Philadelphia: All Is Not Well with the Statin Story

19 July 2004. One of the field's biggest hopes for a quick and easy new AD therapy received a punch in the stomach today as the 9th International Conference on Alzheimer's Disease and Related Disorders got under way in Philadelphia. John Breitner, of the Veterans Affairs Puget Sound Health Care System, Seattle, reported that three new prospective studies—together accounting for a mighty 30,000+ person-years of risk for AD—do not indicate any protection against future development of AD from prior statin use. This new work contradicts the original data linking statin use to reduced AD. What's more, quite possibly this original data may have been an artifact generated because physicians prescribed statins less frequently to patients with dementia, Breitner charged provocatively. While ongoing treatment trials of statins in AD should continue, this new data weakens the argument in favor of launching costly prevention trials, Breitner argues.

Statins burst on the scene of AD research in the early and mid-1990s, when case-control trials reported that people who took these cholesterol-lowing drugs to prevent heart attacks and strokes appeared to have a lower risk of developing AD, too (e.g., Wolozin et al., 2000; Jick et al., 2000). By now there are seven such studies, and utterly unscientific surveys of researchers in the field ("Are you on it?") suggest that many cognoscenti take these relatively safe drugs themselves with an eye toward preventing dementia down the line.

As is often the case when small epidemiological studies generate an intriguing new hypothesis, cell and molecular biologists began investigating mechanisms by which these drugs might act in AD. In the case of cholesterol and statins, scientists indeed have established solid in-vitro as well as mouse and guinea pig data showing, for example, that cholesterol and its related forms regulate APP processing. This would suggest that statins might be able to prevent AD, but data on the ability of statins to affect Aβ levels in humans are mixed. Basic science also has described cholesterol- and APP-independent effects statins may exert on processes relevant to AD, such as antiinflammatory or neuroprotective actions that result from the ability of statins to inhibit isoprenylation of a variety of proteins. The genetics front has done its small part by linking a half dozen genes related to cholesterol metabolism to AD, albeit in small studies that are not yet reproduced. Finally, hints of clinical success are on the horizon with small, published trials (Simons et al. 2002, Vega et al, 2004) and more recently a 12-month, controlled trial of atorvastatin conducted by Larry Sparks at the Sun Health Research Center in Arizona. This April, Sparks reported positive data at the Springfield Symposium in Montreal, where they were well received, but the full report of the trial is currently under review. Robustly stemming AD progression with a safe statin drug would be a sensational result, so researchers are eagerly awaiting publication of the full dataset of this trial.

While this good news is trickling in, however, epidemiologists trying to assess the potential of statins in AD more carefully have run into snags. To date, add-on studies looked for cognitive decline in three large, randomized, controlled trials of statins for prevention of cardiovascular disease. They are the Heart Protection Study of simvastatin, the PROSPER trial of pravastatin, and the CRISP trial of cerivastatin. All three failed to show any protection against dementia. Admittedly, Breitner said, the outcome measures used to indicate dementia were crude but

even so, at least an inkling of protection clearly should have emerged from trials as large as these. In the Heart Protection Study alone, 20,000 people took drug, or placebo, for five years.

Here now is the disheartening news: Three new prospective, observational studies on AD also found no protective effect against AD. They are the ACT (adult changes in thought) study, the Cardiovascular Health Study, and the Cache County Study; two papers are in press, one is under review, Breitner said.

“The case-control studies were impressive, the prospective data are null. What is going on?” Breitner asked. He suggests the answer lies in the timing of drug exposure and measuring the outcome. The case-control studies were cross-sectional in nature, meaning they took data on exposed, unexposed, and demented cases in the same year. By contrast, the prospective studies asked specifically about antecedent exposure and AD ensuing later. Indeed, to simulate the early case-control studies, the authors took the original data from each of these three new studies and analyzed them as mock cross-sectional studies. Low and behold, now they saw a statistically significant (but entirely spurious) protective effect for statins from the same dataset that yielded a null result when analyzed properly.

The issue boils down to putting sufficient time between exposure to the test agent at hand, and the endpoint measured, i.e., incident AD, when trying to test prevention or risk reduction by that agent. Indeed, in separate addresses on other issues in AD epidemiology, Miia Kivipelto of the University of Kuopio, Finland, Lenore Launer of NIH in Bethesda, and Laura Fratiglioni of the Karolinska Institute in Stockholm, Maryland, all emphasized this same point. The case control studies compared exposed, unexposed, and demented cases in the same year, while in the prospective studies, cases are exposed to the agent under study, then there is a follow-up period of at least a year, and then scientists measure AD incidence. That is a key difference. “We need to time exposure to statins to the critical period of opportunity. We have not found that critical period and have no data in hand right now to do so,” Breitner said.

