A Prospective Study on Treatment of Hypercholesterolemia With Lovastatin in Renal Transplant Patients Receiving Cyclosporine

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ABSTRACT

Hypercholesterolemia occurs commonly in renal transplant recipients and may contribute to the high cardiovascular morbidity and mortality in these patients. Although an effective hypolipidemic agent, lovastatin has been associated with rhabdomyolysis and acute renal failure in patients on cyclosporin A (CsA). In this study, lovastatin was administered at 10 mg/day for 8 wk followed by 20 mg/day for 12 wk to six renal transplant recipients who were receiving CsA concomitantly. The 10-mg/day dose was effective, but an additional lipid-lowering effect was seen with the 20-mg/day dose. Both serum total cholesterol and low-density lipoprotein cholesterol levels decreased by 27% at the end of the 20 wk of lovastatin administration. Serum high-density lipoprotein cholesterol and triglyceride levels remained unchanged. No significant clinical or laboratory adverse effects were observed, including muscular symptoms, ophthalmologic abnormalities, or alterations in serum creatine kinase, urea nitrogen, creatinine, transaminases, and CsA levels. Peak and trough plasma concentrations of active lovastatin were comparable to those reported in normal subjects receiving a higher lovastatin dose without CsA. It was concluded that the administration of low-dose (10 to 20 mg/day) lovastatin to renal transplant recipients receiving concomitant CsA can be safe and effective in lowering serum cholesterol.

Key Words: Renal transplant, cholesterol, hyperlipidemia, cyclosporin A, lovastatin

Hypercholesterolemia from diverse causes has been well established to be a risk factor for premature atherosclerosis. Studies in the general population have clearly established the value of lowering serum cholesterol in reducing cardiovascular morbidity and mortality from ischemic heart disease (1-3).

Hypercholesterolemia occurs commonly in renal transplant recipients (4-6), many of whom develop the defect de novo after the transplantation (5). Serum triglyceride levels are elevated much less frequently. When these dyslipidemic states are classified according to the lipoprotein compositions, the patients most frequently exhibit a type IIa pattern (elevated low-density lipoprotein or LDL) (4). Occasionally, a type IIb (elevated LDL and very low-density lipoprotein [VLDL]) phenotype is observed. The pathogenesis of hypercholesterolemia in renal transplant recipients is probably multifactorial, including contributions from medications, diabetes mellitus, and diet.

Because cardiovascular events are a major cause of death in the renal transplant population (7), it would seem appropriate to treat the lipid abnormality of these patients aggressively. Many lipid-lowering agents, such as cholestyramine, clofibrate, and nicotinic acid, are associated with intolerable adverse effects (4). Lovastatin was the first commercially available drug that belongs to the class of agents that inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the enzyme for the rate-limiting step of cholesterol synthesis. It is very effective in lowering serum LDL cholesterol levels by reducing its synthesis and by promoting its degradation via up-regulation of LDL receptors (8-10). In dosages between 20 and 80 mg/day, lovastatin reduces serum LDL cholesterol by 22 to 41%. In addition, a 6 to 12% increase in HDL cholesterol and a 8 to 27% decrease in plasma triglycerides have been observed (11). One major potential disadvantage of lovastatin in renal transplant recipients receiving concomitant CsA is the occurrence of myositis (12-14). The manifestations of lovastatin-induced myositis include weak-
ness, tenderness, and swelling. Severe rhabdomyolysis and acute renal failure have been reported (13).

Animal studies indicate that, in very high doses, lovastatin is toxic to muscle fibers (15). Limited information in the literature has suggested that the administration of lovastatin to patients increases serum CsA levels significantly (12–14). In sporadic cases where severe myositis occurred, serum lovastatin levels have been found to be elevated several-fold above the normal therapeutic range (12–14). This drug interaction resulting in elevated plasma lovastatin concentration may be the mechanism by which the coadministration of lovastatin and CsA induces muscle damage. Lowering the dosage of lovastatin can theoretically diminish the muscle toxicity in the presence of CsA. We report herein the efficacy and safety of low-dose lovastatin (10 to 20 mg/day) in the treatment of hypercholesterolemia in renal transplant recipients who are receiving immunosuppression including CsA.

