Comparative Beneficial Effects of Simvastatin and Pravastatin on Cardiac Allograft Rejection and Survival

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OBJECTIVES

We sought to evaluate the relative effects of low doses of pravastatin (20 mg/day) and simvastatin (10 mg/day) on indices of cardiac allograft rejection. We further examined the relative efficacy and safety of these two drugs on lipid-lowering in heart transplantation.

BACKGROUND

The immunomodulatory effects of hydroxymethyl glutaryl-coenzyme A reductase inhibitors have been increasingly recognized. Previous studies have demonstrated an ameliorative influence of pravastatin on hemodynamically compromising rejection after heart transplantation. A recent observational trial suggested that simvastatin 20 mg/day was associated with trends to lower survival and more adverse effects than pravastatin 40 mg/day.

METHODS

In a 12-month prospective, open-label study, 50 heart transplant recipients received either open-label pravastatin 20 mg daily (n = 24) or simvastatin 10 mg daily (n = 26) within four weeks of transplantation. Indices of allograft rejection including treated rejection, rejection with hemodynamic compromise, noncellular rejection, and mean one-year biopsy score were compared between the two cohorts, as well as with a statin-naive control population (n = 37). Lipid levels, safety, and post-transplant outcomes were also assessed as secondary end points.

RESULTS

We found no significant differences in any allograft rejection parameter between the two groups. However, total low-density lipoprotein (LDL), but not high-density lipoprotein cholesterol or triglycerides, were lower in the simvastatin arm (~23% vs. ~11%, p = 0.02). No cases of rhabdomyolysis or myositis occurred in either group. Survival at one year was similar in both treatment groups (91% for patients on pravastatin and 92% for patients on simvastatin). Both groups had better survival compared with the statin-naive control group (80%, p = 0.04).

CONCLUSIONS

Simvastatin (10 mg/day) and pravastatin (20 mg/day) are associated with similar beneficial effects on cardiac allograft rejection and one-year survival. At these doses, simvastatin decreases LDL cholesterol more so than pravastatin with no increase in adverse effects in heart transplantation. (J Am Coll Cardiol 2002;40:1609–14) © 2002 by the American College of Cardiology Foundation

The emergence of hydroxy methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) has ushered in an era of widespread acceptance for lipid-lowering in heart transplant and in cardiac disease, largely because of their potent effects (1). It has become increasingly apparent that statins exert their beneficial effects on coronary artery disease by a host of pleiotropic effects that involve immunomodulation (2). Exploitation of these immunologic benefits in heart transplantation has been noted in a provocative investigation by Kobashigawa et al. (3) wherein pravastatin (40 mg/day) was shown to not only lessen cardiac rejection associated with hemodynamic compromise but also improve survival.

Whether these salutary effects are unique to pravastatin or shared by other members of this drug class remains controversial. A recent observational investigation by Keogh et al. (4) comparing pravastatin (40 mg/day) with simvastatin (20 mg/day) alluded to a trend toward a better outcome with pravastatin that was attributed to a more favorable immunologic complication profile with pravastatin. Other data by Wenke et al. (5) demonstrated that low-dose simvastatin (10 mg/day) in the long term significantly improves survival and lowers the incidence of cardiac allograft vasculopathy with a tendency for fewer serious rejection episodes.

The purpose of our study was to primarily assess the relative effects of low-dose simvastatin (10 mg/day) and pravastatin (20 mg/day) on cardiac allograft rejection, confirm their lipid-lowering effects, determine safety, and establish one-year clinical outcomes.

METHODS

Patients. All consecutive adult (≥18 years) primary heart transplant recipients between 1995 and 1998 with sustained elevations (on two consecutive and separate measurements) of low-density lipoprotein (LDL) cholesterol (≥130 mg/dl) within four weeks after heart transplantation were screened for enrollment. Patients were excluded if they had any contraindications to statin therapy, a prior history of myopathy or rhabdomyolysis, or renal failure requiring chronic dialysis.

