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Case report: Intensive statin and PCSK-9 inhibitor combo reduces plaque volume and stenosis in ischemic stroke patient

Weiqi Zeng [a,1], Yunfei Shi [b,1], Meng Fan [c], Changzheng Shi [c], Zefeng Tan [a,*]

[a] Department of Neurology, The First People's Hospital of Foshan, Foshan, Guangdong, China
[b] Department of Internal Medicine, Guangzhou Tianhe District People's Hospital, Guangzhou, Guangdong, China
[c] Department of Neurology, Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong, China

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ABSTRACT

Intracranial atherosclerotic ischemic stroke dramatically impacts the quality of life among the elderly. Statins therapy has been proven to be effective in plaque stabilization and alleviation in patients with intracranial atherosclerotic ischemic stroke. According to recent studies, these effects may be directly related to lipid levels rather than specific lipid-lowering drugs. *Anti*-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (PCSK-9 inhibitor) are newer effective lipid-lowering drugs increasingly prescribed to patients at high cardiovascular risk to lower LDL cholesterol. Studies have provided evidence that PCSK9 inhibitor combined with statin therapy can lead to a decrease in the plaque volume measured by intravascular ultrasound in coronary heart disease patients. But the efficacy of combination of the two drugs in symptomatic intracranial artery stenosis has been unknown. Here we provide a case which was reported to suggest that a combination of Evolocumab and intensive statin therapy might reverse or alleviate symptomatic intracranial artery stenosis.

1. Introduction

Low density lipoprotein cholesterol (LDL-C) is a significant modifiable risk factors in intracranial atherosclerotic (ICAS) ischemic stroke. However, according to the findings of European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE III) survey, it was observed that approximately two-thirds of patients failed to achieve the recommended target levels of LDL-C, which emphasizes the need for more effective management and control of this risk factor [1]. Previous study showed that PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitor Evolocumab stabilizes symptomatic atherosclerotic plaques and prevents plaque rupture in the coronary artery [2]. The latest cholesterol management guidelines recommended that coronary artery disease patients with LDL-C >1.8 mmol/L should receive additional PCSK9 inhibitor therapy, suggesting that future recommendations may seek even lower LDL-C levels. However, there is a lack of studies on the effect of PCSK9 inhibitor combined with intensive statins therapy on the regression and stability of symptomatic intracranial arterial stenotic plaques in symptomatic ICAS patients. Vascular wall imaging techniques, such as high-resolution magnetic resonance imaging (HR-MRI), have recently been introduced, showing the morphology of atherosclerotic plaques, arterial walls, and surrounding structures in intracranial arteries. 3D T1WI of HR-MRI can detect abnormal signals of intracranial blood vessels wall and evaluate changes of plaques using the CUBE technique [3,4].

* Corresponding author.
E-mail address: tanzaister@gmail.com (Z. Tan).
[1] These authors have contributed equally to this work.

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Here we provide a case which was reported to suggest that a combination of Evolocumab and intensive statin therapy might reverse or alleviate symptomatic ICAS.

1.1. Case description

A 39-year-old male presented with right limb weakness and numbness for 4 days. The patient had recurrent stereotypic episodes of right-sided limb weakness and numbness over the past four days, each lasting approximately 3 minutes with complete recovery. The patient had no history of hypertension or diabetes mellitus and smoked about 3–4 cigarettes per day. Physical examination revealed right-sided central facial palsy and muscle weakness with a NIHSS score of 3 points. Brain MRI diffusion-weighted imaging and MR angiography within 24 hours of admission suggested acute left-sided radial coronal cerebral infarction with severe stenosis of the left middle cerebral artery (Fig. 1d). The initial HR-MRI showed severe stenosis in the M1 segment of left middle cerebral artery (MCA) as well as the initial transcranial doppler (TCD) and whole-brain digital subtracts angiography. The stenosis was measured on the 3D CUBE T1-weighted sequence, illustrating that the vessel area was 21.88 mm^2 and lumen area was 0.89 mm^2, with the stenosis rate of 92.5% (Fig. 1a). After the initial HR-MRI examination, the patient regularly received combined lipid-lowering therapy (Rosuvastatin, 20 mg, q. d. and Evolocumab, 140 mg, q.2. w.), as well as antiplatelet therapy (Aspirin 100 mg and clopidogrel 75mg per day for 3 months followed by Aspirin 100mg daily). During the two-year follow-up period, we monitored the lipid level, HR-MRI, and TCD for the patient. The patient did not report any stroke attack or adverse reactions during the follow-up period.

