alzheimer's research&therapy

REVIEW

Prevention of Alzheimer's disease in high risk groups: statin therapy in subjects with *PSEN1* mutations or heterozygosity for apolipoprotein Eε4

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Abstract

Because cerebrospinal fluid (CSF) abnormalities in presymptomatic subjects with *PSEN1* (presenilin 1) mutations may be observed 4 to 12 years prior to the estimated age at onset, it is possible to test putative therapies on the CSF analytes that correlate with neurodegeneration during this presymptomatic window of clinical opportunity. It is also possible to test the same therapy on a comparison group with increased risk status conferred by both hyperlipidemia and heterozygosity for apolipoprotein Eε4. To our knowledge, the only putative therapy thus far tested in such a common design has been statin therapy. The results of these tests show increases in soluble amyloid precursor protein (sAPP)α correlating with statin-induced decreases in serum cholesterol levels in the non-*PSEN1* subjects. This result could be one functional correlate for part of the substantial risk reduction for late onset Alzheimer's disease recently reported in the Rotterdam study, a large, long-term prospective statin trial. Statin therapy significantly decreased both sAPPα and sAPPβ in presymptomatic *PSEN1* subjects. Initially, elevated phospho-tau levels in *PSEN1* subjects did not further increase during the 2 to 3 years of statin therapy, possibly indicative of a prophylactic effect. These results suggest that large and longer term trials of statin therapy correlating changes in CSF biomarker levels with clinical course may be warranted in both presymptomatic *PSEN1* and non-*PSEN1* subjects.

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Introduction

To date, there have been no systematic treatment studies on subjects with presenilin (PSEN) mutations [1] who inherit an autosomal dominant form of early onset familial Alzheimer's disease (AD). The principal objective of this review is to summarize the existing published pilot studies that address the issues of presymptomatic intervention in early onset familial AD and to compare these results with analogous treatment studies in hyperlipidemic subjects who are heterozygous for apolipoprotein Eε4 (ApoEε4). Our decision to focus on studies of presymptomatic rather than symptomatic subjects was based on the premise that most putative therapies for AD are likely to have more demonstrable effects on normal subjects compared to those with overt AD whose brains have already been subject to extensive neurodegenerative changes. We also recognize that it is not yet known whether any preventative opportunities that may arise as a consequence of an understanding of the pathogenesis of *PSEN1* mutations will be applicable to the vastly larger number of cases of mild cognitive impairment and late onset AD (LOAD).

Both groups of subjects exhibit early increased brain deposition of amyloid-beta 42 (Aβ42) which many researchers [2,3] have proposed is either a direct or intermediary toxic agent in the genesis of the neurodegeneration that subsequently leads to AD. Homozygotes for ApoEε4 are at far greater risk for late onset AD than are heterozygotes, but we did not identify a sufficiently large enough group of the former to comprise a separate study group. Decreases in cerebral spinal fluid (CSF) Aβ42 levels precede cognitive decline in subjects with *PSEN1* mutations [4,5]. Consequently, in these subjects there is a window of opportunity - estimated as at least 4 to 12 years - to evaluate the ability of any putative prophylactic therapy to decrease, arrest or reverse abnormalities in Aβ42 metabolism many years before clinical symptoms of AD occur. For example, increased levels of CSF phospho-tau and total tau, which are direct measurements that neurodegeneration is

already occurring, also precede clinical symptoms in *PSEN1* carriers [4,5].

Epidemiological and interventional studies of statins and Alzheimer's disease

Over a decade ago, retrospective epidemiological studies strongly suggested that statin therapy reduced the risk of LOAD [6,7]. More recently, the prospective Rotterdam study [8], which included 6,992 participants followed for a mean of 9 years, has reported that statin therapy substantially reduced the risk of LOAD by almost 50%. Several recent studies of large cohorts have reached similar conclusions [9,10]. However, contrary findings were found in other large epidemiological studies [11-13]. Methodological differences and the time and extent of the clinical assessments may account for some of these conflicting results and their interpretations [8,14]. Prospective studies failing to report a protective effect of statins tended to be characterized by limited durations of follow-up, often 3 years or less, to have a lower number of incident cases and sometimes inclusion of older subjects than in those studies reporting protective effects [8,14].

However, assuming that these protective effects of statins are genuine, it is not yet clear how statins may produce such effects and whether they are more related to the lipid lowering effects of statins or to the 'pleiotropic' effects of statins. Such non-lipid effects of statins with respect to possible risk-reduction of LOAD include the improvement of endothelial function, the reduction of reactive oxygen species and the suppression of inflammatory reactions [15,16]. Nor is there yet a consensus as to whether statins with a greater lipophilicity are associated with increased therapeutic benefit. However, the Rotterdam study [8] showed that the protective effects are independent of statin lipophilicity, although there was no reported comparison of the effects of atorvastatin with those of simvastatin, which is the more lipophilic of these two statins.

