Journal of Alzheimer's Disease 42 (2014) S315–S320
DOI 10.3233/JAD-132366
IOS Press

Review

Statins and Vascular Dementia: A Review

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Accepted 5 February 2014

Abstract. The impact of statin therapy on dementia has been a hot topic of debate over the last decade and still remains highly controversial. Among all causes of dementia, vascular dementia (VaD) is the one type that is more likely to benefit from statins. To date no randomized clinical trials have been published and no systematic review has investigated a possible preventive effect of statins on the VaD subtype. In the present literature review, we tried to identify all available data on the effect of statins specifically in patients with VaD, and to further discuss this possible association. Our literature search highlighted two cross-sectional studies, two prospective cohort studies, and one retrospective cohort study. Two of the studies found a significant positive effect of statin treatment on VaD, depicted by the lower incidence of VaD in statin users, while the others reported non-significant associations. The relatively small numbers of VaD patients and statin users, as well as the presence of confounders and biases, make the interpretation of results extremely difficult. Statins may exert a benefit in the prevention of all-type dementia and VaD, through several mechanisms except for hyperlipidemia reduction. A well-designed randomized clinical trial is the ideal study design to address the effect of statin therapy in VaD and to draw final conclusions.

Keywords: Cholesterol, HMG-CoA inhibitors, lipid lowering agents, statins, vascular dementia

INTRODUCTION

Conflicting results have been published so far about the association of statins and Alzheimer's disease (AD) or all-type dementia. Some of the observational studies suggest that a positive relationship exists and that statins delay both the onset and progression of dementia [1–4]. Results from other studies, however, support that statin use has no significant effect on cognitive decline [5–8]. Statin use has also been criticized for having a negative effect on cognitive decline after the publication of 60 case reports of cognitive impairment after statin treatment [9]. A decisive impact on the topic was made by the secondary endpoints from two large placebo-control randomized clinical trials (RCT)—the Heart Protection Study and the PROSPER study—that found a similar risk of dementia among statin and non-statin users [10, 11]. The subsequently published systematic reviews also reported that patients with cognitive decline [7] or incident dementia [12–14] are unlikely to benefit from statin treatment. However, the aforementioned reviews combined all types of dementia into a single outcome and thus were unable to uncover a possible preventive effect of statins on particular subtypes, e.g., vascular dementia (VaD).

In the present literature review, we tried to identify all available data about the effect of statins specifically

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ISSN 1387-2877/14/$27.50

Table 1
Observational studies addressing the association of statin treatment with vascular dementia (VaD, vascular dementia; DSM, Diagnostic and Statistical Manual; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; MMSE, Mini-Mental State Examination; CDT, clock drawing test; T2DM, diabetes mellitus type 2; HD, heart disease; HTN, hypertension; OR, odds ratio; HR, hazard ratio)

Author, year	Location	Study type	No. of patients with dementia	VaD prevalence/ criteria	Cognitive tests/ diagnostic incidence	Comorbidity	Statin prevalence/ incidence	OR/HR
Fei et al., 2013 [15]	China	cross-sectional study	132	28,00%	DSM-IV	T2DM	40.8%	0.87 (0.84–0.91)
Hajjar et al., 2002 [16]	USA	retrospective cohort study	233	25.3%	MMSE, CDT	hypercholesterolemia	17.0%	0.25 (0.08–0.085)
Rea et al., 2005 [17]	USA	prospective cohort study	480	12.9%	NINCDS	–	8.5%	1.36 (0.61–3.06)
Reitz et al., 2004 [18]	USA	cross-sectional study	594	20,00%	DSM-III	T2DM, HD, HTN	16.9%	0.87 (0.49–1.56)
Reitz et al., 2004 [18]	USA	prospective cohort study	173	31.2%	DSM-III	T2DM, HD, HTN	11.6%	1.45 (0.65–3.28)

in patients with VaD, and subsequently to further discuss the possible association of statins and VaD.

METHODS

Our literature search through MEDLINE and EMBASE was based on the combination of the terms: 'vascular dementia', 'statins', 'HMG-CoA inhibitors', 'cholesterol', and 'lipid lowering agents'. References of retrieved articles were also screened. Reference lists of all articles that met the criteria of relevant review articles were examined to identify studies that may have been missed by the database search. The last search was done on 11 January 2014.

We evaluated data and conducted a narrative review from all retrieved cohort and cross-sectional studies published in English. Studies and case reports published in languages other than the English language were excluded from the present review. Duplicate publications were excluded from further evaluation.