METHODS

Patient Population

The study was conducted with the approval of the Institutional Review Board of the University of Utah and the informed consent of all participants. Patients were eligible for entry into the study if they were medically stable at least 6 months post-renal transplant, received chronic maintenance immunosuppression with CsA and prednisone, and exhibited serum total cholesterol levels above 240 mg/dL after dietary intervention. Exclusion criteria were serum creatinine concentration above 5 mg/dL or abnormal liver function tests.

The clinical characteristics of the six patients enrolled into the study are summarized in Table 1. There were two women and four men. The daily oral doses of CsA and prednisone were 4.3±0.5 (range, 3.0 to 6.8) mg/kg and 7.5±0.6 mg (range, 5.0 to 10.0), respectively. Five patients were also taking azathioprine (range, 50 to 100 mg/day). The dosage of immunosuppressive medications, including CsA, prednisone (taken as a single dose in the morning), and azathioprine, remained constant throughout the entire period of the study for all patients. One patient (patient 3) developed deep venous thrombosis 1 month before entry into the study and was maintained on a stable dose of coumadin (5.0 and 7.5 mg on alternate days) for 3 months. The three diabetic patients received maintenance insulin, three patients (patients 3 through 5) received furosemide, and one patient (patient 1) took oral contraceptives daily throughout the study. No patient was taking thiazides, β-adrenergic blockers, or other medications that are known to affect lipid levels.

Study Protocol

All patients were monitored as outpatients in the Renal Transplant Clinic at the University of Utah Medical Center. Hypolipidemic drugs were withdrawn, and dietary restrictions were instituted at week −6 (washout). The diet was instructed by a renal dietitian and consisted of 55% carbohydrates, 30% fat (saturated:polyunsaturated ratio of ~1.0; 300 mg of cholesterol), and 15% protein per day. Dietary compliance was assured by periodic 24-h recalls.

Fasting morning blood samples were obtained at baseline (week −2 and week 0) and throughout the course of the study. These samples were analyzed for (1) serum lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides); (2) complete blood count; (3) serum chemistry profiles; (4) serum creatine kinase; (5) serum CsA; and (6) plasma lovastatin. Slit lamp examination of the eyes was performed by an ophthalmologist at the University of Utah Medical Center during the washout period and at the conclusion of the study.

Lovastatin was started at 10 mg/day as a single oral dose in the morning at week 0. The patient was seen every 2 weeks and questioned about the developmen
opment of new symptoms, especially those related to the muscular and gastrointestinal systems. If no significant clinical or laboratory side effects were observed, the dose of lovastatin was increased to 20 mg/day as a single oral dose at week 8. After week 10, the patients were seen in the clinic monthly. Lovastatin was discontinued at week 20, and the patients were monitored for an additional 4 wk thereafter.

Analytical Methods

All blood samples were analyzed at the University of Utah affiliated clinical laboratory (Associated and Regional University Pathologists, Inc., Salt Lake City, UT), except for the lovastatin levels, which were determined in the laboratory of Dr. Evan Stein (Medical Research Laboratory, Cincinnati, OH). The lovastatin assay measures the ability of the plasma to inhibit HMG-CoA reductase in hepatic microsomes and therefore detects only the active form of the drug (16). Chemistry profiles, CK, and triglycerides were determined with a Hitachi 747 autoanalyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). HDL cholesterol was also measured with the autoanalyzer after precipitation with magnesium dextran. LDL cholesterol and VLDL cholesterol were calculated from total cholesterol, HDL cholesterol, and triglycerides by use of the equations of Friedewald et al. (17). Complete blood count was determined with a Coulter® counter (STKR; Coulter Corp., Hialeah, FL). CsA levels were determined in the serum by use of an RIA (Incstar Corp., Stillwater, MN) after the blood was allowed to clot at room temperature for 2 h.

Data Analyses

All laboratory values are expressed as means ± SE. Values at different times were analyzed by analysis of variance for repeated measures with commercial computer software (SYSTAT; SYSTAT Inc., Evanston, IL [18]) and compared with the corresponding baseline values by paired t test. P values of <0.05 are considered to be statistically significant.