Over the course of the treatment, the patient achieved a significant reduction in lipid level and plaque volume and a significant improvement in wall area and stenosis rate in the stenosed MCA segment. (87.0% reduction in LDL-C level; 43.5% reduction in plaque volume, 34.5% reduction in wall area, Fig. 2f) The doppler spectrum for left MCA gradually improved and eddy signal reduced as well (Fig. 1). On Time-of-Flight MRA image, the stenosis of left MCA relieved overtime (Fig. 2a–d). The detailed changes in HR-MRI were shown in Table 1.

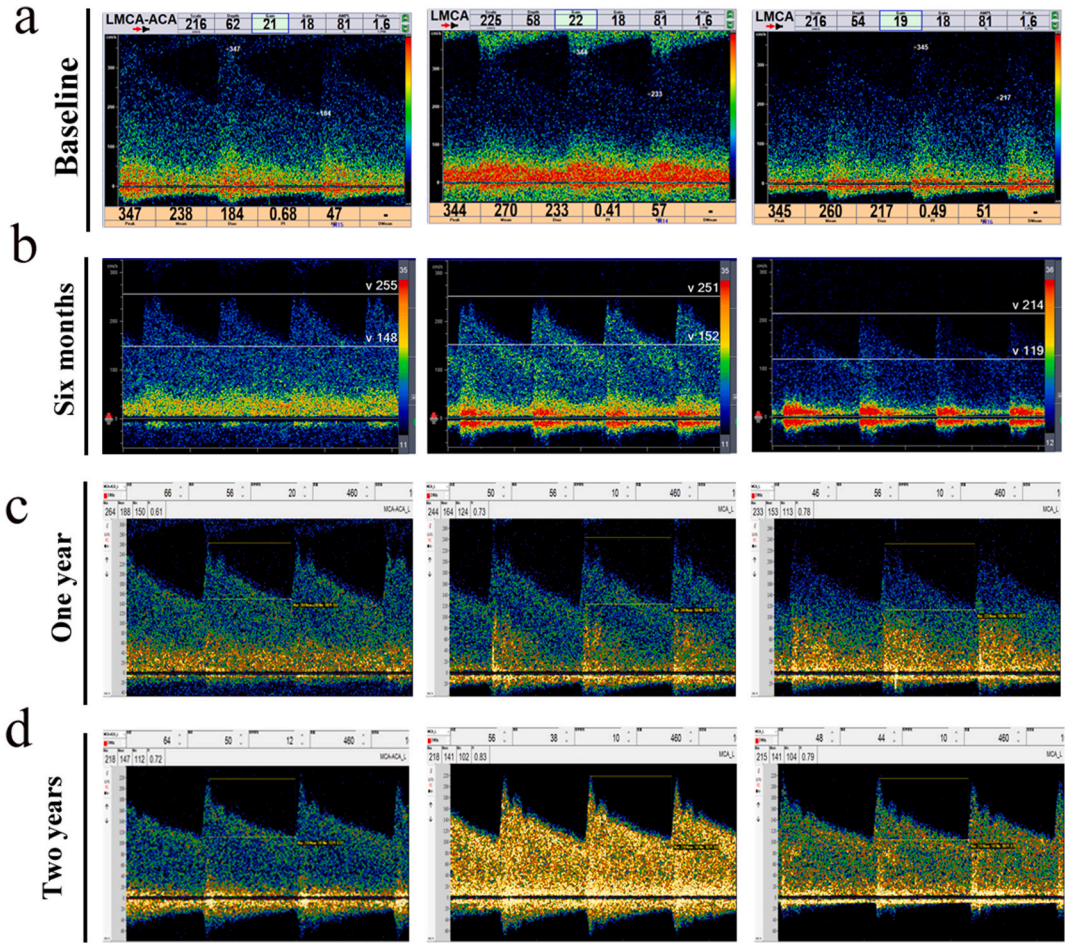

Fig. 1. Changes in the TCD spectrum image of left MCA. (a) TCD spectrum image of left MCA at baseline. It indicated eddy formation and accelerated segmental blood flow in the left MCA. (b) TCD spectrum image of left MCA at one-year follow up. Doppler spectrum of left MCA improved and eddy also reduced. (c) TCD spectrum image of left MCA at two-year follow up. The eddy was disappeared.