The major confounding problems in the original studies may have been prescribing bias by physicians, Breitner said. At the time the cross-sectional data was gathered in the early 90s, a doctor who saw a demented patient would have worried about the dementia more than about preventing a heart attack 10 years later. What’s more, at that time statins were new and not yet widely used. So Breitner and colleagues suspect that physicians simply prescribed statins less frequently to people with high cholesterol if they also had dementia. Yet this is not testable, Breitner noted, because today awareness and use of statins have expanded greatly.

In a related presentation, Murali Doraiswamy and colleagues at Duke University in Durham, North Carolina, described data from a small study examining what effect statin use had on hippocampal volume in elderly people with mild cognitive impairment. After two and four years of follow-up, neither hippocampal volume nor white matter was different in people who took statins from those who did not, indicating that statin use over this time period was unable to stem the hippocampal loss that is usually seen as people with MCI progress to AD.

The broader issues underlying this therapeutic approach saw spirited debate between Breitner and Ben Wolozin on the one hand, and Mary Sano, Larry Refolo, and Tobias Hartmann on the other, at the Challenging Views of Alzheimer’s Disease meeting held here in Philadelphia yesterday.—Gabrielle Strobel.

Comments on News and Primary Papers
Comment by: John Breitner, ARF Advisor
Submitted 19 July 2004 Posted 19 July 2004

A point of clarification about my presentation: Prescribing bias could indeed account for some of the results in the Jick study, but Jick's design DID assure that statin exposures were antecedent to onset of clinical dementia. Thus, the timing issue alone cannot explain the discrepant results.

Some of us ought to look NOW at the cross-sectional relationship between statin use and incident dementia. With the use of statins now so much more common, prescribing bias should be less likely to produce a spurious inverse association between statin use and AD.

View all comments by John Breitner

Comment by: Tobias Hartmann
Submitted 20 July 2004 Posted 20 July 2004

Epidemiological data are just one of the many things in the toolbox. Perfect as hypothesis factory, but then to be tested by entirely different methods. But do these and other statin-epi studies tell us whether to continue or discontinue therapeutic approaches when more specific information is already available? Clearly, not! Moreover, specific aspects need to be addressed. Foremost here are dosing, time on drug, vascular risk factor history starting no later than mid-life, and maybe drug-brain penetrance or BBB issues of relevance.

1. Statin effects develop slowly. It takes an approximate 6 weeks before steady state LDL/HDL levels are achieved in plasma and very little information is available how long it takes to achieve the respective steady state in brain. With an overall biological half-life of brain cholesterol (and the brain contains lots of cholesterol) of 6 months, it is safe to assume that we are looking here at many months, if not years. This is as bad a fact for epidemiological studies as it is for AD prevention/treatment trials. Since years long treatment trials are indispensable to observe the well-established beneficial outcome in heart disease, we can expect that significantly longer timing will be essential for AD prevention trials. Accordingly, in epidemiological studies patients should be on statins for even longer. Given the rather short time since statins have become the ubiquitous drug they are today, this demand is hard to meet. (Re)searching for the magic AD pill to swallow for a short time and expect to observe a drastic effect? Well, what is known about statins, cholesterol and brain does not support such an approach. Without better and more detailed data from clinical studies it has to be assumed that several years of low dosage use of statins, sufficient to lower cholesterol levels to something in range of what is currently considered to be “normal” cholesterol levels, are needed for AD prevention.

2. To what extend do cholesterol levels impact the effectiveness of AD prevention or treatment? It can be safely assumed that in epidemiological studies all participants on statins had cholesterol levels warranting treatment. This is a severe and inherent bias that strongly reduces the value of all AD statin-epi studies.

3. Obviously, time might be traded for high dosage. Not surprisingly, even the scarce clinical treatment trial data available to date indicate that this is possible. Positive outcomes were reported by the studies that used the maximum FDA-approved dosage. In our study (80mg simvastatin) normocholesterolemic AD patients were treated for 6 months, with positive outcomes for mild AD. Larry Sparks has now used 80mg of atorvastatin for 12 months and recorded beneficial outcome for moderate AD, as well. In contrast to this, clinical trials using a lower dosage and/or shorter treatment duration thus far failed to observe improvements, although Kaj Blennow's group observed some changes in brain APP processing, but no changes in Ab.

4. The two studies by Larry Friedhoff & Joe Buxbaum clearly support that dosage matters and indicate that statins are indeed a great deal faster outside of the brain. Using controlled-release lovastatin for 3 months, serum Ab levels dropped strongly at the two highest concentrations used but basically failed at lower concentrations. Using a different statin and a single concentration, Hoglund et al. found no change in Ab plasma levels.

