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Repeated In-Stent Restenosis Despite Aggressive Lipid Lowering by PCSK-9 Inhibitor Treatment: A Case Report

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A 76-year-old woman with unstable angina underwent coronary stent implantation. At the same time, rosuvastatin therapy was started. However, she experienced repeated in-stent restenosis (ISR). Treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor along with rosuvastatin (5 mg/day) reduced plasma low-density lipoprotein cholesterol to 10 mg/dL, but failed to prevent further ISR. Eventually, an increase in the rosuvastatin dose to the permitted maximum of 20 mg/day succeeded in preventing further in-stent restenosis. Rather than using PCSK9 inhibitors, intensive statin treatment, using the maximum dose of statins, should be prioritized for the secondary prevention of coronary artery disease.

Keywords: in-stent restenosis; low-density lipoprotein cholesterol; proprotein convertase subtilisin/kexin type 9 inhibitors; statin
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Introduction

There are a growing number of clinical trials in which aggressive statin therapy succeeded in the secondary prevention of coronary artery disease (CAD), and provided evidence that the lower the plasma low-density lipoprotein cholesterol (LDL-C) level the better the outcome (de Lemos et al. 2004; Cannon et al. 2004; LaRosa et al. 2005; Pedersen et al. 2005; Cholesterol Treatment Trialists' (CTT) Collaboration et al. 2010). In addition, recent trials of non-statin lipid lowering therapy, such as ezetimibe, targeting the Niemann-Pick C1-like 1 (NPC1L1) protein (Cannon et al. 2015), or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (Sabatine et al. 2017), have strengthened the policy of 'the lower is the better' for the LDL-C level. However, 'the lower, the better' concept was based on American and European evidence, and it is uncertain whether the concept also applies to Japanese and east Asian CAD patients, who have lower cardiovascular event risks than CAD patients in Western countries. Here, we report a patient who underwent percutaneous coronary intervention (PCI) but experienced repeated in-stent restenosis (ISR) in spite of her LDL-C level being aggressively lowered by the use of a PCSK-9 inhibitor combined with a statin.

Case Presentation

A 76-year-old woman with unstable angina underwent PCI first in May 2015. Two drug-eluting stents (DESs), durable polymer everolimus-eluting stents (Xience Alpine®3.0*15mm and 2.5*18mm, Abott Laboratories, Chicago, IL, USA), were placed to treat a stenotic lesion proximal to the mid left anterior descending artery (Fig. 1A, B). The minimum stent area after stent deployment was 6.47 mm^2 and minimum stent diameter was 2.61 mm by intravascular ultrasound. She had only hypertension as a coronary risk factor, which had been well controlled by medication with an angiotensin receptor-blocker, olmesartan (5 mg/day), and a calcium channel-blocker, azelnidipine (8 mg/day). Although LDL-C was not very high at 109 mg/dL immediately after PCI, we thought statin treatment was advisable for secondary prevention of CAD. Rosuvastatin was initiated at the dose of 2.5 mg/day, and reduced the LDL-C level to 63 mg/dL. However, the high-sensitivity C-reactive protein (hs-CRP) level remained somewhat high at 0.72 mg/dL.