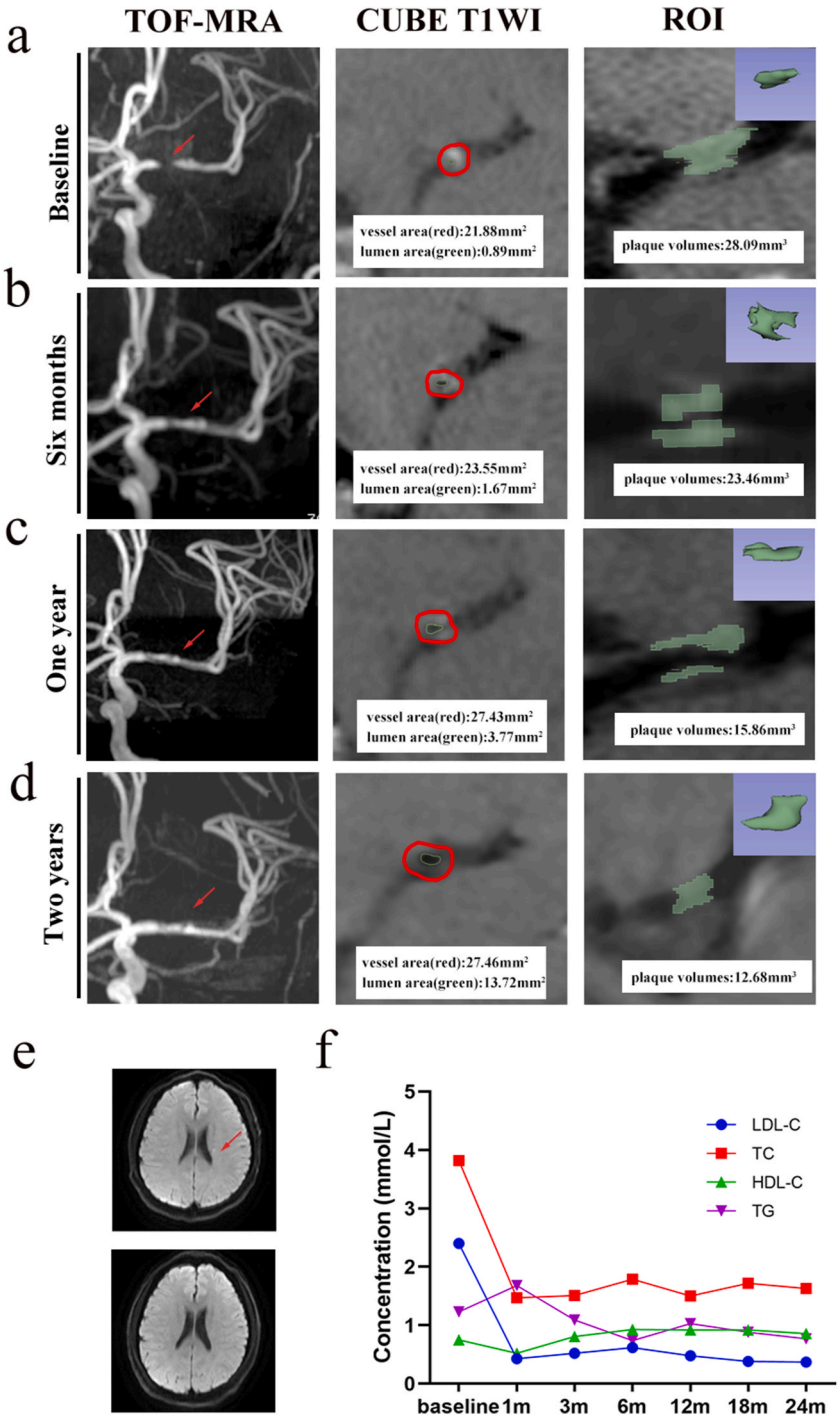

Fig. 2. Changes in the MRI and level of blood lipid. (a) The MRA images at baseline. The stenosis at M1 segment of left MCA was shown (red arrow). The vessel area and lumen area of the stenosis was 21.88 mm^2 and 0.89 mm^2. The plaque volumes were 28.09 mm^3. (b) The MRA images at six-month follow up. The stenosis at M1 segment of left MCA was improved (red arrow). The vessel area and lumen area of the stenosis was 23.55 mm^2 and 1.67 mm^2. The plaque volumes were 23.46 mm^3. (c) The MRA images at one-year follow up. The stenosis at M1 segment of left MCA was improved (red arrow). The vessel area and lumen area of the stenosis was 27.43 mm^2 and 3.77 mm^2. The plaque volumes were 15.86 mm^3. (d) The MRA images at two-year follow up. The stenosis at M1 segment of left MCA was further improved (red arrow). The vessel area and lumen area of the stenosis was 27.46 mm^2 and 13.72 mm^2. The plaque volumes were 12.68 mm^3. (e) The DWI sequence at baseline (upper image) and two-year follow up (lower image). A small left basal ganglia infarction was seen on baseline image (red arrow). (f) The line chart of blood lipid at baseline, 1-month, 3-month, 6-month, 12-month, 18-month, and 24-month follow up.

2. Discussion

