



# Stabilization of vulnerable carotid plaques with proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab

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## Abstract

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a novel class of monoclonal antibodies, reduce low-density lipoprotein cholesterol levels and improve outcomes of myocardial infarction and stroke. However, the effects of PCSK9 inhibitors on carotid plaques remain unclear. We describe three patients treated with PCSK9 inhibitor alirocumab for progressive carotid stenosis despite lipid-lowering statin therapy. All three patients had vulnerable plaques on magnetic resonance (MR) plaque imaging. After alirocumab treatment initiation, no patients suffered stroke or adverse events, and the stabilization of the carotid plaques was observed on MR plaque imaging.

**Keywords** Carotid artery · Progressive · Alirocumab · Proprotein convertase subtilisin/kexin type 9 inhibitor · Magnetic resonance imaging

## Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are monoclonal antibodies that bind PCSK9 and reduce low-density lipoprotein cholesterol (LDL-C) levels by approximately 60% and the risk of myocardial infarction and stroke by approximately 20% after > 2 years of treatment [5]. The Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial evaluated changes in coronary atherosclerosis using serial intravascular ultrasound evaluations in subjects taking statins or statins plus PCSK9 inhibitors and found that a greater plaque regression at 76 weeks was found in subjects

receiving additional PCSK9 inhibitors than those treated with statins alone [3]. However, the effects of PCSK9 inhibitors on carotid plaques remain unclear. We chose the PCSK9 inhibitor as an additional medication for three patients with progressive carotid stenosis who refused carotid endarterectomy and carotid artery stenting. In this report, we describe the efficacy of PCSK9 inhibitor alirocumab in three patients with progressive carotid stenosis despite lipid-lowering statin therapy and demonstrate the stabilization of the carotid plaques using magnetic resonance (MR) plaque imaging.

## Case report

### Case 1

In an 82-year-old male with hypertension who was treated with losartan, asymptomatic mild stenosis of the left carotid artery was found on carotid ultrasonography (US) and time-of-flight (TOF)-MR angiogram (MRA) (Fig. 1a). At the time, his serum LDL-C was 110 mg/dl. He was initiated on atorvastatin; however, on TOF-MRA, carotid stenosis was observed to have progressed (Fig. 1b) at 18 months after atorvastatin treatment initiation, with a serum LDL-C level of 86 mg/dl. He was started on 75 mg alirocumab s.q. every 2 weeks, and his serum LDL-C level was 54 mg/dl 2 weeks later. A

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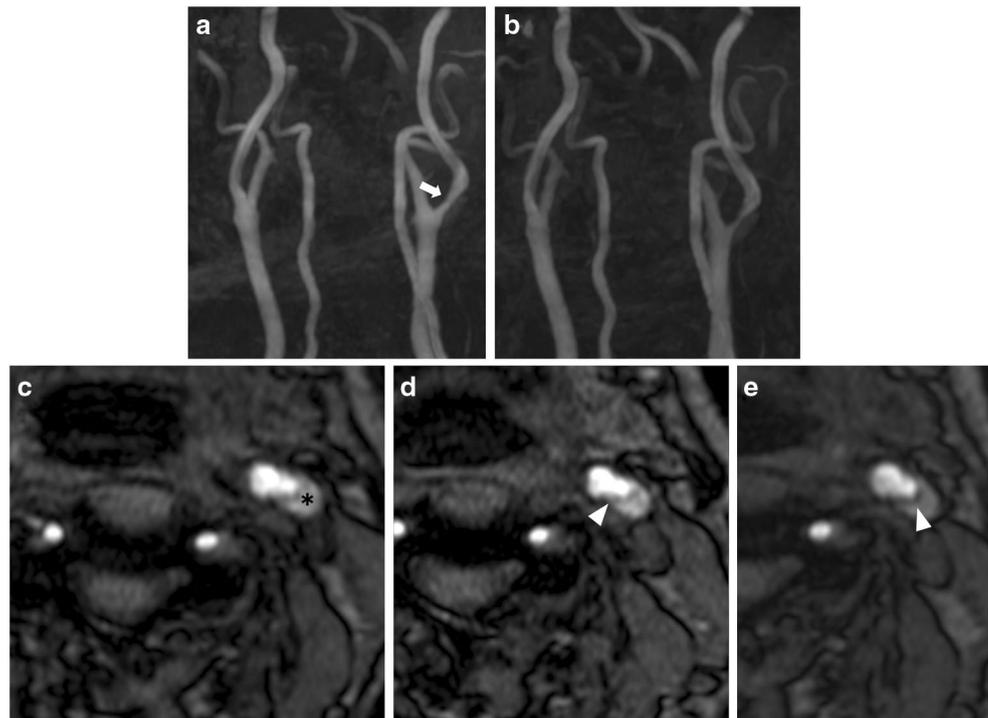
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**Fig. 1** Time-of-flight magnetic resonance angiogram (TOF-MRA) of case 1 before (a–c), 6 months after (d), and 12 months after (e) alirocumab treatment initiation. a TOF-MRA indicates left internal carotid artery stenosis (arrow). b Eighteen months after the initiation of statin therapy, progression of the left internal carotid artery stenosis is observed. c–e TOF-MRA at 6 and 12 months after alirocumab treatment showing a high-intensity plaque in the left internal carotid artery (asterisk) and serial increases in the hypointense band surrounding the bright lumen (arrowheads).

