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Editorial

A First-in-Class Drug, Lomitapide, Tailored to Patients with Homozygous Familial Hypercholesterolemia is Just about Meeting with Good News to Them

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A raised low-density lipoprotein (LDL) cholesterol (LDL-C) is one of the major risk factors for atherosclerotic cardiovascular disease (ASCVD)[1-3]. Homozygous family hypercholesterolemia (HoFH) is a rare inherited disease characterized by markedly elevated levels of LDL-C, generally more than 500 mg/dL when untreated, and a high risk of premature ASCVD[4]. HoFH is caused by loss-of-function mutations in the LDL receptor-related genes, including *LDLR* true homozygotes, two *LDLR* compound heterozygotes, and gene mutations accompanied with gain-of-function of proprotein convertase subtilisin/kixin type 9 (PCSK9)[4-7]. In any case, LDL receptors of HoFH patients are absent or defective.

Statins are a main first-line drug for LDL-lowering therapy with certainty, but the recent developments in LDL-lowering drugs have been remarkable[8]. This lineup is composed of the cholesterol absorption inhibitor ezetimibe, monoclonal antibodies against PCSK9, and inhibitors of apolipoprotein B-containing lipoprotein production. European Atherosclerosis Society and American Heart Association similarly have defined the LDL-C target for HoFH adults as less than 100 mg/dL or 70 mg/dL in the presence of ASCVD[1, 9]. The Japan Atherosclerosis Society recommends the primary LDL-C target as less than 100 mg/dL and the secondary target as less than 50% reduction from pretreatment LDL-C levels[10]. Statins and PCSK9 inhibitors would be effective in a limited manner for LDL-lowering and ASCVD prevention in HoFH with the absent or defective LDL receptors because these drugs decrease LDL-C levels by up-regulating LDL receptors although it has reported that LDL-lowering therapy mainly with statins is associated with delayed cardiovascular events and prolonged survival in HoFH patients[11].

Nowadays, lomitapide is approved as a first-in-class drug for lowering LDL-C levels in HoFH adults in western countries and Japan, and it is a selective inhibitor of microsomal triglyceride transfer protein (MTP) that transfers triglycerides onto newly synthesized apolipoprotein B leading to the formation of very-low-density lipoprotein (VLDL) in the liver[8, 12]. Loss of function mutations in both alleles of *MTTP* results in abetalipoproteinemia, which is characterized by the absence of apolipoprotein B, VLDL, and LDL in the plasma due to failure of the liver to produce VLDL. Lomitapide therapy inhibits MTP activity and reduces the production and secretion of chylomicrons by the intestine and VLDL by the liver leading to reductions in LDL-C, apolipoprotein B, triglyceride, non–high-density lipoprotein (HDL) cholesterol, and lipoprotein (a) [Lp(a)]. Namely, lomitapide is expected to lower LDL-C through LDL receptor independent mechanisms.

The present study conducted by Dr. Mariko Harada-Shiba, *et al*. has demonstrated that the add-on lomitapide to ongoing treatment with standard therapy, including statins and LDL apheresis, brought about rapid and significant reductions in LDL-C and other apolipoprotein B-containing lipoproteins, including Lp(a), in Japanese HoFH adults albeit a small-sized study (n=9)[13]. LDL-C was decreased by 42% at week 26 and by 38% at week 56 from baseline. These lomitapide effects were comparable to previous study results in non-Japanese HoFH patients[12, 14, 15]. The established target of LDL-C reduction could not necessarily be achieved with the new performance of lomitapide but could be attained near the target level. Therefore, the appropriate combination of lomitapide and other medications (e.g., statins, PCSK9 inhibi-

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tors, ezetimibe) should be administered. As expected from its mechanism of action, lomitapide is known to cause adverse events in the gastrointestinal (GI) tract and liver[8, 12]. In the GI tract events, diarrhea, nausea, vomiting, and dyspepsia occur commonly because of a mechanism-based increase in intracellular triglyceride rather than a reduced absorption of fat from the gut lumen. One-year data from lomitapide registry (LOWER) exhibited a 10% discontinuation rate because of adverse events, the most common of which was diarrhea[8]. GI symptoms were similarly observed in this study, but these GI symptoms could be minimized with a low-fat diet, dosing in the fasted state, and a gradual dose-escalation regimen similar to this study efficacy phase. However, lomitapide reduces the absorption of fat soluble vitamins and essential fatty acids, and therefore, patients need to take vitamin supplements as shown in this study. These lomitapide adverse effects observed in this study also were comparable to previous study results in non-Japanese HoFH patients[12, 14, 15].

Lomitapide, tailored to patients with HoFH, may be meeting with good news to them. Lomitapide can decrease LDL-C, TG, and Lp(a) independently of LDL-receptor pathway, and these lipids are considered as true risk factors of coronary artery disease as judged by mendelian randomization studies[1]. As reported previously albeit a large cohort of patients with heterozygous FH, Lp(a) is an independent predictor of cardiovascular disease in males and females with FH, who are at a high risk with an Lp(a) level >50 mg/dL and carrying a receptor-negative mutation in the *LDLR* gene[16]. Although these lipids-lowering effects of lomitapide may provide clinical benefits to HoFH patients, several issues to be resolved are hanging over before lomitapide becomes a true fortune to HoFH patients because lomitapide therapy may come with adverse events as described above. In fact, probably, the benefits may be great and the side-effects may be small, but lomitapide to be administered over a long term may devote the conceivable double-edged-sword to FH patients. Therefore, the first issue is that the clear-cut diagnosis of HoFH is required but genetic testing has not yet been approved by medical care insurance in Japan. The second issue is that *MTP* gene variants are involved in response to lomitapide[17]. This issue may affect the therapeutic benefit, but it needs further investigations. The third issue is that the drug price of lomitapide is highly expensive. From the viewpoint of curbing growth in medical spending, the cost-effectiveness of recent-day new lipid-lowering drugs is one of the critically important problems as seen in the case of PCSK9 inhibitors[18, 19]. Discontinuation of lomitapide may be avoidable possibly because the medical cost in HoFH designated as an intractable disease is supported by the Japanese government as far as it goes. The fourth issue is that long-term clinical trials are needed to demonstrate hard outcome benefit for the prevention of ASCVD and long-term safety.

Currently, we have lomitapide to intensively lower LDL-C for HoFH patients beyond the mechanism of LDL receptor pathway. According to the conditions, it may be possible to decrease the frequency of LDL apheresis[13, 15]. Lomitapide also can decrease Lp(a) and TG related to a cardiovascular residual risk, and the emergence of lomitapide and PCSK9 inhibitors to reduce Lp(a) safely and robustly would open new doors to prevent ASCVD[19, 20]. However, we should also consider the so-called "precision medicine" for FH patients keeping insightful eye on the efficacy, safety, and cost-effectiveness of such new therapeutics to improve health and treat disease appropriately.

Conflict of Interest

None.

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