Impact of simvastatin on cerebral blood flow, pulsatility, and Alzheimer's disease biomarkers: a clinical trial

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BACKGROUND

- Alzheimer's Disease (AD) is a neurodegenerative disease which causes progressive cognitive and behavioral dysfunction, usually impairing memory and causing medial temporal lobe atrophy.[1]
- Today, an estimated 5.4 million American adults over 65 have AD[2], and this figure is predicted to triple by 2050.
- To improve treatment and prevention, clinicians and researchers need to better understand the causes and risk factors for AD.
- Cerebral amyloid-β (Aβ) is a neurotoxin which causes synaptic dysfunction and neurodegeneration.[2]
- Vascular risk factors significantly contribute to cognitive decline and progression of Alzheimer's disease (AD).[3,4]
- Epidemiologic and animal studies suggest that statins may be effective in reducing Aβ42 burden, possibly via increased clearance and decreased production.
- Previous studies indicate that statin therapy in midlife could beneficially modify factors associated with AD onset.[5,6]
- We hypothesized that simvastatin therapy would, via effects on cerebral blood flow and vessel elasticity, mediate a decrease in cerebral spinal fluid (CSF) Aβ in a middle aged population at risk for AD.

OBJECTIVE

To determine if changes in arterial and venous cerebral blood flow (CBF) and pulsatility index (PI) predict changes in Aβ after long-term simvastatin therapy.

METHODS

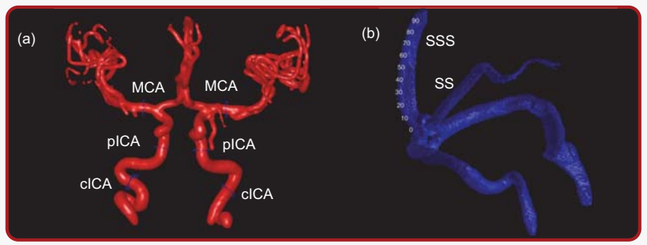

Figure 1. (a) PC-VIPR MR angiogram with arteries of interest. **(b)** Example selection of SSS analysis. A centerline point was chosen and a 2D plane placed orthogonal to the direction of flow. CBF was calculated as the average of three points surrounding the point of interest (mL/s). Only waveforms with good cardiac gating were used for PI. PI = [(maximum flow rate – minimum flow rate)/ average flow rate]

Participants and Protocol:

Recruitment from Wisconsin Alzheimer's Disease Research Center or community
↓
282 Approached + 100 Screened
↓
Inclusion Criteria: Middle-aged adults (aged 40-72 years) with a parental history of AD
↓
Exclusion Criteria: dementia or mild cognitive impairment on baseline screening; use or contraindications to use of statins, MRI, or LP; history of cardiovascular disease that would require statin use; or active participation in another research study
↓
Baseline: 88 Enrolled + Randomized n=44 per group, stratified by sex and APOE allele status
↓
At baseline, month 12, and month 18: MRI with PC-VIPR sequences, LP, and cognitive assessments.
↓
Month 18: 83 individuals (simvastatin, n=42; placebo, n=41)

Imaging: PC-VIPR

- *Phase contrast vastly undersampled isotropic projection imaging* is a novel 4D flow MRI technique for angiography of cerebral vessels.[7]
- Three arterial and two venous segments were identified using MATLAB from PC angiograms created from 4D MRI data.[8]

Statistical Analysis

- Independent two-sided T tests for baseline group differences
- Linear regressions to investigate the role of treatment over time on CBF and PI, and to investigate the ability of CBF and PI to independently predict CSF biomarkers using ratios to account for change from baseline.
- Covariates included sex, age, *APOE4* allele status, and education (for cognition).

FIGURES & TABLES

Table 1: Demographic and Diagnostic Information

Information	Placebo (n=44)	Simvastatin (n=44)	Total (n=91)*	Difference p value
Age [mean, (SD)]	54.43 (7.79)	55.95 (6.18)	55.11 (6.93)	0.309
Sex [n female, (%)]	32 (72.73)	31 (70.45)	64 (70.33)	0.816
Caucasian [n, (%)]	43 (97.7)	44 (100)	89 (97.8)	0.323
Years of Education [mean, (SD)]	15.61 (2.63)	16.30 (2.23)	15.92 (2.44)	0.192
MMSE [mean, (SD)]	29.30 (0.85)	29.50 (0.79)	29.41 (0.82)	0.247
APOE ε4 positive [n, (%)]	17 (38.64)	17 (38.64)	35 (38.46)	1.000
Hypertension [n, (%)]	1 (2.27)	3 (6.82)	5 (5.49)	0.312
ASCVD 10-year risk score [mean, (SD)]	3.34 (3.353)	4.08 (3.77)	3.813 (3.719)	0.350
BMI, kg/m² [mean, (SD)]	27.58 (5.59)	27.20 (5.63)	27.68 (5.79	0.749
Baseline Total Cholesterol [mean, (SD)]	206.64 (34.22)	207.23 (35.65)	206.77 (34.4)	0.937
Baseline LDL [mean, (SD)]	122.80 (28.08)	122.25 (28.36)	122.57 (27.91)	0.819
Baseline HDL [mean, (SD)]	63.46 (17.18)	62.52 (20.77)	62.23 (19.21)	0.928
Baseline Triglycerides [mean, (SD)]	101.77 (40.08)	112.39 (57.61)	109.85 (53.05)	0.319

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; MMSE, Mini Mental State Exam
* Three subjects were included in baseline analyses but withdrew before randomization to treatment.