Mechanisms of putative benefits of statins in Alzheimer's disease

Other work [17] has suggested that the putative benefits of statins may be attributed to a decrease in cholesterol levels in cellular membranes that would increase membrane fluidity so as to permit α-secretase to cleave amyloid precursor protein (APP) along non-amyloidogenic pathways. This would reduce the production of soluble APPβ (sAPPβ) that, in turn, would decrease the amount of substrate available for conversion by γ-secretase to Aβ42, which is assumed by many to be an agent within a cascade eventually responsible for neurodegeneration [2,3]. Pilot studies to date on presymptomatic subjects with *PSEN1* mutations have also assessed the effects of statins as a function of their lipophilicity [18], as will be discussed.

The accessible relevant CSF analytes for such studies are the neurodegenerative triad of Aβ42, phospho-tau, and total tau, as well as the APP cleavage products sAPPα and sAPPβ, representing the initial stages of APP metabolism, and cholesterol, its precursor lathosterol, and its metabolite 24(s)-hydroxycholesterol. These lipids serve as surrogate markers for changes in brain levels of these analytes following statin therapy. The descriptive data on our subjects and our experimental results with respect to the above analytes have been published [19].

Recruitment of subjects

Subjects with presymptomatic *PSEN1* mutations were recruited from a large cohort that has participated in our studies since 1985 [20]. Affected members of this cohort carry the C410Y *PSEN1* mutation [1]. Approximately 40 at-risk members of this cohort were contacted, of whom roughly half either had already had presymptomatic genetic testing or agreed to such testing. Eight presymptomatic carriers were identified and six of these agreed to participate in the statin studies. Another cohort in the Worcester, Massachusetts area with double *PSEN1* mutation**s** (P242H, R352H) was also identified, but only two presymptomatic carriers agreed to participate. Eleven non-*PSEN1* subjects who were hyperlipidemic and who, except for two cases, were heterozygous for ApoEε4 also agreed to participate.

There were hurdles to recruiting subjects that were different in the two cohorts.

A substantial number of at-risk subjects for the *PSEN1* mutation did not wish to know their genetic status, a concern expressed by most at-risk subjects in other *PSEN1* cohorts [21]. In both groups, some subjects declined to participate based on their reluctance to undergo pre-treatment and post-treatment lumbar punctures. Nevertheless, the obstacle of the limited number of participating subjects was partially compensated for by a series of observations over time for most *PSEN1* subjects (6 months, 1 year, 2 years and 3 years after statin treatment in comparison to pre-statin baseline levels). In addition, the application of general linear mixed statistical models [18] coupled with the large effects of statins over time on some of the tested analytes permitted a number of conclusions of robust significance.

The discovery that CSF abnormalities in neurodegenerative markers may occur a decade before clinical symptoms occur provides an opportunity to detect the effects of a putative treatment on CSF analytes many years before a subject would otherwise likely be clinically symptomatic. However, that long clinically asymptomatic duration is a two-edged sword in the sense that major changes in clinical status are unlikely to be easily

Table 1. Effect of statin therapy with simvastatin or atorvastatin on analytes in non-*PSEN1* and *PSEN1* subjects

	Primary objective		Drug effect				Controlled for lipids			
	Statins		Atorvastatin		Simvastatin		Atorvastatin		Simvastatin	
Analyte	% change	*P*-value	% change	*P*-value	% change	*P*-value	% change	*P*-value	% change	*P*-value
Non-*PSEN1*										
sAPPα	7	0.013	-	NS	13.1	0.019	9.6	0.0082	23.7	0.0005
sAPPβ	-	NS	-	NS	-	NS	-	NS	-	NS
Phospho-tau	-	NS	-	NS	-	NS	-	NS	-	NS
Total tau	-	NS	-	NS	-	NS	-	NS	-	NS
AB42	-	NS	-	NS	-	NS	-	NS	-	NS
PSEN1										
sAPPα	-16.5	0.0014	-	NS	-26.5	0.0002	-	NS	-24.1	0.0003
sAPPβ	-21.2	0.0005	-	NS	-31.5	0.0001	-	NS	-	NS
Phospho-tau	-8.3	0.076	-	NS	-	NS	-	NS	-	NS
Total tau	-	NS	-	NS	-	NS	-	NS	-	NS
AB42	-	NS	-	NS	-	NS	-	NS	-	NS

Aβ42 = amyloid-beta 42; NS, not significant; sAPP, soluble amyloid precursor protein.

detectable unless subjects are studied up to and beyond the average age of risk for a particular kindred. All of our subjects maintained normal neuropsychological status during the relatively brief period of 3 to 4 years over which the studies on CSF analytes were carried out. An insufficient number of subjects remained in the study thereafter to complete longer term assessment of clinical status.

