Significant regression of carotid artery stenosis after treatment with proprotein convertase subtilisin/kexin type 9 serine protease inhibitor

Abstract
Carotid artery stenosis is one of the major causes of ischemic stroke. Optimal medical treatment includes controlling diabetes, hypertension, and hyperlipidemia, smoking cessation, and anti-platelets to slow down the atherosclerotic plaque progression and are important in secondary stroke prevention. Carotid endarterectomy (CEA) or carotid artery stenting (CAS) is the standard of care for patients with symptomatic carotid artery stenosis >70% who has a perioperative stroke or mortality rate <6%. To date, there has been no report on medical revascularization of carotid artery stenosis. Here we report a case of a 94-year-old patient with asymptomatic 85% right internal carotid artery (ICA) stenosis, who benefited a 23% plaque regression after 2 years of evolocumab (Proprotein Convertase Subtilisin/kexin Type 9 Serine Protease Inhibitor) (PCSK-9 inhibitor) injection for her atherosclerotic coronary artery disease. While further studies are necessary, we proposed that PCSK-9 inhibitor could be a safe, promising alternative to CEA or CAS in the revascularization of carotid artery stenosis.

Keywords: carotid artery stenosis, pcsk-9 inhibitor, evolocumab, carotid endarterectomy, carotid artery stenting

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; PCSK 9, proprotein convertase subtilisin kexin type 9; RBMC, Raritan bay medical center; ASCD, atherosclerotic coronary artery disease; LDLR, LDL receptors; ICA, internal carotid artery

Introduction
Cerebrovascular accident is the fifth most common cause of death and the leading cause of disability in the United States. Extracranial carotid artery stenosis accounts for 8% of all ischemic stroke. Carotid artery stenosis is common in the elderly population and reported to be present in about 20% of people above age 70. The management of carotid artery stenosis depends on the extent of stenosis and whether the stenosis is symptomatic or asymptomatic. Carotid artery stenosis is described to be symptomatic when patients experience a transient ischemic attack, amaurosis fugax, or ischemic stroke ipsilateral to the side of stenosis. Medical management of risk factors such as hypertension, diabetes, and hyperlipidemia, anti-platelets, and smoking cessation is recommended for secondary stroke prevention regardless of the extent of stenosis. Carotid endarterectomy (CEA) is known to prevent long-term stroke risk and is indicated in symptomatic patients with carotid artery stenosis >70% who has a perioperative stroke and death risk <6%. For a patient who has a high surgical risk, carotid artery stenting (CAS) has become a favorable alternative. Studies showed there is no significant difference in the effectiveness and durability of revascularization and risks of perioperative stroke and myocardial infarction between CEA and CAS. For asymptomatic carotid artery stenosis, there is no consensus to whether CEA or CAS is indicated. Risks and benefits of either procedure should be carefully analyzed based on patients’ comorbidity, life expectancy, and preference. To date, there is no medical revascularization reported for carotid artery stenosis. Proprotein convertase subtilisin kexin type 9 (PCSK 9) is a protein that binds to LDL-receptors in the hepatocyte and targets them for lysosomal degradation, thereby decreasing the recycling of the LDL receptors to the cell surface. Evolocumab and alirocumab are the two FDA-approved PCSK-9 inhibitors, indicated in familial hypercholesterolemia and atherosclerotic cardiovascular disease. By inhibiting PCSK 9, these drugs increase LDL-receptors on the hepatocyte cell surface, thereby lowering circulating LDL level in the blood. In addition, PCSK-9 inhibitors, when used along with a statin, are also reported to cause atheroma regression in patients with coronary artery disease.

