Effect of probucol on hypercholesterolemia in renal transplant patients

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Background. Hypercholesterolemia is a well-known complication in kidney transplant recipients, although its pathogenesis may be multifactorial. The therapeutic effect of probucol on post-transplant hypercholesterolemia was prospectively evaluated.

Methods. Twelve hypercholesterolemic kidney transplant patients with serum total cholesterol ≥250 mg/dl without diabetes mellitus or hypoproteinemia were prospectively treated with probucol (250 mg, bid, for three months). Before initiating and at the end of treatment, blood was drawn after at least a 12-hour fast to measure lipids in serum and lipoprotein fractions, apoproteins (apo), lipoprotein fractions, lecithin cholesterol acyl transferase (LCAT), free fatty acids (FFAs), and cholesterol ester. The lipid profiles of 17 healthy subjects were also examined.

Results. After treatment with probucol, serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and apo AI were significantly decreased, whereas cholesterol ester increased significantly.

Conclusions. Post-transplant hypercholesterolemia is featured in abnormalities in very low-density lipoprotein (VLDL) metabolism. Although HDL cholesterol decreased, probucol might have acted as an antiatherogenic by modulating HDL metabolism and stimulating reverse transfer of cholesterol from peripheral tissue.

Hyperlipidemia is a well-known complication in kidney transplant recipients. However, opinions in the literature differ concerning the prevalence and the type of lipoprotein abnormalities. Reported changes of serum lipids include an increase in total cholesterol and triglyceride (TG) levels, as well as an increase in very low-density lipoprotein (VLDL) and LDL cholesterol content [1, 2]. These changes may be causally related to multiple factors, including medication, such as prednisolone (PSL) [3] and cyclosporine [4, 5], the patients’ age and sex, and level of renal function [2]. To clarify further the lipoprotein and apoprotein (apo) profile in renal transplant patients treated with PSL and cyclosporine A, a selected subset of these patients showing hypercholesterolemia was prospectively treated with probucol [6].

METHODS

Thirty-seven renal transplant patients immunosuppressed with PSL and cyclosporine A and who had serum creatinine (Cr) levels of less than 3 mg/dl satisfied the inclusion criteria for this study. None were diabetic patients or demonstrated hypoproteinemia or proteinuria. Twelve (five women and seven men, aged 29 to 51 years, mean age ± SEM, 34.2 ± 2.5 years) of the 37 patients whose serum total cholesterol level was 250 mg/dl or higher were submitted to a prospective treatment with probucol (Sineal®, 250 mg, bid, for three months; Daiichi Seiyaku, Co., Tokyo, Japan) after obtaining their informed consent. Their donor sources were living related in six patients and cadaveric in six. PSL was started at 1 mg/kg body wt and was then gradually decreased to the maintenance dose of 0.2 mg/kg. Cyclosporine was begun at 6 mg/kg and was then tapered to 3 to 4 mg/kg within three-months post-transplant. The follow-up period after transplantation ranged from 5 to 76 months (mean 37.4 ± 4.9 months), and the latest serum Cr levels ranged from 0.9 to 2.9 mg/dl (mean 1.9 ± 0.5 mg/dl). Before starting and after completing probucol administration, venous blood was drawn after at least 12-hour fasting. Serum was separated at room temperature, and the total cholesterol, TG, and phospholipid (PL) levels immediately measured with an autoanalyzer. Apos A, B, CII, CIII, and E were determined by cytochrome immunoassay, lipoprotein fraction by ultracentrifugation, lecithin acyl transferase (LCAT) by liposome substrate assay, and free fatty acids (FFAs) by colorimetry. Cholesterol ester was calculated as percentage cholesterol ester ratio. The lipid profiles of 17 (10 females and 7 males) age-matched (24 to 59 years of age, mean 36.8 ± 1.6 years) healthy subjects were also examined. Data are shown as mean ± SEM. Statistical differences were

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calculated using the Mann–Whitney U-test. P values of less than 0.05 were taken to be statistically significant.

RESULTS
Following probucol treatment, serum total cholesterol and LDL cholesterol, as well as PL, LDL-PL, and apo AI, were significantly decreased (Table 1). However, it should be noted that HDL cholesterol also showed a parallel decrease (59.4 ± 3.96 vs. 45.0 ± 5.24 mg/dl). On the other hand, cholesterol ester significantly increased following probucol administration. Neither LCAT nor FFAs showed any significant changes.

DISCUSSION
The increases in serum total cholesterol, TG, and PL in our post-transplant patients immunosuppressed with PSL and cyclosporine A were compatible with those of previous reports on cyclosporine A-treated patients with manifest hypercholesterolemia [2] and patients conventionally treated with PSL and azathioprine (AZA) who showed a preferential increase in TG. These lipid abnormalities together with increased apo B may be atherogenic. Although the levels of apo AI and AII were not different compared with control subjects, the correlation between cholesterol ester and VLDL cholesterol observed in normal controls was lost (data not shown). These data may be compatible with the deranged reverse transfer of cholesterol from peripheral tissue, although no direct evidence on the role of cyclosporine A was obtained from this study.

Probucol [6], known to have important antioxidant properties, was given to cyclosporine A-treated renal transplant patients by Gallego et al, as well as to our patients, in an attempt to modulate hypercholesterolemia [7]. The drug decreased the levels of both serum total cholesterol and LDL cholesterol. Also, a concurrent decrease in HDL cholesterol level was observed, as was previously reported by Matsuzawa et al [8]. They showed that probucol stimulated the reverse transfer of CHL from peripheral tissue to HDL. Although we have no data of our own regarding the effects of probucol on the reverse cholesterol system, it may have caused a decrease in the serum HDL level and a contraction of atheromatous plaque in the vessel wall [8]. Increased levels of cholesterol ester following probucol treatment are compatible with an enhanced HDL reverse transfer. Through this mechanism, probucol may reduce atherogenesis, although it lowers HDL cholesterol. Its long-term effect on renal transplant patients remains to be determined.

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