Results of statin therapy on CSF lipid levels

All the data on the age, sex, *PSEN1* status and APOE genotype of our subjects together with statin type and dose over time with resultant serum total cholesterol and low density lipoprotein levels have been published [19]. Additionally, the resultant changes in CSF levels for lathosterol, cholesterol and 24(s)-hydroxycholesterol as a result of statin treatment have also been reported [19]. These CSF lipid levels reached a minimum at 7 months, a return to baseline at 15 months, an overshoot that peaked at 24 months and a drop towards baseline at 36 months. There were no differences in the effects of the two statins with respect to CSF lipid levels nor in *PSEN1* versus non-*PSEN1* subjects.

Statin therapy and APP metabolism

The results of statin therapy on levels of CSF sAPPα, sAPPβ, phospho-tau, total tau and Aβ42 [18] are shown for non-*PSEN1* and *PSEN1* subjects in Table 1. The first set of results - called 'Primary objectives' - gives the average effects of treatment independent of statin type. There was a significant increase in sAPPα of 7% (P = 0.013) in the non-*PSEN1* subjects and a significant decrease in sAPPα of -16.5% (P = 0.0014) and in sAPPβ of -21.2% (P = 0.0005) in the *PSEN1* subjects. The decrease of -8.3% in phospho-tau in the *PSEN1* subjects approaches significance (P = 0.076).

When the changes in these same CSF analytes are correlated with the specific drugs ('Drug effect' columns in Table 1), but not with reduction in serum lipid levels, all of the significant changes in sAPPα and sAPPβ in both subject groups are associated with simvastatin therapy. However, when the data are correlated both with specific drug and the extent of reduction in serum lipid levels ('Controlled for lipids' columns in Table 1), there is a significant increase in sAPPα of 9.6% (P = 0.0082) in the non-*PSEN1* subjects on atorvastatin and an increase of 23.7% (P = 0.0005) for non-*PSEN1* subjects on simvastatin. However, the difference between the two statins with regard to increased sAPPα in this subject group was not significant.

In the *PSEN1* subjects, there was a reduction in sAPPα for the subjects on simvastatin. Moreover, the decrease in sAPPβ after simvastatin therapy found when not controlling for serum lipid levels was not significant when we controlled for reduction in serum lipid levels. Whether these discordant results indicate that the statin-induced reduction in sAPPβ in this subject group is not dependent on statin dose nor on the statin dose-related reduction in serum lipid levels or to other factors is not clear.

The above results related to APP metabolism were well fitted by general linear methods. However, fitting the temporally diphasic responses of statin-induced changes in CSF lipids required quadratic models. Consequently, it is unlikely that the changes observed in the CSF biomarkers are dependent upon CSF lipid levels.

Changes in sAPPβ in the non-*PSEN1* subjects were not significant nor were there any significant changes in Aβ42, phospho-tau and total tau.

Effects of statin therapy on CSF analytes

The increase in sAPPα in the non-*PSEN1* asymptomatic subjects without a corresponding decrease in sAPPβ is at first glance surprising because, in general, it has been assumed that enhanced cleavage of APP by α-secretase results in a corresponding decrease in sAPPβ because less APP would be available as substrate for its generation [22]. However, that hypothesis, although apparently correct under many circumstances, does not always appear to be valid [23,24]. For example, a lack of exclusivity in the production of Aβ and sAPPα has been demonstrated in multiple human cell lines and in a transgenic mouse model in response to various activators [23].

In theory, the increases in sAPPα may be beneficial in risk-reduction of AD independent of whether there is a corresponding decrease in sAPPβ. For example, Kojro and colleagues [17] in their initial α-secretase study noted that increased sAPPα has trophic effects [25], stimulates neurite outgrowth [26], regulates synaptogenesis [27], stabilizes neuronal calcium homeostasis [28], protects hippocampal and cortical neurons against the toxic effects of glutamate and AB peptide [29] and has memory-enhancing effects in normal and amnestic mice [30].