Intervention. The patients were randomly treated with either pravastatin 20 mg/day (n = 24) or simvastatin 10
mg/day (n = 26) for at least one year. In addition, all patients underwent dietary counseling from a nutritionist to follow a low-fat diet. The primary immunosuppression regimen included cyclosporine (microemulsion), azathioprine, and corticosteroids in accordance with the institutional protocol as indicated elsewhere. A statin-naive group of 37 heart transplant recipients were used to compare outcomes with the statin therapy group. This group was assembled as a parallel cohort in whom the transplant cardiologist chose not to prescribe lipid-lowering therapy. The statin-naive group consisted of parallel cohort transplanted during the same period as the treatment cohort but in whom the transplant cardiologist felt that lipid-lowering therapy was not mandatory owing to lower baseline lipid levels.

Cardiac allograft rejection. Serial surveillance endomyocardial biopsies were obtained at predetermined temporal frequencies. Endomyocardial biopsies were performed at weeks 1, 2, 3, 4, 6, 8, 10, and 12, then at months 4, 5, 6, 9, and 12. Rejection was treated where there was International Society for Heart and Lung Transplantation grade 3A rejection or higher or a lower grade in the presence of hemodynamic compromise. Treated episodes of cellular rejection (grade ≥3A), rejection with hemodynamic compromise (any cellular infiltrate ≥1A; left ventricular ejection fraction decrease by 20%, cardiac index decrease or pulmonary capillary wedge pressure increase by 25% from baseline), and noncellular rejection (hemodynamic compromise in the absence of a cellular infiltrate or positive tissue immunofluorescence) were definitions used to quantify allograft rejection. Furthermore, a one-year mean biopsy rejection score to account for clinical and subclinical rejection was also assessed as previously reported by our group (6). We also compared the biopsy score findings in each group with the parallel statin-naive cohort.

Lipid-lowering efficacy and safety. Detailed fasting lipid profiles, hepatic function tests (serum alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase, and serum bilirubin), and serum creatinine phosphokinase were obtained at fortnightly intervals during the first month after initiation of treatment and then at three monthly intervals. Elevation of alanine aminotransferase levels to more than 3 times the normal level and creatinine phosphokinase to more than 10 times the normal level were considered abnormal and a side effect of statin therapy. In addition, clinical evaluations for development of adverse effects were routinely performed in all the patients by monthly clinical visits. Drug compliance and withdrawals were also assessed. Concomitant use of cytochrome p450 inhibitors was prohibited for the duration of the trial.

Clinical outcomes. One-year all-cause survival was computed for the study group with cause of death recorded. Although surveillance angiography was performed in all survivors at one year, the data were not analyzed because it was felt that the one-year time point using angiography was too short to make any meaningful conclusions regarding cardiac allograft vasculopathy. Intravascular ultrasound was not routinely performed in the patient cohort.

Statistical analysis. Comparisons of baseline characteristics and six-month data between groups were performed using the unpaired Student t test for continuous variables and chi-square analysis or Fisher exact test (if the expected frequency was smaller than five) as appropriate for categorical variables. Changes in indices of allograft rejection and lipids over time were examined by paired Student t tests. The Pearson product-moment correlation coefficient was used to evaluate the relationship between the degree of LDL cholesterol lowering and the mean biopsy rejection score. All data are presented as mean ± SD. Significance was set at p < 0.05.

RESULTS

Patients and statin dose. Fifty transplant recipients met the inclusion criteria for enrollment. The study cohort consisted of 39 men and 11 women (mean recipient age 53 ± 9 years, donor age 26 ± 11 years). The mean dose of pravastatin was 20 ± 5 mg/day; the mean dose of simvastatin was 11 ± 6 mg/day. No differences in immunosuppression were noted in the two groups. Additionally, there were no baseline differences between the two groups with regard to age, race, gender, status at time of transplantation, ischemic time, human leukocyte-antigen matches, or immunosuppression used. Compared with the treatment group, the statin-naive patients shared the same baseline characteristics except for lower lipid levels at inception and higher nonischemic etiology of heart failure at time of transplantation (Table 1).

