Published in final edited form as:

Transl Stroke Res. 2020 June ; 11(3): 319–321. doi:10.1007/s12975-019-00737-4.

Effect of Simvastatin on Permeability in Cerebral Cavernous Malformation Type 1 Patients: Results from a Pilot Small Randomized Controlled Clinical Trial

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Cerebral cavernous malformations (CCMs) are low-flow vascular malformations that can occur in sporadic or familial forms, with familial CCM syndrome caused by an inherited mutation in one of the three known CCM genes [1–3]. The clinical course is highly variable, particularly in familial CCM patients where CCMs can number into hundreds and patients can range from being asymptomatic to having seizures, headaches, focal neurological deficits, intracranial hemorrhage, or death. Although CCMs can be associated with significant morbidity, treatment options are generally limited to surgical resection of selected symptomatic lesions. Ideally, a medical therapy would be able to prevent the formation of new CCMs and decrease the risk of hemorrhage and growth of CCMs. Statins have been identified as a potential therapy for CCMs as they have been shown to prevent CCM formation and decrease permeability in animal models through Rho kinase inhibition [4–8]. Since CCMs form, enlarge, and hemorrhage at a relatively low rate, a therapeutic trial monitoring hemorrhage or formation and enlargement of CCMs would require many years, a large number of patients, and huge expense [1, 2, 9]. Dynamic contrast-enhanced perfusion MRI (DCEMRI) is a T1-based MRI technique that has demonstrated the capacity to measure

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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low-level permeability within CCMs and has been identified as a potential quantitative biomarker [10–13]. Permeability of CCMs as measured by DCEMRI would be an ideal biomarker to assess therapeutic effects of drugs on CCMs. We initiated a small, prospective, randomized, controlled trial as a pilot study to test the feasibility of using DCEMRI to evaluate permeability in CCM patients treated with simvastatin and control CCM patients not treated with simvastatin; we aimed to evaluate feasibility, safety, and the exploratory hypothesis that simvastatin treatment would alter permeability as measured by DCEMRI.

Twelve patients with CCM1 underwent informed consent for this institutional review board-approved study and were randomized to receive simvastatin ($n = 6$) or be in the control group ($n = 6$). Inclusion criteria for the study were diagnosis of CCM1 Common Hispanic Mutation and willingness to travel for 5 visits over 3 months; exclusion criteria were incarceration, inability to pass MRI safety screening, liver or kidney dysfunction, allergy to gadolinium or statins, currently taking statins or within last 6 months, consumption of large amounts of alcohol, elevated creatine kinase, triglycerides, or liver enzymes, or taking potentially interacting medications. The treatment arm patients received 20 mg of simvastatin daily by mouth for the first month and then 40 mg of simvastatin by mouth for the second and third months with laboratory monitoring. Patients underwent 3-T DCEMRI at baseline before treatment and again after 3 months. CCMs and normal-appearing white matter were segmented from anatomic images, and CCM and normal-appearing white matter mean permeability (K_i) were calculated for each study [10]. A total of 10 pairs of DCEMRI studies were of adequate quality for processing and analysis (5 simvastatin and 5 control patients). We tested whether characteristics and permeability differed between groups using t tests with unequal variances for continuous variables and Fisher's exact tests for categorical variables. For total and large lesion counts, statistical comparisons were made using log-transformed values to accommodate outliers. We analyzed CCM permeability by comparing the percentage change in CCM permeability between the second and first DCEMRIs without and with normalizing to permeability in normal-appearing white matter, expecting a greater reduction in the simvastatin group.