Although our result that there was no change in CSF Aβ42 levels, at least for the non-*PSEN1* subjects, is at first glance disappointing from a possible therapeutic perspective, it is not surprising given a similar result in human subjects with AD [24,31]. However, high doses of simvastatin have been shown to reduce both Aβ42 and Aβ40 in both the CSF and brain homogenates of guinea pig [32]. We have no data on Aβ40 metabolism given that all our CSF samples were assayed by Athena Diagnostics for Aβ42, phospho-tau and total tau; this laboratory did not offer assays for Aβ40. Consequently, our lack of accessibility to Aβ40 levels also precluded study of the effects of statin treatment on Aβ42/Aβ40 ratios.

We do not know whether the oppositely directed changes in sAPPα by statins in the *PSEN1* and non-*PSEN1* subjects are the consequence of a different stage in the development of clinically presymptomatic neurodegeneration in these two groups, whether the mutation itself alters the accessibility of cleavage sites for APP metabolism, or whether there is greater underlying heterogeneity in the non-*PSEN1* subjects that favors the observed results.

The phospho-tau levels were normal to begin with in the non-*PSEN1* subjects and were not changed by statin therapy. Previous studies [33] observed that simvastatin, but not pravastatin, slightly reduced the levels of phospho-tau-181 in hypercholesterolemic subjects without dementia. Moreover, statin therapy has been reported to reduce neurofibrillary tangle burden found at autopsy [34]. In our studies of *PSEN1* subjects, statin therapy reduced the phospho-tau values by 8.3% approaching significance ($P = 0.076$) but with no significant changes in total tau or Aβ42.

Nevertheless, the average pre-statin phospho-tau level in *PSEN1* carriers was already abnormally elevated at the onset of our studies and would be expected to have risen without treatment during the period of the study. Thus, the result that the phospho-tau levels did not rise during the course of our studies may suggest that further tests of statins in a larger group of *PSEN1* subjects may be warranted.

As for the non-*PSEN1* subjects, the increases in sAPPα after statin therapy are quite substantial and might be one of the factors contributing to the decreased risk of AD in subjects undergoing long-term statin therapy in several recent long-term trials [9-11].

Neurotoxic effects on Aβ42

There are many potential mechanisms by which Aβ42 may lead to downstream neurodegeneration. These include direct neurotoxicity [2,3], direct vascular endothelial dysfunction [35] and neuroinflammation [36]. The direct neurotoxic affects of Aβ42 oligomers [2,3] include reductions in glutamatergic synaptic transmission and plasticity and attenuation of excitatory synaptic transmission by decreasing the number of surface AMPA and NMDA receptors associated with a collapse of glutamatergic dendritic spines.

At present, it does not seem possible to detemine the relative neurotoxicities of the various effects of Aβ42 and their relative contributions could differ depending on the stage of disease. However, even if statin therapy does not decrease sAPPβ and Aβ42 in non-*PSEN1* subjects, there remains the possibility that increases in α-secretase activity activate a pathway that substantially reduces the neurotoxicity of Aβ42.

There is a possible relationship between our findings and recent work on a connection between cellular prion protein (PrP^c) and Aβ42 metabolism [37-38]. For example, PrP^c has been reported to mediate the impairment of synaptic plasticity by Aβ oligomers [37]. According to these authors, the blockade of long-term potentiation may be rescued by anti-PrP antibodies that prevent Aβ oligomers from binding to PrP^c [38]. These studies [37-38] conclude that PrP^c is a mediator of Aβ oligomer-induced synaptic dysfunction and that PrP^c-specific pharmacologic interventions may have therapeutic potential for the treatment of AD. Moreover, studies of memory impairment in a mouse model of AD have found that the deletion of PrP^c expression dissociated Aβ

accumulation from behavioral impairment in mice, suggesting that the cognitive deficit normally resulting from some aspect of the Aβ42 cascade selectively requires PrP^c [39].

However, even more recently, three groups [40-42] studying different model systems from those utilized by the above authors, although confirming the high avidity of Aβ42 for PrP^c, failed to confirm any reduction in the neurotoxicity of Aβ42 in the absence of its binding to PrP^c. Clearly, it would be of great interest if it could be determined whether the original results apply to humans. Moreover, α-secretase has been reported to be responsible for the physiological processing of PrP^c in the middle of its toxic sequence [43-45]. Thus, Cisse and Mucke [45] suggest that one way to prevent both Aβ production and the downstream mediation of PrP^c might be to increase α-secretase activity. We suggest the possibility that a statin-induced increase in α-secretase activity could, assuming that the Aβ42-PrP^c link for the neurotoxicity of Aβ42 applies in humans, lead to the reduction of the neurotoxicity of Aβ42 even if its concentration was not reduced. Thus, our recent findings preceding publications about the proposed link between Aβ42 oligomers and PrP^c (together with their cleavage by α-secretase) may take on added significance, at least for the reduction of AD risk in non-*PSEN1* subjects, depending upon the outcome of the Aβ42-PrP^c controversy.