Cardiac allograft rejection. Simvastatin- and pravastatin-treated heart transplant recipients had no significant differences in the rates of treated cellular rejection (11% vs. 8.3%), rejections with hemodynamic compromise (11% vs. 12.5%), noncellular rejection (7.6% vs. 0%), or the sum of cellular and noncellular rejection (27% vs. 25%). In addition, the one-year mean biopsy rejection score was also similar in both groups (0.78 ± 0.03 vs. 0.74 ± 0.04). Compared with a parallel “statin-naive” cohort of 37 patients, both simvastatin- and pravastatin-treated patients exhibited significantly lower mean biopsy scores (0.96 ± 0.05, p < 0.05 compared with simvastatin and pravastatin groups) (Figs. 1 and 2).

Lipid variables. BASELINE LIPIDS. Baseline total cholesterol levels were similar in the two study groups (243 ± 46 mg/dl in the pravastatin group vs. 257 ± 49 mg/dl in the
simvastatin group); initial LDL cholesterol was 154 ± 56 mg/dl in the pravastatin group and 167 ± 53 mg/dl in the simvastatin group; starting triglyceride levels were also similar in the two study groups (200 ± 120 mg/dl in the pravastatin group vs. 193 ± 94 mg/dl in the simvastatin group); and the high-density lipoprotein (HDL) cholesterol levels were also no different between the groups (38 ± 6 mg/dl vs. 39 ± 8 mg/dl) (all p = NS).

**ABSOLUTE CHANGES AT 12 MONTHS.** The total cholesterol levels at 12 months of treatment were 218 ± 54 mg/dl in the pravastatin group (p < 0.01) and 204 ± 41 mg/dl in the simvastatin group (p < 0.01). The LDL cholesterol was 131 ± 47 mg/dl in the pravastatin group (p < 0.05) and 120 ± 34 mg/dl in the simvastatin group (p < 0.05). There was a significant difference between the absolute reductions in LDL cholesterol between the pravastatin and simvastatin groups (p < 0.01). Triglyceride levels were 186 ± 97 mg/dl in the pravastatin group and 185 ± 113 mg/dl in the simvastatin group (p = NS). Similarly, no significant differences in HDL cholesterol elevations were noted among the groups.

**RELATIVE CHANGES AT 12 MONTHS.** The percentage reduction in total cholesterol was 9.2% in the pravastatin group compared with 18.8% in the simvastatin group (p = 0.08). Percentage reduction in LDL cholesterol was significantly higher in the simvastatin group versus pravastatin (23.3% vs. 14.9%; p = 0.04). The relative reductions in triglyceride levels were similar in both the study groups (6.2% in the pravastatin group vs. 8.1% in the simvastatin group; p = NS). With regard to HDL cholesterol levels, only modest increases were noted in the pravastatin versus simvastatin groups (4% ± 3% vs. 6% ± 4%, p = NS).

**CORRELATION OF LDL LOWERING AND ALLOGRAFT REJECTION.** No significant correlation of degree of LDL cholesterol lowering and mean biopsy rejection score on linear regression was identified (r = 0.2, p = NS).

**Adverse effects.** At the study doses, no significant episodes of transaminase elevation requiring drug withdrawal were noted in either study group. No clinical or laboratory evidence of myopathy or rhabdomyolysis was seen in the study groups. No drug withdrawals occurred, and patient compliance with drug regimens exceeded 97%.