In October 2018, she developed unstable angina and

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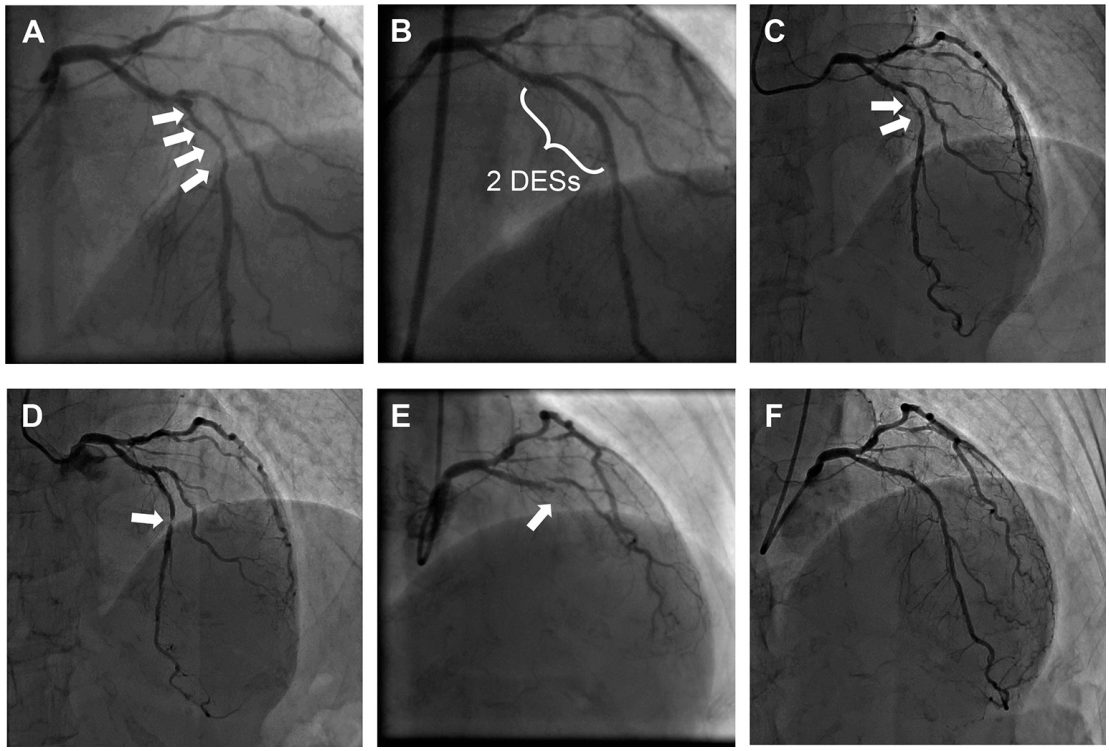

Fig. 1. Series of coronary angiography.
(A) Initial coronary angiography in April, 2015. A long stenotic lesion was observed proximal to the mid left anterior descending artery (arrows). (B) Two drug-eluting stents (DESs), durable polymer everolimus-eluting stents (Xience Alpine®), were placed. (C) In October 2018, in-stent restenosis developed (arrows). Coronary angiography shows a diffuse restenotic lesion. (D) In January 2019, in-stent restenosis again developed. Coronary angiography shows a localized restenotic lesion (an arrow). (E) In April 2019, in-stent restenosis developed once again. Coronary angiography shows total occlusion (an arrow). (F) In September 2019, coronary angiography no longer showed new lesions or restenosis.

ISR was observed (Fig. 1C), despite her LDL-C being very low at 52 mg/dL. On the other hand, her hs-CRP level was 0.53 mg/dL. She successfully underwent a second session of PCI, using a drug-coated balloon (DCB; SeQuent® Please, B. Braun Melsungen AG, Melsungen, Germany). Intravascular ultrasound imaging confirmed stent struts expansion and smooth muscle proliferation in the ISR. The dose of rosuvastatin was increased to 5.0 mg/day.

Nevertheless, in January 2019, she developed unstable angina again on account of ISR (Fig. 1D), despite her LDL-C level being even lower at 41 mg/dL and her hs-CRP level having decreased to 0.24 mg/dL. After the third session of PCI using the DCB, we started PCSK-9 inhibitor treatment in addition to 5.0 mg/day rosuvastatin, 420 mg evolocumab being given every month by subcutaneous injection. This lowered the LDL-C level to 10 mg/dL, while the hs-CRP level remained at 0.24 mg/dL.

Despite such an extremely low LDL-C, in April 2019 she developed unstable angina once more, again caused by ISR (Fig. 1E). We also suspected metal allergies and performed a skin patch test. However, the test for cobalt chromium, a material for Xience Alpine® stent, was negative. Furthermore, no eosinophilia in peripheral blood was observed during the course after stent implantation. She underwent a fourth session of PCI with the DCB, and we finally increased the dose of rosuvastatin to the permitted maximum of 20 mg/dL, while continuing with evolocumab. Thereafter, she no longer had symptoms of angina.

