Lipid-Lowering Therapy With Monoclonal Antibodies to Proprotein Convertase Subtilisin-Kexin Type 9 — Lessons From Recent Clinical Trials —

Hideki Ishii, MD, PhD; Toyoaki Murohara, MD, PhD

Atherosclerotic cardiovascular disease is the most common cause of death in the world and dyslipidemia is one of the most important therapeutic targets for the prevention of cardiovascular diseases. Recently, several clinical trials designed to inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9), including alirocumab, evolocumab and inclisiran, have been published.

In those studies, treatments inhibiting PCSK9 dramatically decreased low-density lipoprotein cholesterol (LDL-C) levels. Moreover, recent GLAGOV and FOURIER trials have shown that PCSK9 inhibitors prevent progression of atherosclerosis and improve clinical outcomes in patients with coronary artery disease or in those with atherosclerotic cardiovascular disease.

The European Society of Cardiology and European Atherosclerosis Society recommend in their recent guidelines that LDL-C level of 70 mg/dL or a reduction of at least 50% of the baseline level should be attained in very high risk patients with a history of documented cardiovascular disease such as myocardial infarction, acute coronary syndrome, and coronary revascularization or severe renal insufficiency.

However, the target goal of LDL for secondary prevention of myocardial infarction is ≤100 mg/dL in the guidelines of the Japanese Society of Cardiology and Japanese Atherosclerosis Society. The topic of ‘achievement of lower LDL-C levels is better’ as adapted for Japanese subjects has been discussed. There are limited Japanese data showing beneficial effects of intensive and aggressive LDL-C lowering therapy, and we hopeful about the results of upcoming studies with large numbers of patients such as the Randomized Evaluation of Aggressive

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received May 15, 2017; accepted May 22, 2017; released online June 3, 2017

Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Mailing address: Hideki Ishii, MD, PhD, Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. E-mail: hlkishi@med.nagoya-u.ac.jp

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Circulation Journal Vol.81, October 2017
or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease (REAL-CAD) and the Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy (EMPATHY) Study. In addition, a trial called ODYSSEY J-IVUS is ongoing to show the effects of alirocumab on coronary plaque regression using an intravascular ultrasound trial in Japanese patients hospitalized for acute coronary syndrome with hypercholesterolemia. These studies will show us the future clinical implications (Figure). On the other hand, as with severe chronic kidney disease (CKD), the characteristics of Japanese subjects seem to be different from those of Caucasians. Particularly, hemodialysis patients with coronary artery disease have quite low LDL-C levels. From these points of view, Japanese data are warranted.

Some Japanese studies have already shown that treatment with evolocumab or alirocumab is well tolerated and induces sustained LDL-C reduction. 

4 In addition, one of the problems in the use of bococizumab was wide variability in the reduction of LDL-C. These phenomena have not been observed with other agents in this class, fully humanized monoclonal antibodies. Probably because of these unfavorable properties, the company responsible has given up further development of bococizumab. Potential for immunogenicity is much lower or almost negligible in fully humanized monoclonal antibodies such as evolocumab and alirocumab, compared with humanized one such as bococizumab.

5 Thus, innovation for full humanization is a critical issue in the case of therapeutic monoclonal antibodies.

One of the most important topics that should be addressed is cost effectiveness. A study has reported that the cost-effectiveness of PCSK9 inhibitors is only seen in the secondary prevention for older patients with high risk of cardiovascular disease when compared to ezetimibe and standard treatment. 

6 Indeed, the number needed to treat was 50 in the FOURIER trial. 

7 Thus, it is unclear whether PCSK9 inhibitors should be used for all subjects at high risk of cardiovascular events. The situation will change as the cost of PCSK9 inhibitors decreases. However, when using PCSK9 inhibitors, we have to pay keen attention to the selection of subjects who may receive strong and beneficial effects. Moreover, an experimental study has suggested that PCSK9 may be associated with atherosclerotic events through not only lipid but also non-lipid-dependent pathways.

8 Thus, further investigations are needed from various points of view in terms of PCSK9 inhibitors.

Disclosures


References