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Editorial

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New Horizons for Probucol, an Old, Mysterious Drug

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Intensive low-density lipoprotein (LDL)-lowering therapies involving statins, intestinal cholesterol transporter inhibitor (ezetimibe), and proprotein convertase subtilisin/kexin type 9 inhibitors are associated with a significantly lower number of atherosclerotic cardiovascular events. However, these events have not been completely prevented to date. Therefore, additional pharmacological interventions may be crucial to mitigate "residual risks" other than serum LDL cholesterol (LDL-C) levels.

Probucol was developed as an anti-oxidative compound to prevent the degradation of tire rubber and later applied to reduce serum LDL-C levels in patients with hypercholesterolemia. The effect of probucol on the reduction of serum LDL-C levels was not substantial; however, probucol has been widely used in Japan before the launch of statins, particularly in patients with familial hypercholesterolemia (FH). Japanese researchers have demonstrated that probucol reduces LDL-C levels even in Watanabe heritable hyperlipidemic (WHHL) rabbits[1)] and in patients with homozygous and heterozygous FH and LDL receptor (LDL-R) deficiency[2, 3)] via an enhanced catabolism of LDL independent of LDL-R[4)] and increased cholesterol excretion into the bile[5)]. Probucol also reduces skin and tendon xanthomas in patients with FH despite a marked reduction in high-density lipoprotein (HDL) cholesterol (HDL-C) due to enhanced cholesteryl ester transfer protein activity[6)] and hepatic expression of scavenger receptor class B type I[7)]. Probucol reportedly attenuated atherosclerosis in WHHL rabbits[1)], and thereafter, many studies have proven its clinical efficacy in preventing atherosclerotic cardiovascular events and coronary restenosis after percutaneous coronary intervention as reviewed[8)].

After their launch, statins have become the first-line drug choice for the treatment of patients with high LDL-C levels owing to their strong LDL-C lowering effect. Conversely, a randomized controlled trial—Probucol Quantitative Regression Swedish Trial (PQRST)[9)]—revealed that administration of probucol for 3 years in patients with hypercholesterolemia lowered LDL-C levels but did not increase the lumen volume of femoral arteries, as revealed by angiography. Thereafter, probucol has disappeared from the market worldwide, except for Japan, partly due to the failure of PQRST, reduction in serum HDL-C level, and possible prolongation of QT interval. However, probucol has been used by Japanese clinicians, particularly lipidologists.

We hypothesized for the first time worldwide that reduction in HDL-C levels by probucol may not be harmful but can rather reflect the acceleration of reverse cholesterol transport (RCT), thereby leading to regression of atherosclerotic plaque and xanthomas[3, 10)]. Recent evidences have strongly suggested that probucol not only has potent anti-oxidative properties but also enhances HDL-mediated RCT, leading to regression of atherosclerotic plaque as reviewed[11)]. In the Probucol Observational Study Illuminating Therapeutic Impact on Vascular Events (POSITIVE)[12)], the long-term effects of probucol on cardiovascular events were evaluated in 410 patients with heterozygous FH. The primary outcome was the time to first cardiovascular event involving hospitalization. Multivariate Cox regression analysis revealed that the hazard ratio of probucol use for secondary prevention was 0.13 [95% confidence interval (CI) 0.05–0.34, $P<0.001$], suggesting that long-term probucol treatment prevents secondary cardiovascular events in very high-risk

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patients, such as those with FH. Although several studies have investigated the effects of probucol on cardiovascular events and coronary restenosis as reviewed[8], there has been no consensus on the preventive effects of probucol on cardiovascular events in high-risk patients.

In an issue of the Journal of Atherosclerosis and Thrombosis, Kang *et al.*[13] have reported the long-term effects of probucol or probucol and cilostazol with statin on carotid mean intima-media thickness (IMT) in a prospective, randomized, multinational, open-blinded endpoint study. In this study, 281 patients with hypercholesterolemia with coronary artery disease (CAD) randomized to three groups received the study drugs for 3 years: control group received statin alone; probucol group received statin and probucol; and combo group received statin, probucol, and cilostazol. The primary endpoint was changes in the mean carotid IMT at 3 years, whereas the secondary endpoints were biomarkers, major adverse cerebro- and cardiovascular events (MACCEs), and safety. All the three groups exhibited significant regression of carotid IMT at 3 years compared with baseline. The decrease in mean carotid IMT was significantly greater in the combo group than in the control group at 1 year, but no significant differences were observed in the changes of mean carotid IMT among the groups at 3 years. MACCEs were frequent in the control group without a statistical significance (control group 10.8% vs. probucol group 4.4% vs. combo group 6.9%, $p=0.35$). Compared with statin alone, probucol or probucol and cilostazol with statin could not reduce the mean carotid IMT; however, the reduction in MACCEs in the probucol and combo groups suggested the need for further studies.