5. ApoE adds another layer of complexity. Statins have been increasingly designed not to enter the brain easily, however, Larry Refolo and colleagues could show that atorvastatin affects brain ApoE levels in mice. It is therefore reasonable to assume that response strength and type of response might differ somewhat between different statins.

Maybe the initial epidemiological data should be re-evaluated, maybe not; maybe this would be a research topic on its own. When Ben Wolozin and Jick published their observations some of these complicating aspects were not known, some had already been known and were widely discussed. Nevertheless, these publications never provided a strong enough argument to initiate the line of treatment trials. These decisions were based on in vitro and animal data.

Epidemiological data are always welcome and important. But with crystal-clear data available on cellular mechanisms, and first clinical data indicating the direction to go, epidemiological studies have to be extremely well-designed if they are to give additional useful information to this therapeutic approach. The answer will come from nowhere else than from costly clinical treatment trials, planned, designed and conducted to answer the key question “do statins prevent or cure AD?”

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Comment by: John Breitner, ARF Advisor
Submitted 21 July 2004 Posted 21 July 2004

Tobias is right, of course. It is only through formal experiment that one can test such specifics as dose and duration of treatment. The fact remains that the epi data gave the statins story a huge "shot in the arm," and the new data from the prospective studies suggest that most of that reported effect is artefact. Note also that the epi data say nothing about treatment trials, like the one reported by Larry Sparks (Larry, when are you going to publish these data?). A lot of experience now suggests caution when extrapolating treatment data to efficacy in prevention (and, of course, vice versa). Typically, agents that seem to prevent AD are useless once dementia is evident. Contrariwise, in theory at least, statins might be useful for treatment but

have no utility for prevention. That said, I'll bet a nickel this is not the case. To test my bet, it's essential that we continue the current treatment trials with statins, and that we collect further epi data (e.g., with longer exposure times and greater variability of exposure timing in relation to disease onset). This story is far from finished.

View all comments by John Breitner

Comment by: Alexei R. Koudinov
Submitted 21 July 2004 Posted 22 July 2004

Additional insight on the role of statins in Alzheimer's is provided in the recent article by Rebeck (1) and Koudinov and Koudinova (2), as well as in several articles listed at the Noteworthy collections of the Neurobiology of Lipids (3).

References:
1. Rebeck GW. Induction of cholesterol efflux in the CNS. Neurobiol. Lipids Vol.3, 1 (2004), Published online February 29, 2004, Available at: http://neurobiologyoflipids.org/content/3/1/
2. Koudinov AR, Koudinova NV. Amyloid beta protein restores hippocampal long term potentiation: a central role for cholesterol? Neurobiol. Lipids Vol.1, 8 (2003), Published online September 15, 2003, Available at: http://neurobiologyoflipids.org/content/1/8/ 3. http://neurobiologyoflipids.org/noteworthy/

View all comments by Alexei R. Koudinov

Comment by: Dieter Lütjohann
Submitted 25 July 2004 Posted 27 July 2004

24S-hydroxycholesterol, an important oxidative cholesterol degradation product, can be used as a surrogate serum or CSF marker to monitor changes in brain cholesterol synthesis in humans and, with some restrictions, in animals. In serum samples, the concentrations of 24S-hydroxycholesterol are highly correlated with the concentrations of cholesterol, transported in the same lipoprotein fractions. Thus, comparison of absolute serum levels alone of this oxysterol cannot give an answer to the question of whether brain cholesterol synthesis is influenced by cholesterol-lowering agents such as HMG-CoA reductase inhibitors (statins).

From the experience of all our statin-related studies, in part cited in John Breitner`s statement, we really did find lowering of the serum ratios of 24S-hydroxycholesterol to cholesterol (cholesterol corrected) but only in those patients who received the highest dose of simvastatin that is permitted in Europe, i.e. 80 mg simvastatin per day (Locatelli, Lütjohann et al. and Simons et al.) No equipotentially lower dosage of a statin showed a really satisfying effect on this oxysterol serum marker in this context.

The efficiency of a drug is mainly described by its bioavailability. This is regulated interindividually, and in part genetically, by different mechanisms including absorption rate (presumably influenced by food), protein binding capacity, catabolism in the liver, and interaction with other drugs, especially cytochrome P450 interations. In none of the published and ongoing studies has the real, circulating, efficient serum or CSF concentration of a statin or

its respective metabolite been measured, nor is it correlated concerning its efficiency to lower Abeta production or other AD pathologies.