OBSERVATIONAL STUDIES INVESTIGATING THE EFFECT OF STATIN TREATMENT ON VASCULAR DEMENTIA

In a prospective cross-sectional study of Chinese diabetic patients with prevalent dementia, Fei and colleagues found that statin use was associated with a reduced risk for both all-cause dementia (Odds Ratio (OR) = 0.94; 95% confidence interval (CI), 0.89–0.98) and VaD (OR = 0.87, 95% CI = 0.84–0. 91), after multivariate logistic regression analysis [15]. Similarly, Hajjar et al. reported that statin treatment was independently associated with lower prevalence of both VaD (OR = 0.25; 95% CI, 0.08–0.85; $p = 0.027$) and all-cause dementia (OR = 0.23; 95% CI, 0.1–0.56, $p = 0.005$) in a retrospective cohort study of patients with dementia and/or hypercholesterolemia from a community-based, medical school-affiliated practice in South Carolina, USA. Moreover, statin treatment has also been associated with significantly improved results in reassessment with the Mini-Mental Status Examination and Clock drawing tests after a mean follow-up period of 10.6 ± 6 months [16].

However, results from a prospective population-based cohort study (the Cardiovascular Health Cognition Study) do not further confirm that previous statin use in patients without dementia at baseline is associated with a lower risk of both VaD (Hazard Ratio = 1.36; 95% CI, 0.61–3.06) and all-causes dementia (HR = 0.69; 95% CI, 0.46–1.02). The dose, duration, and lipophilicity of statin were found to have no impact on the aforementioned risk of developing dementia [17]. Treatment with lipid-lowering agents was neither associated with the risk of prevalent VaD in the cross-sectional analysis (OR = 0.87; 95% CI, 0.49–1.56; $p = 0.65$), nor with the risk of incident VaD (HR = 1.45; 95% CI, 0.65–3.28; $p = 0.36$) in the prospective analysis of a cohort from Northern Manhattan residents older than 65 years of age by Reitz et al. [18] (Table 1). The last two studies by Rea et al. and Reitz et al. were included in a systematic review of nine studies (one nested case-control study, six cohort studies, two meta-analyses) by Muangpaisan et al., in which no significant effect of statins was found in the prevention of VaD or dementia. The risk of dementia was neither associated with the duration of treatment, nor the average daily dose nor the lipophilicity of the drug [12].

EFFECTS OF STATINS ON PATHOPHYSIOLOGICAL MECHANISMS RELATED TO VASCULAR DEMENTIA

In a cross-sectional study by Trkanjec and coworkers, VaD patients were found to have higher cholesterol levels (total cholesterol, LDL cholesterol, and HDL cholesterol) compared to controls. However, the aforementioned differences did not reach statistical significance [19]. Similarly, in the study by Reitz et al., the risk of VaD was weakly associated with high non-HDL, high LDL, and low HDL levels, in both cross-sectional and prospective analysis [18]. In contrast, an even moderate elevation of midlife serum total cholesterol levels was associated with an increased risk of both AD and VaD in a large multiethnic cohort by Solomon and colleagues [20]. To date, no other study has reported a significant association between total cholesterol levels measured in midlife or late-life and VaD [21].

Low levels of antioxidants in brains of VaD patients may lead to a higher susceptibility to oxidative stress, and to a subsequent higher grade of LDL cholesterol oxidation. The HDL-associated paraoxonase, one of the antioxidative enzymes that may reduce LDL oxidation, was found to have significantly lower activity in patients with VaD compared to controls [22, 23]. Moreover, a study by Li et al. found that LDL oxidative modification is increased in patients with VaD, and is furthermore inversely associated with cognitive decline [24]. It should also be noted that HDL cholesterol is the prominent lipoprotein in the brain and possibly plays a role in removing cholesterol from the central nervous system through an active receptor-mediated transfer at the blood-brain barrier [25].

Carotid artery intima-media thickness and the presence of atherosclerotic plaques were also significantly associated with VaD in multiple logistic regression analysis by Ban et al. Multiple logistic regression analysis also revealed an independent association of increased plasma levels of serotonin (5-HT), a potent vasoconstrictor of large cerebral arteries, and human urotensin II, a cyclic neuropeptide with potent vasoconstrictive activity, with the pathogenesis and progression of VaD [26, 27]. Similarly, results from the Rotterdam study, a single center population-based cross-sectional study, suggest that the presence of atherosclerotic carotid artery plaques and peripheral arterial atherosclerosis were both independently associated with impaired cognitive performance [28].

On the other hand, abundant experimental evidence support the potent anti-inflammatory properties of statins in vascular and myocardial endothelium and the induced nitric oxide bioavailability [29]. Endothelial nitric oxide synthase augmentation, observed after long-term statin treatment in laboratory settings, presumably augments both cerebral vasomotor reactivity and cerebral blood flow regulation and provides an alternative explanation for the improved clinical outcomes associated with their use [30]. Statins also significantly suppress TNF-α synthesis in glia, a response to various physical or metabolic insults of the brain which in turn damages other healthy neurons [31]. Finally, experimental and clinical studies have revealed a relation between amyloid-β and cholesterol levels, suggesting that presently unidentified molecular mechanisms may regulate neuronal amyloid-β production through cholesterol [32]. The aforementioned possible effects and pathophysiological mechanisms of statins on cerebral blood flow and neuronal damage may provide a partial explanation for their beneficial effects on the prevention and/or progression of VaD (Fig. 1).

