeability have arisen. Secondary analyses of effect based on cholesterol panel may reveal different outcomes than primary outcome analyses developed during the conduct of these studies. If that is the case, then further studies will need to consider cholesterol patterns and genotypes in future clinical trial design in statin treatment trials for the treatment of Alzheimer's disease.

Acknowledgements

Supported by AG 019610 and the Sun Health Research Institute

Dr Sabbagh receives grant funding from Pfizer, Eisai, Novartis, GSK, Elan, Wyeth, Medivation, and Abbott. Dr Sabbagh is on the speaker's bureau for Pfizer, Eisai, Ortho-McNeil Neurologics, Novartis, Forest, and Abbott. Dr Sabbagh is a consultant to Eli Lilly, Baxter and Eisai. Outcome data to the LEADe study have not been disclosed to Dr Sabbagh.

References

1. Jones RW, Kivipelto M, Feldman H, Sparks L, Doody R, Waters D, Hey-Hadavi J, Breanza A, Schindler RJ, Ramos H on behalf of the LEADe investigators. The Atorvastatin/Donepezil in Alzheimer's Disease Study (LEADe): design and baseline characteristics. *Alzheimer's and Dementia*. 2008
2. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 2000 Oct; 57(10):1439–1443. [PubMed: 11030795]
3. Dufouil C, Richard F, Fiévet N, Dartigues JF, Ritchie K, Tzourio C, Amouyel P, Alpérovitch A. APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. *Neurology* 2005 May 10;64(9):1531–1538. [PubMed: 15883313]
4. Green RC, McNagny SE, Jayakumar P, et al. Statin use and the risk of Alzheimer's disease: the MIRAGE study. *Alzheimer's and Dementia* 2006;2:96–103.
5. Rockwood K, Kirkland S, Hogan DB, MacKnight C, Merry H, Verreault R, Wolfson C, McDowell I. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol* 2002 Feb;59(2):223–227. [PubMed: 11843693]

6. Zamrini E, McGwin G, Roseman JM. Association between statin use and Alzheimer's disease. *Neuroepidemiology* 2004 Jan-Apr;23(1-2):94-98. [PubMed: 14739574]
7. Zandi PP, Sparks DL, Khachaturian AS, Tschanz J, Norton M, Steinberg M, Welsh-Bohmer KA, Breitner JC. Cache County Study investigators. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry* 2005 Feb;62(2):217-224. [PubMed: 15699299]
8. Rea TD, Breitner JC, Psaty BM, Fitzpatrick AL, Lopez OL, Newman AB, Hazzard WR, Zandi PP, Burke GL, Lyketos CG, Bernick C, Kuller LH. Statin use and the risk of incident dementia: the Cardiovascular Health Study. *Arch Neurol* 2005 Jul;62(7):1047-1051. [PubMed: 16009757]
9. Li G, Higdon R, Kukull WA, Peskind E, Van Valen Moore K, Tsuang D, van Belle G, McCormick W, Bowen JD, Teri L, Schellenberg GD, Larson EB. Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology* 2004 Nov 9;63(9):1624-1628. [PubMed: 15534246]
10. Crisby M, Carlson LA, Winblad B. Statins in the prevention and treatment of Alzheimer disease. *Alzheimer Dis Assoc Disord* 2002 Jul-Sep;16(3):131-136. [PubMed: 12218642]Review
11. Sabbagh MN, Zahiri HR, Ceimo J, Cooper K, Gaul W, Connor DJ, Sparks DL. Is there a characteristic lipid profile in Alzheimer's disease? *Journal of Alzheimer's Disease* 2004;6(6):585-589.
12. Sabbagh MN, Shawn S, Lahti T, Kolody H, Silverberg NB, Sparks DL. What is the effect of the apolipoprotein E genotype on the lipid profile in Alzheimer's disease? *Current Alzheimer's Research* 2006;3(2):157-160.
13. Sparks DL, Sabbagh MN, Connor DJ, Lopez J, Launer LJ, Petanceska S, Browne P, Wassar D, Johnson-Traver S, Lochhead J, Ziolkowski C. Benefit of Atorvastatin in the treatment of mild to moderate Alzheimer's disease: results from the Alzheimer's disease cholesterol lowering treatment (ADCLT) trial. *Archives of Neurology* 2005;62:753-757. [PubMed: 15883262]
14. Sparks DL, Sabbagh MN, Connor DJ, Lopez J, Launer LJ, Browne P, Johnson-Traver S, Lochhead J, Ziolkowski C. Atorvastatin therapy lowers circulating cholesterol but not free radical activity in advance of identifiable clinically benefit in the treatment of mild-to-moderate AD. *Current Alzheimer's Research* 2005 Jul;2(3):343-353.
15. Sparks DL, Petanceska S, Sabbagh M, Connor D, Soares H, Adler C, Lopez J, Ziolkowski C, Lochhead J, Browne P. Cholesterol, copper and Aβ in controls, MCI, AD and the AD cholesterol-lowering treatment trial (ADCLT). *Curr Alzheimer Res* 2005 Dec;2(5):527-539. [PubMed: 16375656]
16. Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. Circulating cholesterol levels, apolipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: results of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. *Acta Neurol Scand Suppl* 2006;185:3-7. [PubMed: 16866904]