In September 2019, a follow-up coronary angiography showed no ISR (Fig. 1F), at which time her LDL-C level was 9 mg/dL, and her hs-CRP level was 0.09 mg/dL (Fig. 2).

Discussion

It has been established that an elevated LDL-C level is a major risk factor for cardiovascular events, and that statins are effective for primary and secondary prevention of CAD (Scandinavian Simvastatin Survival Study Group 1994). Moreover, compared with standard statin therapy, aggressive LDL-C lowering by high-dose statin therapy showed greater benefit for reduction of cardiovascular events (de Lemos et al. 2004; Cannon et al. 2004; LaRosa et al. 2005; Pedersen et al. 2005). A meta-analysis of several trials, which compared more intensive versus standard statin regimens, concluded that a level below 70 mg/dL is recommended for LDL-C lowering management in CAD patients (Cholesterol Treatment Trialists' (CTT) Collaboration et al. 2010). Recently, ezetimibe, which

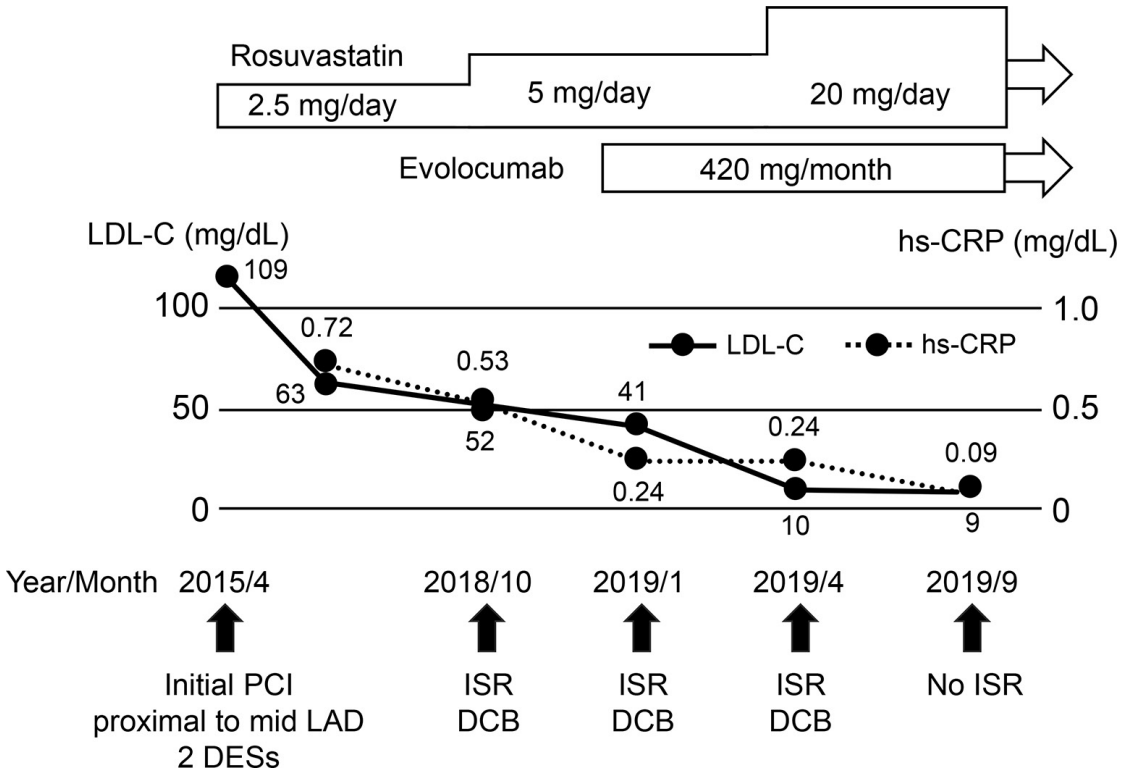

Fig. 2. Clinical courses of lipid-lowering therapy and percutaneous coronary intervention.
LDL-C, low-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; DESs, drug-eluting stents; ISR, in-stent restenosis; DCB, drug-coated balloon.