An important finding in this case report is that in a patient with symptomatic MCA stenosis treated with the combination of intensive statin and Evolocumab therapy, there was a significant reduction in plaque volume and a significant improvement in wall area and stenosis in the intracranial artery stenosis, but no significant difference in the vascular remodeling index. The results reported in this case report were similar to those reported in previous studies of patients with coronary arteries disease and symptomatic ICAS treated with intensive statin therapy alone [2,5].

In the ODYSSEY OUTCOMES study, Jukema et al. investigated the effect of alirocumab, a PCSK9 inhibitor, on stroke incidence in patients with recent acute coronary syndrome (ACS) and dyslipidemia [6], which study found that the addition of alirocumab to intensive statin therapy would lead to a further reduction in the risk of stroke in these patients. The results of this trial are particularly relevant to our case report, as the patient presented with symptomatic MCA stenosis and was treated with a combination of intensive statin and Alirocumab, another PCSK9 inhibitor. This is particularly relevant to our case report, as the patient experienced a significant reduction in plaque volume and improvement in wall area and stenosis in the intracranial artery stenosis after treatment with the combination of intensive statin and Evolocumab therapy. Although the vascular remodeling index did not show a significant difference, the overall results indicate that the combination therapy may be beneficial in patients with symptomatic MCA stenosis.