**One-year outcome.** Similar 12-month survival was noted among the simvastatin (92%) and pravastatin (91%) study arms. The two deaths in the simvastatin arm were related to a cerebrovascular accident and multi-organ failure in the presence of systemic bacterial infection. The pravastatin study arm included one death from septic shock and a second attributable to the development of accelerated coronary artery disease as noted on pathology. Compared with both statin groups, the statin-naive group demonstrated lower one-year survival (80%, p = 0.04). Of seven deaths in the control group, three deaths occurred as a result of refractory allograft rejection with hemodynamic compromise, two deaths were caused by septic shock, one was due to cerebrovascular accident, and the remaining deaths were attributed to coronary artery disease. Thus, five of seven deaths could be attributed to “immunologic deaths.”

**Figure 1.** Rates of allograft rejection (%) between pravastatin (black bars) and simvastatin (white bars). HDC = hemodynamic compromise.
DISCUSSION

Study findings. The results of our investigation suggest that at low doses, immunologic outcomes are similar in simvastatin- and pravastatin-treated heart transplant recipients. Compared with statin-naive patients, both simvastatin and pravastatin are associated not only with superior rejection-related outcomes but also with one-year survival. Although unexpected, simvastatin was noted to provide better LDL cholesterol lowering than pravastatin; however, this did not appear to influence first-year outcome.

Mechanisms of non–lipid-lowering statin effects. In addition to lipid-lowering effects, statins exhibit ubiquitous vascular properties that include plaque stabilization, inhibition of smooth muscle cell proliferation, improved endothelial function, and decreased inflammation (2). Statins inhibit HMG-CoA reductase, the enzyme that catalyzes the conversion of 3-hydroxy-3-methylglutaryl-CoA to mevalonate. In doing so, statins also reduce the downstream products of mevalonate in the cholesterol synthesis pathway. Two of these downstream products, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are the lipid moieties that can modulate the function of certain essential signaling proteins that influence smooth muscle cells and generation of nitric oxide (NO) (7). In particular, the small geranylgeranyl transferase-binding protein, Rho, whose membrane localization and activity are affected by post-translational isoprenylation, may play an important role in mediating the direct vascular effects of statins (8). Recent in vitro studies have suggested that statins, by inhibiting the farnesylation of Rho, may decrease smooth muscle proliferation (9). In addition to inhibiting farnesylation, statins have recently been shown to improve endothelial function, vasomotor tone, and markers of inflammation by increasing the availability of NO, providing another explanation for their surprising allogeneic protective effects (8). Thus, statin use may result in increased expression of endothelial NO synthase and greater NO production (10). Kureishi et al. (11) demonstrated that mevalonate, the product of HMG-CoA reductase, inhibits a central signaling molecule, phosphatidylinositol-3 kinase, which might result in up-regulation of NO and improved vasomotor tone and endothelial function.

Anti-inflammatory properties of statins. Accumulating more evidence for an anti-inflammatory effect of statins independent of their lipid-lowering effect, Jialal et al. (12) have recently demonstrated that simvastatin, pravastatin, and atorvastatin decrease high-sensitivity C-reactive protein in a similar manner independent of their lipid-lowering effects. In this study, the investigators were unable to establish a link with interleukin-6 levels but did demonstrate an association with triglycerides, a particularly potent risk factor for outcomes after heart transplantation. Major histocompatability complex (MHC) class II molecules are directly involved in the control of the immune response. Major histocompatability complex (MHC) class II molecules are directly involved in the control of the immune response. During allograft implantation, the cells become MHC II expressive. Kwak et al. (13) have demonstrated that statins act as direct inhibitors of MHC II induced T-cell activation. This action is a result of the inhibition of the inducible promoter IV of the class II transactivator. This effect may form an important basis for the understanding of immunomodulation. Other properties of statins in transplantation may bear note as modulators of allograft outcome. Holschermann et al. (14) have reported the effects of low-dose simvastatin on inhibiting expression of monocyte tissue
factor and reduction in the hypercoagulability seen in transplant recipients. This specific form of immunomodulation might be protective for the late development of allograft vasculopathy. Katznelson et al. (15) have studied the effects of pravastatin on natural killer cell cytotoxicity. These investigators have shown that pravastatin and cyclosporine act synergistically to reduce cytotoxic T lymphocyte activity, suggesting that this specific effect is unique to transplant recipients. More recently, Weis et al. (16) have demonstrated improved endothelial function and reduced cytokine activation in clinical heart transplantation with simvastatin.