Moreover, other agents increase the production of α-secretase, at least in cell lines. For example, both testosterone [46] and estradiol [47] increase the secretion of the non-amyloidogenic APP fragment, sAPPα, and decrease the secretion of Aβ peptides. It would be of great interest to know whether testosterone and estradiol have similar actions in human males and females, respectively, for carriers of *PSEN1* mutations as well as for carriers of ApoEε4 alleles.

It is also well established that mid-life serum total cholesterol levels are associated with an increased risk of both AD and vascular dementia [48]. Clearly, dementia risk factors are best addressed well before disease symptoms appear. While there is strong evidence that these conclusions apply to non-*PSEN1* subjects, it is important to know whether or not they apply to *PSEN1* subjects as well.

Although this review has focused on the relationship of putative statin therapy with excess Aβ42 assumed to be part of the cascade that leads to neurodegenerative factors, pleiotropic effects of statins must be considered. For example, others have suggested that the putative beneficial effects of statins might be through the production of nitric oxide at the microvascular endothelial level [5]. Moreover, a recent study suggests that mutations in *PSEN1* genes may produce defective lysosomal proteolysis, which could itself represent a basis for pathologic protein accumulations in neuronal cell death leading to the identification of novel therapeutic targets [49].

Conclusion

Long-term statin therapy in non-*PSEN1* hyperlipidemic subjects largely heterozygous for ApoEε4 produced substantial increases in CSF sAPPα. It would be of great interest to know whether this effect, if confirmed in larger studies, contributes to the substantial reduction of risk of AD shown in several large and long-term prospective studies [24].

It would also be of great interest to know whether presymptomatic subjects with *PSEN1* mutations would experience beneficial clinical results given our finding that statins decreased sAPPβ in such subjects, and that initially elevated CSF phospho-tau levels did not further rise over the 2 to 3 years of statin therapy.

It is the hope of many researchers in this field that RNA interference [50] or the application of microRNA techniques [51,52] will eventually lead to breakthroughs in the correction of the increased risk factors conferred by the early onset AD mutations as well as the risk of AD associated with ApoEε4 alleles. However, such aspirations should not diminish present efforts to pursue some of the current approaches described here.

In this respect, perhaps the most exciting prospect of the work reviewed here are the relatively large (23.7%) and statistically robust ($P \leq 0.001$) increases in sAPPα in our statin-treated asymptomatic subjects who were heterozygous for ApoEε4 when controlling for statin-induced decreases in serum cholesterol levels [18]. If an increase in sAPPα is a prophylactic target for the prevention of AD, then these studies open the way for both augmentation studies of such effects and to compare the magnitude of the static effects observed here with those of other putative therapeutic agents.

Finally, we note that statin therapy has, in general, not been effective in treatment of established AD. For example, a 2002 randomized placebo-controlled 26-week trial of simvastatin in 44 patients with probable LOAD (genetic associations not specified) found no significant alteration of CSF Aβ40 or Aβ42 levels, but patients with mild AD showed a reduction in CSF Aβ40 that was correlated with a reduction of 24S-hydroxycholesterol [31]. The Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial examined the effects of atorvastatin over the course of 1 year in 98 individuals with mild to moderate LOAD and found hypercholesterolemic ApoEε4 carriers with mild to moderate AD were most likely to show modest benefits on the ADAS-Cog after 6 months of treatment [53], but no such positive result was found in the much larger LEADe study encompassing 640 patients over 72 weeks [54]. Similarly, no reduction

in the rate of decline in neuropsychological test performance was found among the 5,804 participants aged 72 to 80 years with pronounced vascular risks in the PROSPER study randomized to either receive pravastatin or placebo over a 3-year period of observation [55]. A recent Cochrane review update has therefore maintained its conclusion that statin therapy is of no proven benefit for the prevention of AD [56]. However, none of these negative results of statin therapy in established AD or in the very elderly with severe vascular risk factors excludes the possibility that statins must be started before neurodegenerative processes are well under way to be effective in reducing risk of AD.

Abbreviations

Aβ42, amyloid-beta 42; AD, Alzheimer's disease; ApoEε4, apolipoprotein Eε4; APP, amyloid precursor protein; CSF, cerebral spinal fluid; PrP, prion protein; PrP^c, cellular prion protein; PSEN, presenilin; sAPP, soluble amyloid precursor protein.

Competing interests

The authors declare that they have no competing interests.

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