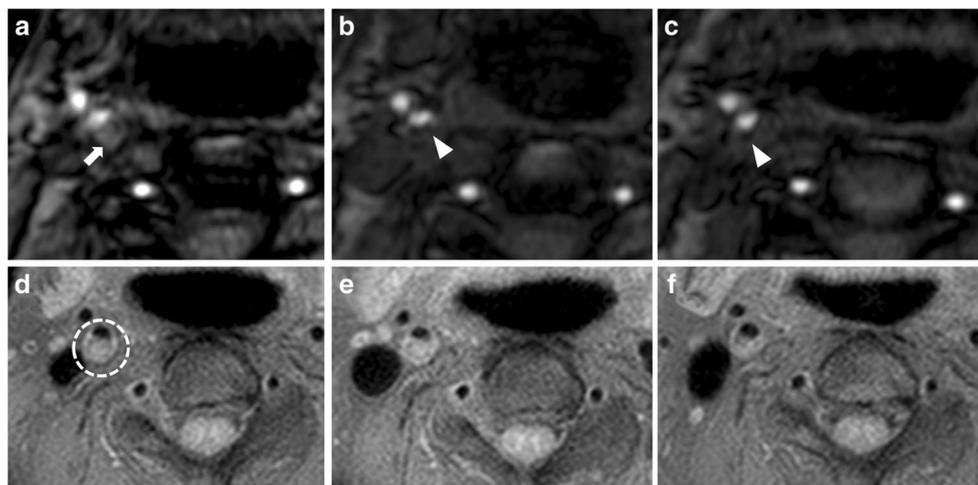


hypointense band surrounding a bright lumen was observed on TOF-MRA imaging at 6 and 12 months after alirocumab treatment initiation (Fig. 1c–e). He did not suffer stroke or any adverse events.

## Case 2

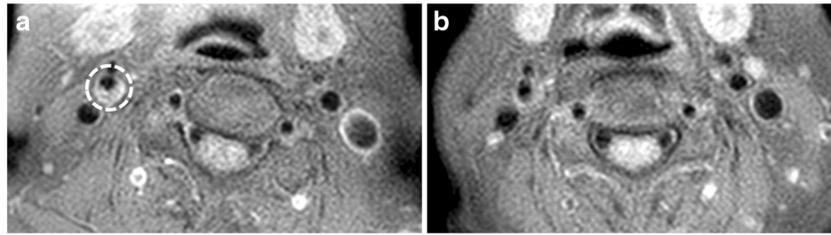
An 87-year-old male with hypertension who was treated with olmesartan was found to have asymptomatic severe stenosis of the right carotid artery by carotid US and TOF-MRA and

was initiated on atorvastatin and aspirin. However, on US, the peak flow velocity (PSV) of the right internal carotid artery was demonstrated to be significantly increased 6 months after treatment initiation, indicating progressive carotid stenosis. At the time, his serum LDL-C level was 81 mg/dl, and he was started on 75 mg alirocumab s.q. every 2 weeks, and his serum LDL-C level was 18 mg/dl 9 weeks later. On TOF-MRA, a hypointense band surrounding a bright lumen was observed at 3 and 6 months after alirocumab treatment initiation (Fig. 2a–c). Additionally, the plaque signal intensity was decreased on