DISCUSSION

The impact of statin therapy on dementia has been a hot topic of debate over the last decade, and still remains highly controversial. Although the American Heart Association, the American Stroke Association, and the British Association for Psychopharmacology converge that evidence is insufficient for the use of statins in patients with dementia [33, 34], a substantial proportion of clinicians favor the use of statins in both primary and secondary prevention of vascular cognitive impairment despite the lack of definite evidence [35].

Among all causes of dementia, VaD is the one type that is more likely to benefit from statins and no randomized clinical trials have been published to date [13, 14, 36]. VaD is the second most common dementing illness after AD; however, no pharmacological agents for its treatment or prevention have been approved so far. This seems paradox, as VaD is known to share the same risk factors with ischemic stroke, which is a highly preventable condition [37]. Although both elevated levels of serum total cholesterol, LDL, and non-HDL, and decreased levels of HDL have been associated with the risk for VaD, not all observational studies have shown a decreased risk for cognitive impairment with statin therapy [38].

Our literature search highlighted two cross-sectional studies, two prospective cohort studies, and one

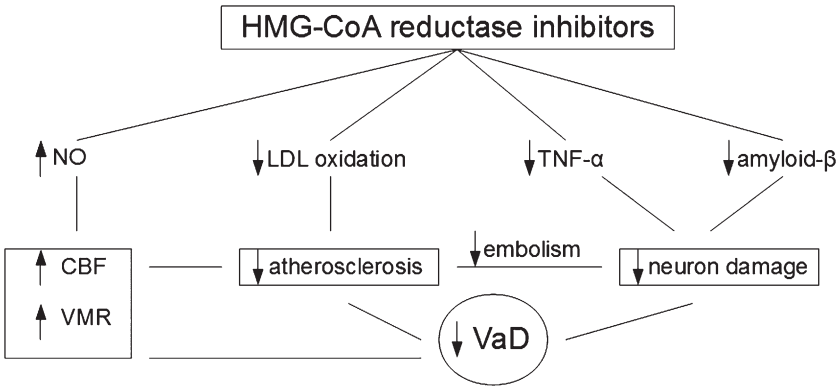

Fig. 1. Possible effects and pathophysiological mechanisms of statins on vascular dementia (NO, nitric oxide; TNF-α, tumor necrosis factor α; CBF, cerebral blood flow; VMR, vasomotor reactivity; VaD, vascular dementia).

retrospective cohort study addressing the association between statin treatment and VaD. Two of the studies (one cross-sectional and one retrospective) found that statin treatment was associated with a lower incidence of VaD [15, 16], while the others reported non-significant associations [17, 18]. Neither a randomized clinical trial on the topic, nor a subgroup analysis of patients with VaD from the HPS and PROSPER study have been published so far [10, 11].

All the aforementioned observational studies, except for one, were conducted in the US. The number of patients with dementia was relatively small in all studies (mean number of patients with dementia = 322, range = 132–594), and even smaller was the prevalence/incidence of VaD in those demented patients (mean number of VaD patients = 66, range = 37–119) and statin use (mean number of patients treated with statins = 51, range = 20–100). The presence of comorbidities that are known risk factors for VaD (diabetes mellitus, heart disease, hypertension) and the use of different cognitive tests and diagnostic criteria make the overall analysis and interpretation of the results from observational studies even more difficult (Table 1).

The dramatic differences between observational studies could therefore be explained by five obvious confounders: 1) the length of the treatment period; 2) the statin type (lipophilic-hydrophilic); 3) the inclusion of patients with advanced disease and advanced age, who are already at risk for vascular disease and have multiple vascular risk factors; 4) the different assessment tests; and 5) the heterogeneity of VaD pathophysiology and its interplay with AD [39–42]. The discrepancy between observational studies might additionally be explained by prescription and indication biases, as impaired patients and patients of lower socioeconomic status are less likely to have been prescribed a statin [43].

Finally, the observed differences in the results from cross-sectional/retrospective studies and prospective studies could also be explained by the differences in study properties, as by study design prospective studies are able to remove more confounders than retrospective studies. Therefore, RCTs are the necessary instrument to eliminate confounding, address bias, and to further investigate the effect of different statins on cognitive function and VaD.

CONCLUSION

The use of statin therapy in established VaD is a relatively unexplored area. Statins may exert a benefit in the prevention of all-type dementia and VaD through several mechanisms except hyperlipidemia reduction. Results from cohort and cross-sectional studies should be interpreted with caution, due to the presence of confounders and biases.

A well-designed RCT is the ideal study design to address the effect of statin therapy in VaD. However, an RCT in this research area could be both very expensive and difficult, as patients over 65 years of age should be recruited and followed-up for a long period of time. Until RCTs on the field become available, data from the prospective cohort studies published so far should be considered the highest quality evidence available to date.

ACKNOWLEDGMENTS

Dr. Georgios Tsivgoulis was supported by the European Regional Development Fund-Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123).

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2142).

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