Comparisons between the simvastatin and control groups are provided in Table 1. All 20 DCEMRI studies demonstrated elevated permeability in CCMs compared with normal-appearing white matter (mean ratio of 2.73 ± 1.07 , $p < 0.001$). There was no statistically significant difference in the percentage change in permeability between the simvastatin and control groups without ($4.7\% \pm 32.2\%$ vs. $-20.4\% \pm 22.6\%$, $p = 0.171$) or with normalizing to white matter ($-23.9\% \pm 35.8\%$ vs. $-14.3\% \pm 22.6\%$, $p = 0.626$). The patients treated with simvastatin did however demonstrate increased permeability in the white matter ($47.2\% \pm 12.3$ vs. $-5.2\% \pm 7.4$, $p = 0.009$).

This pilot study was the first randomized controlled drug trial in familial CCM patients and will be of great interest to the CCM community with regard to the potential validity of DCEMRI as a biomarker and simvastatin as a potential treatment. We demonstrated feasibility of using DCEMRI to evaluate permeability in a statin trial with 10/12 (83.3%) of the patients ultimately having usable data sets for analysis, 2 having inadequate DCEMRI pairs for analysis, a finding that could be planned for in future studies. While our study was not planned as a safety study due to the routine clinical use of simvastatin, we did not

encounter any adverse events during our study. In agreement with other studies, we found elevated permeability in CCMs relative to background normal-appearing white matter [10–13]. We did not find a statistically significant difference in CCM permeability between the patients who received simvastatin for 3 months and those who did not, but unexpectedly found statistically significantly increased white matter permeability in the simvastatin group following treatment (47.2% increase compared with baseline MRI). This may indicate an effect of simvastatin on background permeability and warrants further investigation. Limitations of our study include the underpowered nature with a small sample size, mild differences in background characteristics due to randomization (although not statistically significant), that 80% of the patients were female, a relatively short treatment period, and potentially the fact that we did not focus on recently hemorrhaged CCMs. Our study was targeted towards feasibility and investigating a potential imaging biomarker as opposed to clinical efficacy of simvastatin and therefore should not discourage further investigation into the role of statins (including atorvastatin which is a more potent Rho kinase inhibitor) as potential treatments for CCMs. Indeed, a phase I/II randomized controlled trial is currently ongoing to test dosing and safety of 40–80-mg atorvastatin use in CCM [14]. We look forward to the results of further ongoing studies regarding DCEMRI and statin treatment in CCM patients, which are focusing on recently hemorrhaged CCMs that are at higher risk for rehemorrhage and may be more likely to have altered permeability [9, 14].

ClinicalTrials.gov Identifier: [NCT01764451](https://clinicaltrials.gov/ct2/show/study/NCT01764451).

Acknowledgments

Funding information This study was funded by the National Institute of Health-National Institute of Neurological Disorders and Stroke (grant number U54 NS065705).

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Summary statistics and comparisons

Table 1

Characteristic	No simvastatin	Simvastatin	<i>p</i> value
Count	5	5	n/a
Female	4 (80%)	4 (80%)	1.000
Age at first scan (years)	38.0 ± 16.7	46.9 ± 10.6	0.350
Time between scans (days)	103 ± 14	107 ± 5	0.795
Total lesion count at enrollment	27 (7–98)	31 (8–104)	0.791
Large lesion count at enrollment	5 (3–10)	4 (1–14)	0.608
History of past symptomatic hemorrhage	5 (100%)	2 (40%)	0.167
History of seizures	5 (100%)	3 (60%)	0.444
History of headaches	5 (100%)	3 (60%)	0.444
History of symptomatic hemorrhage in the last 3 years	0	0	1.000
Adverse event or hemorrhage during the study	0	0	1.000
CCM lesion volume (cm ³)	13.2 ± 10.2	8.0 ± 7.5	0.394
% change in CCM permeability	– 20.4 ± 16.3	4.7 ± 32.2	0.171
% change in WM permeability	– 5.2 ± 7.4	47.2 ± 12.3	0.009
% change in CCM permeability (proportional to WM)	– 14.3 ± 22.6	– 23.9 ± 35.8	0.626

Values are mean ± SD, median (range), or *n* (%)

p values are from Fisher's exact test or two-sample *t* test allowing for unequal variances