Figure 2: PC-VIPR data shown as color maps of pulsatility index in the venous segments of interest in two selected, similarly aged participants from the control (a) and treatment group (b).

Table 2: ANCOVAs* for effects of simvastatin vs. placebo on CBF, PI, and CSF Aβ outcomes

		Month 12 to Baseline Percent Change				Month 18 to Baseline Percent Change			
Assessment		Placebo	Simvastatin	β**	p value	Placebo	Simvastatin	β**	p value
Cerebral Blood Flow	pICA	97.1	96.8	-0.3	0.953	91.2	103.7	**12.5**	**0.063**
	cICA	100.2	100.8	0.6	0.896	93.3	102.5	9.2	0.095
	MCA	96.6	99.8	3.2	0.629	91.3	99.9	8.6	0.326
	SSS	105.1	101.2	-3.9	0.381	95.1	101.1	6.1	0.258
	SS	104.2	103.6	-0.6	0.874	103.7	99.5	-4.2	0.644
Pulsatility Index	pICA	149.7	110.2	-39.5	0.057	197.3	109.4	**-87.9**	**0.060**
	cICA	143.4	109.0	-34.3	0.115	196.5	108.4	**-88.1**	**0.070**
	MCA	144.3	106.0	-38.3	0.088	138.8	111.3	-27.5	0.243
	SSS	146.9	112.2	-34.7	0.198	187.5	96.5	**-91.0**	**0.012**
	SS	146.5	109.8	-36.6	0.091	245.0	95.8	**-149.2**	**0.042**
CSFAβ	Aβ42 Tr	100.0	99.5	-0.5	0.862	98.3	102.4	4.1	0.167
	Aβ42 xM	103.9	102.4	-1.5	0.704	99.2	100.5	1.3	0.713
	Aβ42/40 Tr	99.4	99.3	-0.1	0.955	99.8	99.6	-0.2	0.913

pICA, petrous internal carotid artery; cICA, cervical internal carotid artery; SSS, superior sagittal sinus; SS, straight sinus; Tr, triplex; xM, xMAP. Values reported as percentages.
*ANCOVA covariates in all models included: sex, age, and APOE4 allele status. **Unstandardized regression coefficient β for treatment

RESULTS

Baseline Group Differences

- No differences at baseline between *APOE4* allele carriers and non-carriers (all p values > 0.19).
- Baseline straight sinus CBF (p = 0.036) and working memory performance (p = 0.035) were greater in the treatment group than placebo group.
- Women performed better on memory and learning tasks than men (p = 0.046).

Effects of Simvastatin on Outcome Measures (Table 2)

- The simvastatin group trended towards increased pICA CBF (p = 0.063).
- The simvastatin group had decreased PI in venous segments at month 18 (SSS, p = 0.012; SS, p = 0.042).
- The simvastatin group showed trends towards decreased PI in multiple arterial vessels (pICA, p = 0.06; cICA, p = 0.07).

Relationship between PC-VIPR measures and CSF Aβ

- Change in CBF or PI over time did not predict change in CSF Aβ over time (all p values > 0.24).
- Change in cICA PI predicted change in CSF Aβ42 xMAP from baseline to month 12 (p=0.005).

CONCLUSIONS

- 18-month simvastatin therapy in a middle aged population with a family history of AD decreased PI but did not significantly impact Aβ42 burden.
- Simvastatin treatment decreased pulsatility index in cerebral veins.
- Simvastatin treatment showed trends towards beneficially lowering pulsatility index and increasing blood flow in cerebral arteries
- This study supports the hypothesis that cerebrovascular changes precede detectible change[4,10,11] in AD neurotoxins in healthy, middle aged adults.[4,12,13]
- This study provides novel evidence supporting a cascade from increased vessel stiffness to increased Aβ42 burden.

↑ Cholesterol → ↑ Arterial + venous stiffness → ↓ Cerebral blood flow → ↓ Aβ clearance → ↑ Aβ burden → Cognitive Decline

Figure 3. Proposed sequential cascade from cholesterol to cognitive decline.

- Increased pulsatility index may be an earlier change in cerebrovascular dysfunction than decreased CBF and thus able to detect pathologic changes before detection by traditional biomarker or cognitive assessment.
- The role of cardiovascular risk factors in midlife on AD pathogenesis requires further investigation. Further studies should be lengthened with more diverse participants.
- PC-VIPR is an informative imaging tool for the study of cerebrovascular changes in AD.

REFERENCES + ACKNOWLEDGEMENTS

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