STAMINA (Intensive Statin Treatment in Acute Ischaemic Stroke Patients with Intracranial Atherosclerosis: a High Resolution Magnetic Resonance Imaging study), a single-arm, prospective, serial HR-MRI study, found that intensive statin treatment for 6 months resulted in a higher plaque volume, wall area index and stenosis improved [5]. The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial was designed to assess whether PCSK9 inhibition reduces progression of atherosclerosis as measured by intravascular ultrasound, which found a linear relationship between plaque volume reduction and LDL levels (concentration range from 20 to 110 mg/dl), and a 64% reduction in percent of atheroma volume in the Evolocumab group [2]. By which we assumed that in patients with acute symptomatic MCA stenosis, rapid controlling of LDL at lower levels may indirectly achieve a reduced risk of short-term recurrence of stroke by reversing plaque formation and alleviating the degree of stenosis and stabilizing the plaque.

In addition, it should be noted that this was a young patient. A study on ischemic stroke in young adults found that up to 55.3% patients had Dyslipidemia [7]. The rationale for using aggressive lipid-lowering therapy in young patients with intracranial stenosis lies in the fact that they have a shorter course of arteriosclerosis, which is the underlying cause of stenosis. Arteriosclerosis refers to the thickening and hardening of the arterial walls due to the accumulation of cholesterol and other substances, a process that typically progresses over time. In younger patients, this process may be in its early stages, and aggressive lipid-lowering therapy has the potential to halt or even reverse the progression of arteriosclerosis, thereby reducing the risk of stroke and other cardiovascular events [8].

The morphology of plaques in the patient was also studied. According to baseline HR-MRI findings, plaque showed thin and enhanced signal on the surface, with thick and low signal inside; In 3 demension CUBE (GE health care), increased T1 weighted image (T1WI) signal area depicts fibrous cap (due to plaques capillaries), while low signal area indicates lipid or calcification (low signal on T1WI or T2WI indicates calcification, while the relatively high signal on both T1WI and T2 WI indicates lipid) [3,9]. Large lipid core, thin fibrous cap, and ulcer surface are the main characteristics of vulnerable plaque [10]. Therefore, this plaque is a vulnerable plaque. We assume aggressive lipid lowering treatment might have more effect on vulnerable plaques than non-vulnerable plaque. However, this conclusion needs to be supported by more data.

Studies have provided evidence that either intensive statin or PCSK9 inhibition can lead to reduction in LDL-C level and the plaque volume [2,5]. However, there remains a need for prospective study to determine the efficacy and safety of combining intensive statin and PCSK9 inhibition as therapy strategies in atherosclerotic ischemia stroke. By combining intensive statin therapy with PCSK9 inhibitors, rapid control of LDL levels at a lower level may reduce the risk of short-term stroke recurrence in patients with acute symptomatic MCA stenosis by reversing plaque formation, alleviating stenosis, and stabilizing the plaque. Nowadays, a randomized controlled study (NCT05001984) is ongoing to answer the question above and we are looking forward to its result.

Informed consent

The patient has provided informed consent for this case report.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1
HR-MRI vessel wall imaging data at baseline, six-month, one-year, and two-year follow up.

		Vessel area (mm^2)	Lumen area (mm^2)	Plaque volumes (mm^3)	The wall area (mm^2)	Stenosis degree (%)	wall area index	Remodeling index
Target vessel	Baseline	21.88	0.89	28.09	20.99	92.5	1.213	0.748
	six-month follow up	23.55	1.67	23.46	21.88	86.3	1.196	0.771
	one-year follow up	27.43	3.77	15.86	23.66	80.9	1.764	0.827
	two-year follow up	27.46	13.72	12.68	13.74	27.4	1.055	0.860
	Change rate (Baseline *vs.* two-year)	25.37%	323.60%	-43.54%	-34.54%	-70.34%	-13.02%	14.93%
Reference vessel	Baseline	29.24	11.94	–	17.3	–	–	–
	six-month follow up	30.56	12.26	–	18.3	–	–	–
	one-year follow up	33.16	19.75	–	13.41	–	–	–
	two-year follow up	31.93	18.91	–	13.02	–	–	–

Acknowledgements

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