Case report
The patient is a 94-year-old lady who has been following up at our office for primary care since October 2012. Her chronic medical conditions include Type 2 diabetes, hyperlipidemia, and hypertension, for which she was on metformin, linagliptin, atorvastatin, and colsevelam. She had no known history of amaurosis fugax, transient ischemic attack, or stroke. However, on physical examination, she was noted to have right carotid bruit while the rest of the cardiovascular examination was unremarkable. Screening ultrasound showed bilateral plaque in the common carotid arteries in 2012. Her baseline echocardiogram showed mild left ventricular hypertrophy with an estimated ejection fraction of 67%, sclerotic aortic valve, and mild mitral annular calcification. She was started on aspirin 81 mg and clopidogrel 75 mg to prevent cardiovascular and cerebrovascular accidents. In 2014, she was admitted to the hospital (RBMC) for her atherosclerotic coronary artery disease. While further studies are necessary, we proposed that PCSK-9 inhibitor could be a safe, promising alternative to CEA or CAS in the revascularization of carotid artery stenosis.

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Dizziness. A carotid ultrasound performed at RBMC showed 85% stenosis of the right ICA and <70% stenosis in the left ICA. At that time, she was recommended to undergo revascularization via CEA or CAS for her right carotid artery stenosis. However, she declined the intervention due to her advanced age and perioperative risks. In view of her atherosclerotic coronary artery disease, we started her on PCSK-9 inhibitor (Evolocumab 140 mg) bi-weekly injection in March 2015. Her lipid profile before and after PCSK-9 inhibitor is shown in Table 1. Interestingly, her right carotid bruit also disappeared after 2 years of evolocumab bi-weekly injection. Carotid ultrasound on September 2017 showed 62% stenosis in the right ICA and 58% in left ICA.

Discussion
While a patient with atherosclerotic heart disease may or may not have carotid artery stenosis, it is highly likely that a patient with carotid artery stenosis has atherosclerotic coronary artery disease (ASCAD). This is supported by the excess risk of MI following CEA or CAS, which is also an important cause of perioperative death. While CEA and CAS are intended for stroke prophylaxis, 2.3-4.1% of patients ended up with perioperative stroke. Furthermore, even after CEA and CAS are performed, there is still a high risk of severe restenosis (>70%) in about 10% of the patients. In this case, we started the patient on PCSK-9 inhibitor (evolocumab) in view of her ASCD. Prior to evolocumab injection, her lipid profile was poorly controlled for years despite being on the maximal dose of atorvastatin. Following evolocumab injection, her lipid profile significantly improved (Table 1). Incidentally, we also found that there is a 23% reduction in her right carotid artery stenosis over the course of 2 years after the PCSK-9 inhibitor was initiated. The benefit of using PCSK-9 inhibitor is that it confers a significant lipid-lowering ability and plaque regression. The side effects of PCSK-9 inhibitor are minimal and include skin irritation at the injection site and nasopharyngitis. More importantly, unlike CEA and CAS, there is no periprocedural risk of stroke, MI, and death and yet it conferred drastic revascularization of carotid revascularization in our case.

Table 1 Lipid profile before and after PCSK-9 inhibitor injections

<table>
<thead>
<tr>
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<th>Before PCSK-9 inhibitor injections</th>
<th>After PCSK-9 inhibitor injections</th>
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<tbody>
<tr>
<td>Cholesterol Total (mg/dL)</td>
<td>235</td>
<td>208</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>274</td>
<td>237</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>52</td>
<td>46</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>2.5</td>
<td>4.5</td>
</tr>
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</table>

Conclusion
PCSK-9 inhibitor lowers LDL cholesterol by inhibiting the degradation of LDL receptors (LDLR) and permitting LDLR to recycle back to the liver cell surface. It revealed to regress atherosclerotic plaque in carotid artery stenosis. It may be useful in elderly patients with high risk of perioperative complications as an alternative medical therapy to invasive procedures such as CEA and CAS. Further studies are needed to validate PCSK9 inhibitor as a potential medical treatment for revascularization of carotid artery stenosis.

Acknowledgments
None.

Funding details
None.

Conflict of Interests
The author declares there is no conflict of interest.

References

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