Recent reports have demonstrated favorable effects of probucol on high-risk patients with ischemic stroke or CAD. A recent multicenter, randomized controlled trial[14] examined the efficacy and safety of cilostazol versus aspirin with and without probucol in patients with ischemic stroke who have a high risk of cerebral hemorrhage. Patients with ischemic stroke with a history or imaging findings of intracerebral hemorrhage or two or more microbleeds were randomly assigned to receive 1) cilostazol (200 mg/day), 2) aspirin (100 mg/day), 3) cilostazol plus probucol (500 mg/day), or 4) aspirin plus probucol. The incidence of vascular events was significantly lower in the probucol group than in the non-probucol group (hazard ratio 0.69, 95% CI 0.50–0.97; $p=0.0316$). In patients with ischemic stroke who have a high risk of cerebral hemorrhage, cilostazol was not found to be inferior to aspirin in terms of preventing cardiovascular events; however, it did not reduce the risk of hemorrhagic stroke. Conversely, probucol with aspirin or cilostazol was beneficial to reduce the incidence of cardiovascular events in patients with ischemic stroke.

PROSPECTIVE[15] is a recently published multicenter, randomized, prospective study that has tested the hypothesis that the addition of probucol to other lipid-lowering drugs prevents cerebro- and cardiovascular events in Japanese patients with CAD and high LDL-C levels. Although probucol could not significantly prevent cardiovascular events, it exhibited a tendency to reduce them despite the reduction in serum HDL-C levels[16]. Prolongation of QT interval and reduction in serum HDL-C levels by probucol did not increase the number of cerebro- and cardiovascular events, suggesting the feasibility of probucol treatment in high-risk patients treated with statins.

The current IMPACT and PROSPECTIVE studies have similar protocols, except for their primary and secondary endpoints. Therefore, an integrated meta-analysis of these prospective studies in the future may elucidate whether probucol with a conventional lipid-lowering therapy could prevent cerebro- and cardiovascular events in patients with CAD.

Conflicts of Interests

Dr. Yamashita reports grants and personal fees from Kowa Company, Ltd., Bayer Yakuhin, Ltd., MSD K.K., Takeda Pharmaceutical Company, Ltd., Astellas Pharma Inc., grants from Kyowa Medex Co., Ltd., Hayashibara Co., Ltd., and personal fees from Skylight Biotec, Inc., Astellas Amgen, Sanofi, Aegerion, outside the submitted work. Dr. Masuda reports grants and personal fees from Nippon Boehringer Ingelheim Co., Ltd., MSD K.K., Takeda Pharmaceutical Company, Ltd., Daiichi-Sankyo Company, Ltd., Mochida Pharmaceutical Company, Ltd., Kowa Company Ltd., Kissei Pharmaceutical Co., Ltd.; grants from Otsuka Pharmaceutical Co Ltd.; personal fees from Kowa Company, Ltd., Bayer Yakuhin, Ltd, , Kyowa Medex Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Ono Pharmaceutical Company, Ltd., Astellas Pharma Inc., AstraZeneca K.K., non-financial support from Skylight Biotec, Inc., Pfizer Japan Inc., Amgen Astellas Biopharma K.K., Sanofi K.K., , grants from Shionogi & Co., Ltd., grants from Bayer Yakuhin, Ltd., grants from Sanwa Kagaku Kenkyusho Co., Ltd., grants from Astellas Pharma Inc., grants from Hayashibara Co., Ltd., Teijin Pharma Limited, Kaken Pharmaceutical Co., Ltd., outside the submitted work. Dr. Matsuzawa reports personal fees from Teijin Pharma, Kowa, Sumitomo Dainippon Pharma, outside the submitted work.

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