Therefore, the main question is: Do we need a threshold statin concentration in the circulating blood system, firstly, to reach the brain, and secondly, to act efficiently as a local cholesterol-lowering agent? In humans, it is well-established that, under normal conditions, circulating cholesterol levels do not influence brain cholesterol levels. This raises the basic question: Why should a decrease of 30-50 percent in circulating LDL-C, or an increase by a high-cholesterol diet, influence the huge and immobile pool of brain cholesterol, which is well-balanced by regulatory mechanisms within the brain and by the blood-brain barrier? John Dietschy and Stephen Turley recently surveyed our actual knowledge about cholesterol metabolism in the CNS and discussed the interrelation betwee brain cholesterol metabolism and neurodegenerative disease in an excellent, objective manner.

If low-dosage treatment does not effect changes in brain cholesterol metabolism over a longer period of time, the interest for treatment with statins should be focused on patients within high-risk groups for AD. A high, but clinically well-controlled dosage should be used of a statin that finally reaches its target, the CNS. However, the follow-up question is: What will be further, still-unknown biochemical consequences of such a massive intervention into a well-balanced system that is responsible for neuronal development/control, and ultimately our human behavior? Does an AD preventive therapy justify this?

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Locatelli S, Lütjohann D, Schmidt HH, Otto C, Beisiegel U, von Bergmann K. Reduction of plasma 24S-hydroxycholesterol (cerebrosterol) levels using high-dosage simvastatin in patients with hypercholesterolemia: evidence that simvastatin affects cholesterol metabolism in the human brain. Arch Neurol 2002, 59: 213-216. Abstract

Simons M, Schwarzler F, Lütjohann D,von Bergmann K, Beyreuther K, Dichgans J, Wormstall H, Hartmann T, Schulz JB. Ann Neurol 2002, 52: 346-350. Abstract

Dietschy J, Turley S. Thematic review series: Brain Lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. J Lipid Res. 2004;45:1375-1397. Abstract

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Comment by: Iwo Bohr
Submitted 23 June 2005 Posted 27 June 2005

The result of the study showing no effects of statins in AD are not surprising at all for me. Why? I have been arguing for years that cholesterol is not the one to blame in brain, but quite in contrary to praise. There are more and more reports supporting such a concept. You can find part of them in my small item published recently presenting also my basic ideas about the beneficial role played by cholesterol in the brain and in AD in particular. A big apology to those I didn't quote in this little paper, the authors of the commented study at the first place, but also Drs. Koudinov and Koudinova, who launch similar ideas for not citing them enough. Simply, it is

due to the fact that there wasn't enough room; it is very difficult to cite all these new reports, which are easy to miss. All the best to "friends of cholesterol company."

References:
Bohr Iwo J (2005) Does cholesterol act as a protector of cholinergic projections in Alzheimer's disease Lipids Health Dis. 2005 Jun 10;4(1):13

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Comment by: Herbert Walker
Submitted 25 July 2004 Posted 26 July 2004

There was a 15,000-person study in Finland of carrot consumption and heart disease. No improvement was noticed. This study was about five years ago (seen in a newspaper). Have you seen any thing about using liquorice to increase memory? A concentrate was used... some blood pressure problem. This research is done at University of Edinburgh.

References:
La Salute... an Italian weekly health news notices..Republica news paper. number 414

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Comment by: Li-Huei Tsai, ARF Advisor
Submitted 16 August 2004 Posted 16 August 2004

The idea of intraneuronal Aβ contributing to AD pathology certainly appears to be generating momentum, and this was evident at last month's conference. Compelling evidence from new and established Aβ-related transgenic mouse models demonstrated that intraneuronal Aβ42 is an early event which precedes, and appears to correlate with, subsequent neuronal death. However, conflicting findings on postmortem AD brains on whether intraneuronal Aβ is an early event in AD, and is correlative with neuronal toxicity, needs to be resolved.

The evidence presented from the aforementioned transgenic mouse studies gives rise to a number of important questions that may have significant implications in understanding AD pathology. The first question that comes to mind is, what is the site and mechanism of toxicity induced by intraneuronal Aβ? And how does this differ from toxicity induced by the extracellular version? In addition, with increasing evidence for Aβ acting upstream of neurofibrillary tangle formation, it will be interesting to examine whether the neurons containing intracellular Aβ aggregates are prone to neurofibrillary tangle formation, as well. Despite the known spatial disparity between amyloid plaques and neurofibrillary tangles, the paradigm for intracellular Aβ pathology does not preclude the notion that amyloid and neurofibrillary pathology may exist in one and the same neuron.

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