A Unique Antilipidemic Drug—Probucol

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Probucol is a chemical compound with a bisphenol structure and differs from other antilipidemic drugs. It was originally synthesized as an antioxidant by Consolidation Coal Company and screened at Dow Chemical Company for its ability to reduce serum cholesterol. The action mechanism of probucol has not yet been elucidated in detail, although the increased secretion of bile acids has been postulated as a major cause of cholesterol-lowering activity.

Probucol attracted the attention of researchers as it was found that the drug is effective for homozygous familial hypercholesterolemia, which is resistant to other antilipidemic drugs, and causes the marked regression of cutaneous and tendon xanthomas. In vitro experiments showed that the effect of probucol on xanthomas is due to the inhibition of oxidative modification of LDL and that probucol inhibits foam cell formation from THP-1 cells by not only inhibiting lipid accumulation but also by enhancing the release of cholesterol from macrophages. With such a unique action, probucol encouraged Daniel Steinberg to promote his idea “Beyond cholesterol”; oxidation of LDL is an important step in the formation of macrophage-derived foam cells, which initiates the development of atherosclerotic vascular lesions.

In spite of having such unique and interesting characteristics, the use of probucol has been limited since it causes (a) a remarkable reduction in HDL, and (b) elongation of QT intervals on ECG. Clinical studies failed to show a dose-response relationship and there was large individual variation in response to the drug. The appearance of statins on the market and the lack of success in demonstrating the usefulness of probucol by angiography in the prevention/regression of atherosclerotic lesions in femoral arteries forced pharmaceutical companies to retreat from maintaining probucol sales in many countries.

However, as documented in the report by Yamashita et al. (POSITIVE), probucol is still used as an important lipid-lowering agent in Japan, especially in the treatment of both heterozygous and homozygous familial hypercholesterolemia in combination with statins and LDL-apheresis. The results of the POSITIVE study showed that the drug was useful in lowering the risk of cardiovascular events in secondary prevention in spite of causing a decrease in HDL-cholesterol. No significant adverse effect was observed in their study. Unfortunately, this was not so in the primary prevention group, probably because the group of patients given probucol were at higher risk than the control group regarding the extent of hypercholesterolemia and xanthomatosis.

HDL-cholesterol as a surrogate marker of atherosclerosis appears to have been over-exaggerated. Although the antiatherogenic effect of HDL has been well established, the majority of HDL-reduction generally observed in practice is a secondary phenomenon due to an increased triglycerides in the presence of cholesteryl ester transfer protein. The significance of low HDL cholesterol as a risk factor may be cancelled out when adjusted with triglyceride. Recent studies on the mechanism of the decrease in HDL cholesterol with probucol have demonstrated that it is based on a rather favorable metabolic sequence of cholesterol metabolism, that is, the enhancement of SR-B1, as detailed in the discussion section in this paper. Krieger et al. showed that hepatic SR-B1 over-expression increased hepatic uptake of HDL-associated cholesterol followed by the increase in biliary excretion of cholesterol, which confirmed the results of previous studies obtained by the use of isotope-labeled lipoproteins.

SR-B1 must be an opening to an important bypass of serum cholesterol into liver in cases of familial hypercholesterolemia, as also suggested by Arai et al. in their animal experiments. Results of the POSITIVE study demonstrate that the enhancement of this pathway may compensate for the whole sequence of cholesterol metabolism in spite of the decrease in HDL. Combined use of probucol with an agent causing the up-regulation of apo A-I or the infusion of apo
A-I mimic peptides seems to be interesting.

Probucol is also considered to be an important agent in promoting endogenous antioxidant reserve and protecting against increased oxidative stress. Animal experiments have shown that probucol prevents re-stenosis and mediates vascular remodeling after STENT or PTCA. It was also reported that probucol is useful in the treatment of hepatic steatosis. It is difficult to suppress the whole series of complications of the atherosclerotic process only by reducing serum cholesterol, probably due to the presence of many confounding factors mediating the inflammatory reaction and oxidative stress. The significance of the amelioration of such a situation by the use of antioxidants and anti-inflammatory agents should be reevaluated.

References