RESULTS

All six patients who were enrolled completed the study. There were no statistically significant differences in serum levels of total, HDL, and LDL cholesterol, triglycerides, CsA, urea nitrogen, or creatinine between weeks −2 and 0, indicating that the baseline conditions were stable after dietary modification and withdrawal of other hypolipidemic drugs. Only week 0 values are subsequently presented as baseline.

No patient reported noticeable changes in lifestyle or physical activities during the study. Baseline and poststudy body weights were 78.8±12.3 versus 79.1±13.1 kg, respectively (P=0.83).

Analysis of variance showed that, among all of the variables examined, only serum total (P<0.001) cholesterol and LDL (P=0.001) cholesterol levels changed with time during the study. Serum total cholesterol decreased by 12% (from 290±20 mg/dL at week 0 baseline to 255±21 mg/dL; P=0.016) after 4 wk of lovastatin at 10 mg/day (Figure 1). The levels remained relatively stable for the next 12 wk, despite an increase in lovastatin dosage to 20 mg/day at week 8. Twelve weeks after the dosage increase (at week 20), however, total cholesterol levels fell further to 212±11 mg/dL. The total decrease at week 20 was 27% compared with baseline (P=0.002). Four weeks after lovastatin was discontinued, total cholesterol rose to 263±22 mg/dL (P=0.27 versus baseline).

The trend for serum LDL cholesterol levels was similar to that observed for total cholesterol (Figure 1B). LDL cholesterol decreased by 17% (from 184±12 to 153±13 mg/dL; P=0.045 versus baseline) 4 wk after lovastatin was started at 10 mg/day and fell further to 134±9 mg/dL by week 20. The total reduction at week 20 was 27% from baseline (P=0.005). The levels increased to baseline 4 wk after the lovastatin had been discontinued (P=0.66 versus baseline).

There was no significant change in serum HDL cholesterol levels throughout the entire study (Figure 1C). There was a tendency for the LDL:HDL cholesterol ratio (Figure 1D) and total:HDL cholesterol ratio (not shown) to decrease during the period in which lovastatin was administered, but the difference did not reach statistical significance at any time compared with baseline. After lovastatin had been discontinued at week 20, however, the LDL:HDL cholesterol ratio and the total:HDL cholesterol ratio increased by 39% (3.2±0.3 in week 20 versus 4.4±0.5 in week 24; P=0.012) and 26% (5.1±0.4 in week 20 versus 6.4±0.6 in week 24; P=0.015) respectively in 4 wk; the ratios at week 24 were not different from the baseline (P=0.36 and 0.47, respectively).

As can be seen in Figure 2A and B, there were no statistically significant changes in serum VLDL cholesterol and triglyceride levels during the entire observation period.

Trough plasma lovastatin levels ~24 h after administration were in the range of 0.4 to 2.5 ng/mL (Table 2). Measurement of four plasma samples showed that the peak (1 to 2 h) lovastatin levels were 23.10±10.80 ng/mL.

Inasmuch as lovastatin may have pharmacologic interactions with CsA, it is important to monitor serum CsA levels during the treatment. The mean trough serum CsA levels increased from baseline and remained elevated after 8 wk; however, none of these values was significantly different from baseline (Figure 3). After the discontinuation of lovastatin at week 20, CsA levels remained unchanged 4 wk later. These
Figure 1. Serum lipid levels in renal transplant patients taking lovastatin and CsA. Lovastatin was started at 10 mg/day at week 0, increased to 20 mg/day at week 8, and discontinued at week 20. (A) Total cholesterol. (B) LDL cholesterol. (C) HDL cholesterol. (D) LDL/HDL cholesterol ratio. Data are presented as the mean ± SE (N=6 for each time). *P<0.05 versus baseline (week 0).

Figure 2. Serum lipid levels in renal transplant patients taking lovastatin and CsA. (A) VLDL cholesterol. (B) triglycerides. Data are presented as the mean ± SE (N=6 for each time).

Table 2. Trough plasma lovastatin levels

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<th>Patient No</th>
<th>Week 4 (ng/mL)</th>
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*Values <1.0 ng/mL (the detection limit of the assay) is assumed to be 0 in the calculation of the mean. Data for Patient 6 were unavailable.