reduces the absorption of cholesterol from the intestine, lowered LDL-C to 53.7 mg/dL when added to statins and achieved further cardiovascular event reduction in CAD patients compared with statins alone (Cannon et al. 2015). More recently, the PCSK9 inhibitor evolocumab, when added to a statin, achieved an LDL-C level of 30 mg/dL and greater reduction of the risk of cardiovascular events in CAD patients compared with statin treatment alone (Sabatine et al. 2017). This evidence for secondary prevention of CAD by lipid-lowering treatment provided the rationale for the 'the lower, the better' concept, which implies that LDL-C should be as near to zero as possible. The present case experienced ISR three times despite aggressive lipid-lowering by treatment with a PCSK-9 inhibitor, evolocumab, along with a statin, rosuvastatin. She was not a high-risk case, as her only risk factor for CAD was hypertension. Although her baseline LDL-C level was not very high at 109 mg/dL at her first unstable angina attack, we prescribed statin treatment for the purpose of secondary prevention after PCI. Nevertheless, thereafter she experienced repeated ISR. Even after evolocumab had been added to a moderate dose of rosuvastatin (5 mg/day), which achieved an extremely low LDL-C of 10 mg/dL, recurrent ISR was not prevented. We also suspected metal allergies, but skin patch test was negative. From this case, we propose that cardiovascular events can occur even when LDL-C has been reduced to an extremely low level using a PCSK9 inhibitor. In addition to their lipid-lowering effects, it has been suggested that pleiotropic effects of statins, such as direct anti-atherosclerotic effects (anti-inflammatory action, improving vascular endothelial function, inhibition of vascular smooth muscle proliferation, plaque stabilization, etc), greatly contribute to the cardiovascular event reduction (Inoue and Node 2007). Inflammation plays an important role in atherogenesis, atherosclerosis progression, plaque instability, and plaque rupture, as well as in the mechanism of restenosis after PCI, and thereby contributes significantly to development of cardiovascular events (Inoue and Node 2006). Since Ridker et al. (2001) demonstrated that the hs-CRP level has prognostic value for cardiovascular disease, it has been widely measured as an indicator of inflammation in atherosclerosis in clinical studies. Recently, drug-interventions targeting inflammation along with LDL-C (Ridker et al. 2008) or inflammation alone (Ridker et al 2017) have succeeded in improving cardiovascular outcomes. In the present case, the hs-CRP level decreased from 0.72 mg/dL at the first unstable angina attack to 0.53 and 0.24 mg/dL at the first and second ISR, respectively. Nevertheless, this seems to have not been a sufficiently low level. In addition, the hs-CRP level did not change further from 0.24 mg/dL after PCSK9 inhibitor treatment. The cut-off value of the hs-CRP level for increased CAD risk has not been established. However, in the Justification for the Use of Statins in Prevention: an

Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, 20 mg/day rosuvastatin resulted in a 44% reduction of cardiovascular events, compared with the controls, in patients with a hs-CRP level ≥ 0.2 mg/dL and a LDL-C level < 130 mg/dL, defined as high-risk patients (Ridker et al. 2008). Thus, the result would be a rationale for targeting the hs-CRP level at < 0.1 mg/dL. In the present case, the final increase in the dose of rosuvastatin up to a maximum of 20 mg/dL, which corresponds to the dose in the JUPITER trial for primary prevention (Ridker et al. 2008), successfully reduced the hs-CRP level from 0.24 to 0.09 mg/dL. Thereafter, the patient no longer experienced ISR. In a recent Japanese clinical trial, the Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease (REAL-CAD) trial, it was demonstrated that pitavastatin 4 mg/day, the maximum permitted dose, achieved greater reduction of cardiovascular events than 1 mg/day, in Japanese stable CAD patients (Taguchi et al. 2018). This result suggests that intensive statin treatment, using the maximum dose of a statin, might be essential for secondary prevention in Japanese patients with CAD. Also in the present case, when the dose of rosuvastatin was increased up to the maximum permitted of 20 mg/day, it successfully prevented cardiovascular event reoccurrence independent of the targeted LDL-C level. Our experience suggests that intensive statin treatment, using the maximum dose, should be prioritized for secondary prevention in patients with CAD.

Conflict of Interest

The authors declare no conflict of interest.

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