**Fig. 2** Carotid magnetic resonance (MR) plaque images of case 2 before (a, d), 3 months after (b, e), and 6 months after (c, f) alirocumab treatment initiation. Time-of-flight magnetic resonance angiogram (TOF-MRA) and black-blood T1-MR images are presented in the upper and lower panels, respectively. a Hyperintense plaque in the right internal carotid

artery (arrow). b, c Obvious hypointense bands surrounding a bright lumen can be observed (arrowheads). d Hyperintense plaque in the right internal carotid artery (dotted circle). e, f Decrease in the signal intensity of the plaque observed at 6 months after alirocumab treatment initiation



**Fig. 3** Black-blood T1-MRI of case 3. **a** Before alirocumab treatment, a hyperintense plaque is observed in the right internal carotid artery (dotted circle). **b** Six months after alirocumab treatment initiation, the signal intensity of the plaque is decreased

black-blood T1-MRI at 6 months after alirocumab treatment initiation (Fig. 2d–f). He did not experience stroke or any other adverse events.

### Case 3

An 80-year-old female with hypertension and dyslipidemia who was treated with azilsartan, amlodipine, carvedilol, and pitavastatin was found to have asymptomatic mild stenosis of the right carotid artery on carotid US. On US, progressive carotid stenosis was found 7 years later. At the time, her serum LDL-C was 105 mg/dl. She was started on 75 mg alirocumab s.q. every 2 weeks, and her serum LDL-C level was 32 mg/dl 4 weeks later. The plaque signal intensity was decreased on black-blood T1-MRI at 6 months after alirocumab treatment initiation (Fig. 3a, b). She did not suffer stroke or any adverse events.

### Discussion

Fibrous cap can be identified as a hypointense band surrounding a bright lumen on TOF-MRA images, and hyperintense components on T1-MRI indicate a lipid-rich necrotic core [4, 8]. A thin fibrous cap with a lipid-rich necrotic core on MR plaque imaging was shown to be vulnerable and strongly associated with future ischemic stroke [1, 7]. In the three patients presented here, fibrous cap formation and regression of the lipid-rich necrotic core observed on MR plaque imaging were achieved during treatment with PCSK9 inhibitor alirocumab. These are the first cases demonstrating the stabilization of carotid plaque during PCSK9 inhibitor therapy, which was confirmed using MR plaque imaging.

All three patients received statin therapy, and their LDL-C levels were well controlled before the initiation of PCSK9 inhibitor therapy; however, carotid stenosis progressed despite treatment. Progressive carotid stenosis harbors a higher risk of stroke in asymptomatic patients than in those without progressive stenosis [2]. A Chinese cohort study including 643 healthy participants found a significant relationship between plasma PCSK9 concentrations and atherosclerosis progression as reflected by the total plaque area, which was independent of plasma LDL-C levels and statin use [9]. PCSK9 could

directly impact the plaque as a protein that circulates in the peripheral blood [6]; thus, PCSK9 inhibitors should be considered as an effective treatment approach in patients with progressive carotid stenosis despite statin therapy.

### Compliance with ethical standards

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

**Informed consent** Informed consent was obtained from all patients in this case report.

**Comments** This is a brief and preliminary report but an excellent and important one. These authors document three cases of unstable carotid plaques that had progressed while being medially managed on “standard of care” statin therapy. When these at-risk patients were then subsequently treated with the novel PCSK9 inhibitors, the plaques stabilized and there were no stroke symptoms seen under observation.

The implication is potentially profound for the medical treatment of active carotid plaques with PCSK9 drugs. We will be interested to see larger cases series and further investigations about this treatment.

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