Rhabdomyolysis, if it occurs, can lead to the release of muscle enzymes, hyperkalemia, and acute renal failure. Serum levels of potassium (not shown), BUN (Figure 4A), creatinine (Figure 4B), and CK (Figure 5), however, did not change in this study. There were also no changes in serum transaminases (Figure 6A and B) to suggest hepatic injury from lovastatin. Blood hemoglobin and leukocyte counts also remained stable (data not shown).

Follow-up ophthalmologic examination after the trial did not reveal any alterations from baseline. No
Figure 3. Serum CsA levels in renal transplant patients taking lovastatin and CsA. There was no statistical significance between the baseline (week 0) values and the values at any subsequent time. Data are presented as the mean ± SE (N=6 for each time). Therapeutic levels of CsA are usually 40 to 80 ng/mL by this RIA.

Figure 4. BUN and serum creatinine levels in renal transplant patients taking lovastatin and CsA. (A) BUN. (B) Creatinine. Data are presented as the mean ± SE (N=6 for each time). BUN and creatinine remained unchanged throughout the study.

Figure 5. Serum creatine phosphokinase (CK) levels in renal transplant patients taking lovastatin and CsA. CK levels remained unchanged throughout the study.

Figure 6. Serum liver enzyme levels in renal transplant patients taking lovastatin and CsA. (A) Aspartate aminotransferase (AST). (B) Alanine aminotransferase (ALT). Data are presented as the mean ± SE (N=6 for each time). Liver enzymes remained unchanged throughout the study.

DISCUSSION

Hypercholesterolemia after renal transplantation is common and is probably multifactorial (19). Preex-
isting lipid abnormalities, diabetes mellitus, diet, corticosteroids, antihypertensive agents, and graft proteinuria have been incriminated. More recently, studies in renal transplant patients (20) as well as in nontransplant (e.g., amyotrophic lateral sclerosis [21]) patients suggested that the administration of CsA also contributes to the hypercholesterolemia. When CsA was switched to azathioprine in renal transplant recipients in one study, serum total cholesterol levels fell by 19% (20). The mechanism by which CsA increases cholesterol levels is unclear but may be related to the ability of the drug to inhibit 26-hydroxylase activity and bile acid synthesis in the liver (22). Regardless of the cause, the strong association between high serum cholesterol levels and cardiovascular events in the general population implies that this abnormality in renal transplant recipients should be treated as well.

Previous studies involving the general population (11), patients with nephrotic syndrome (23–25), and cardiac transplant recipients (26,27) have established the efficacy of lovastatin in the treatment of hypercholesterolemia. Serum cholesterol levels decreased by 22 to 41% in the various studies using different dosages. Specifically, in cardiac transplant patients receiving concomitant CsA, 10 to 60 mg of lovastatin reduced total and LDL cholesterol levels by 27 to 28% and 26 to 34%, respectively (26,27). This study showed that lovastatin was equally effective in lowering total (27%) as well as LDL (27%) cholesterol in renal transplant recipients. The dosages of lovastatin used in our study (10 to 20 mg/day) were 25 to 50% of the recommended dosages for the general population (20 to 80 mg/day). Consistent with the results in nephrotic subjects (24,25) and cardiac transplant patients (26,27), lovastatin alone did not affect serum HDL cholesterol appreciably in our renal transplant patients (Figure 1C).

Although 10 mg/day of lovastatin induced a 12% decrease in total and LDL cholesterol by week 4, an additional 15% decrease was observed 12 wk after the dose was increased to 20 mg/day (Figure 1A and B). Whether a more prolonged course of lovastatin at 10 mg/day would achieve the same effect was not addressed by this study. It is also conceivable that further reductions in total and LDL cholesterol over 27% could occur if lovastatin were continued at 20 mg/day beyond 12 wk. Again, this hypothesis was not tested by the experimental design.

A low total: HDL cholesterol ratio and a low LDL: HDL cholesterol ratio portend a low cardiovascular risk in the general population. There was a tendency for these ratios to decrease when the patients were treated with lovastatin (Figure 1D), but none of the values at any time were statistically significant compared with baseline. A significant increase in these ratios, however, was observed when lovastatin was discontinued at the end of the study, suggesting that lovastatin may have a beneficial effect on the LDL/HDL cholesterol ratio in this population.