Comparison with other studies. Several investigators have consistently demonstrated a beneficial impact of the hydrophilic statin, pravastatin, in heart transplantation as well as renal transplantation. In particular, early post-transplant use of this agent has been associated with a decrease in hemodynamically compromising rejection, attenuation of a rise in lipids, improved one-year survival, and trends in favor of a reduction in allograft coronary artery disease (3). Wenke et al. (5) have used simvastatin in low doses as in our investigation, and suggested that in the long term at four years the use of this agent improves outcomes as a consequence of a reduction in significant coronary artery disease after transplantation. More recently, Keogh et al. (4) have reported their results of a nonrandomized observational trial comparing pravastatin and simvastatin wherein they raised caution that higher doses of simvastatin may be associated with poor outcomes and more adverse effects. Our investigation differs significantly from Keogh et al. (4) because we used low doses of simvastatin, prohibited co-administration of drugs that require metabolism through or inhibit the cytochrome p450 pathway (other than cyclosporine), and waited until the renal function in our patients stabilized before initiating drug therapy. These sentinel differences abrogated any significant clinical distinctions between pravastatin and simvastatin as demonstrated by no significant cases of hepatotoxicity or muscle toxicity in our two patient groups. Furthermore, our study also suggests that low doses of statins may be sufficient to exert beneficial effects on 12-month outcome as evidenced by one-year survivals exceeding 90% in both study groups.

Safety of low-dose simvastatin. Although Keogh et al. (4) have raised concern about the safety of simvastatin, other investigators have studied low-dose simvastatin (5 to 10 mg/day) and have demonstrated safety, tolerability, and efficacy in lowering lipid abnormalities. An earlier study by Vanhaecke et al. (17) administered low-dose simvastatin (average dose 10 mg/day) in 26 heart transplant recipients and demonstrated a decrease in cholesterol of 27% and LDL cholesterol of 40%, much more impressive results than in our cohort. Arnadottir et al. (18) conducted a double-blind, randomized, placebo-controlled study with low-dose simvastatin in 40 renal transplant recipients. No cases of myopathy and creatinine kinase enzyme elevation were reported in this study, similar to the findings of our investigation. Nevertheless, it is important to remain cautious in using simvastatin in the presence of other drugs interactive with CYP3A4-dependent metabolic pathways. The primary difference between simvastatin and pravastatin in this regard relates to whether the drug is administered in the lactone form (simvastatin) or in the active non-lactone form (pravastatin). All lactone forms inhibit the cytochrome enzyme pathways more than the acid forms, with pravastatin having the least likelihood of significant interaction (19).

Study limitations. Several study limitations should be taken into account during interpretation of these observations. The numbers of patients studied were small, and the statin-naive group was not randomized as evidenced by baseline differences in lipid perturbations. Although adverse effects were not present with either simvastatin or pravastatin in our relatively small study, our study may not have been powered to detect infrequent, but potentially serious adverse effects, particularly severe myopathy. Notwithstanding these limitations, the observed findings allow comparisons between the two statin-treated groups and suggest that despite lower baseline lipids in the statin-naive group, one-year outcomes were better with either statin-treated group. This lends credence to the potential benefit of statins in not only abrogating rejection but also enhancing survival.

Conclusions. Simvastatin (10 mg/day) and pravastatin (20 mg/day) are associated with similar beneficial effects on cardiac allograft rejection and one-year survival. At these doses, simvastatin decreases LDL cholesterol more than pravastatin with no increase in adverse effects in heart transplantation.

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