A study of another HMG-CoA reductase inhibitor, pravastatin, in renal transplant recipients receiving concomitant CsA has recently been reported by Yoshimura and colleagues (28). In agreement with our results, they also found reductions in total and LDL cholesterol levels without significant changes in either HDL cholesterol or triglyceride levels. Using the lower equivalent dose of pravastatin (10 mg/day), they found a less-pronounced reduction (19%) in total cholesterol, which remained stable during the 6-month treatment period.

A major concern in the use of lovastatin to treat renal transplant patients has been the potential occurrence of muscle damage during concurrent therapy (12–14). The myotoxicity has been associated with acute renal failure resulting from myoglobinuria (13). The several case reports that describe this phenomenon have largely been limited to patients who are taking conventional doses of lovastatin (40 to 80 mg/day) without adjustment for the concomitant administration of CsA or other drugs that may potentiate lovastatin muscle toxicity. The mechanisms by which CsA potentiates the muscle toxicity of lovastatin are unclear; however, other medications, such as fibric acid derivatives, have also been shown to exhibit similar properties (29). Lovastatin is a prodrug with a lactone structure that undergoes extensive first-pass uptake by the liver, where it is hydrolyzed into its active form (30). BothLovastatin (31), and CsA (32) appear to be catabolized by the cytochrome P450IIIA system in the liver. The presence of CsA may therefore interfere with the elimination of the active lovastatin hydroxy acid. This drug interaction is supported by a case report in which the peak plasma lovastatin level was markedly elevated in a patient who developed rhabdomyolysis while taking lovastatin and CsA (14).

In this study, lovastatin was measured by a biosay that detects only the active hydrolyzed drug. The peak (~23 ng/mL) and trough levels (0.4 to 2.5 ng/mL) (Table 2) oflovastatin after oral doses of 10 to 20 mg were comparable to those observed in normal subjects 2 to 3 and 12 h, respectively after a 40-mg dose (33). These data are compatible with the hypothesis that CsA alters the disposition of lovastatin and increases the systemic exposure to activelovastatin (area under the plasma drug concentration versus time curve) (15). They also indicate that a dose reduction oflovastatin to 10 to 20 mg/day results in acceptable plasma levels in patients receiving CsA.

Animal studies have clearly demonstrated induction of muscle injury by HMG-CoA reductase inhibitors, which can be potentiated by the concurrent...
administration of CsA (15). None of the patients in this study developed symptoms of myositis or elevations of serum CK (Figure 5). Similarly, Yoshimura et al. observed stable serum CK levels in patients treated with 10 mg/day of pravastatin (28). Because pravastatin is more hydrophilic than lovastatin and is less likely to penetrate the cytoplasmic membranes in other organs (such as the muscles), those authors postulated that this relative tissue selectivity protects the muscle cells from injury by pravastatin. Our study, however, demonstrated that when plasma lovastatin levels were kept within the therapeutic range by lowering the dosage, muscle damage could be avoided with lovastatin as well.

The effect of lovastatin on CsA metabolism is less obvious but appears to be much less pronounced. In the two studies involving cardiac transplant patients, plasma CsA levels were not altered by lovastatin (26,27). CsA levels were not reported in the renal transplant study by Yoshimura and colleagues (28). In a hyperlipidemic rat model, lovastatin was found to prolong the half-life of CsA, without altering its apparent clearance, area under the curve, volume of distribution, or trough levels (34). Although the serum CsA levels appeared to increase after lovastatin was started in our patients (Figure 3), the increase was not statistically significant and the mean levels remained within the therapeutic range.

Conceivably, lovastatin could cause acute renal failure in renal transplant patients by either inducing rhabdomyolysis or by increasing CsA levels, thereby enhancing CsA toxicity. Neither of these events occurred in our study; renal function remained unchanged throughout the study, as indicated by the stable BUN and creatinine levels (Figure 4).

Other adverse effects of lovastatin that had previously been reported in the general population include gastrointestinal distress, headache, rash, pruritus, hepatic toxicity, and cataracts (11). None of these symptoms was clinically evident or attributable to lovastatin in this study.

In summary, our study shows that lovastatin, given in doses of 10 to 20 mg/day with careful monitoring, is effective and safe in hypercholesterolemic renal transplant recipients who are receiving CsA. Whether the lowering of cholesterol results in long-term benefits, such as a reduction in cardiovascular events and mortality, requires further study.

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