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Hyperlipidemia After Heart Transplantation: Report of a 6-Year Experience, With Treatment Recommendations

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Mean plasma lipid values in 100 patients who survived >3 months after heart transplantation increased significantly at 3 months over pretransplantation values: total cholesterol from 168 ± 7 to 234 ± 7 mg/dl, low density lipoprotein (LDL) cholesterol from 111 ± 6 to 148 ± 6 mg/dl, high density lipoprotein (HDL) cholesterol from 34 ± 1 to 47 ± 1 mg/dl and triglycerides from 107 ± 6 to 195 ± 10 mg/dl. There were no significant increases after this time. The LDL cholesterol values remained ≥130 mg/dl in 64% of patients and triglyceride values remained ≥200 mg/dl in 41% of patients 6 months after postoperative dietary instructions.

Beginning in 1985, select patients whose total cholesterol values remained >300 mg/dl despite 6 months of dietary intervention were treated with lovastatin given alone in a high dose (40 to 80 mg/day) or in combination with another hypolipidemic agent. Four of the five patients so treated developed rhabdomyolysis; two of the four had acute renal failure. Beginning in 1988, a second protocol—lovastatin at 20 mg/day as monotherapy—was used in patients who despite dietary intervention had total cholesterol >240 mg/dl (mean follow-up 13 months). In the 15 patients so treated, mean total cholesterol decreased from 299 ± 10 mg/dl before treatment with lovastatin to 235 ± 9 mg/dl during treatment (21% reduction, $p < 0.001$) and mean LDL cholesterol was reduced from a baseline value of 190 ± 10 to 132 ± 12 mg/dl during treatment (31% reduction, $p < 0.001$).

In this study, lovastatin at a dose of ≤20 mg/day as monotherapy was a well tolerated, effective treatment for hyperlipidemia after heart transplantation. It did not result in rhabdomyolysis and required no alteration in immunosuppressive therapy. However, the dose should not exceed 20 mg/day and combination therapy with either gemfibrozil or nicotinic acid should be avoided, even if the target LDL cholesterol value is not reached.

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Guidelines for the pharmacologic treatment of hyperlipidemia have evolved over the last 2 decades on the basis of a wealth of clinical information. The most recent recommendations of the National Cholesterol Education Program (1) in the United States were formulated by a panel of experts to allow physicians to optimize the benefits of treatment while minimizing its risk. However, treatment of hyperlipidemia after heart transplantation may require different guidelines because of the different risk/benefit ratio in these patients. Although heart transplant recipients have extraordinarily high rates of both hyperlipidemia and accelerated coronary artery disease, the adverse side effects from hypolipidemic agents are increased and the benefits of therapy must be considered untested because of the unique pathophysiology of coronary artery disease in the allograft heart (2).

In this report, we describe a 6-year experience using lovastatin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, to treat dyslipidemia after heart transplantation. In addition, we examine the frequency and pattern of dyslipidemia in all heart transplant recipients at one of our institutions during this period, review the available data on the risks and benefits of the various lipid-lowering agents in the context of heart transplantation and provide treatment recommendations on the basis of these data.

Methods

Patients and laboratory assessments. From September 1985 to March 1990, 100 patients underwent orthotopic heart

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transplantation at The Methodist Hospital and survived >3 months. All patients received immunosuppressive therapy with prednisone and cyclosporine; 82% were also treated with azathioprine. Venous blood samples taken after fasting were obtained before transplantation and at intervals of 1, 3, 6 and 12 months after transplantation. Plasma total cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride levels were measured by standard laboratory methods as previously described (3). Low density lipoprotein (LDL) cholesterol values were estimated by the formula of Friedewald et al. (4). All patients were given instructions on the American Heart Association Step One Diet before discharge from the hospital after heart transplantation. In select cases, total 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitory activity was measured with use of a Merck Laboratories in vitro bioassay system.

Treatment protocols. During the 1st 2 years of the study (1985 to 1987), five select patients who had two or more consecutive total plasma cholesterol readings >300 mg/dl despite dietary intervention for 6 months after transplantation were treated with high dose lovastatin or lovastatin combined with another lipid-lowering agent. Lovastatin therapy was begun at a dose of 20 mg orally once a day in the evening, then increased to a maximum of 40 mg orally twice a day or given in combination with a second drug, or both. Lipoprotein, hepatic transaminase, serum creatine kinase and whole blood cyclosporine levels (measured by radioimmunoassay) were determined every 6 weeks during lovastatin treatment.

This protocol (protocol 1) of high dose (≥40 mg/day) lovastatin or combined therapy was effective (5). However, the protocol—particularly the approach of using a combination of drugs—caused an unacceptably high incidence of myositis (6,7). Therefore, since 1988, both The Methodist Hospital and The Texas Heart Institute have used monotherapy with lovastatin at 20 mg/day (protocol 2) in select heart transplant recipients with plasma total cholesterol >240 mg/dl on two or more consecutive measurements made after 6 months of dietary therapy. The change in the total cholesterol value used as a threshold for treatment was made after the appearance of the National Cholesterol Education Program adult treatment guidelines (1).

Protocol 1 was approved as a "compassionate use" protocol. Protocol 2 was approved by the Institutional Review Board of each institution.

Statistical analyses. Results are expressed as mean values ± SEM. In the natural history analyses, changes in lipid and lipoprotein levels between baseline and subsequent measurements were evaluated by using analysis of variance (ANOVA) and the Bonferroni method. A paired Student *t* test was used to assess changes in the treatment group in lipoprotein levels and other laboratory measurements, unless abnormal distribution was present, in which case a paired Wilcoxon signed-rank test was used.

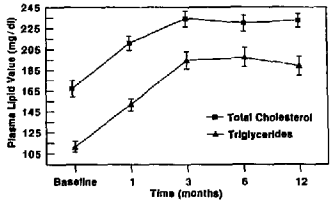

Figure 1. Mean plasma lipid values (±SEM) in 100 patients before and after heart transplantation. All patients received dietary instruction after transplantation; none was yet receiving a lipid-lowering agent. Baseline versus 3-month values are significant at $p < 0.05$ for both total cholesterol and triglycerides.

Results

Natural History Study

The patients were 91 men and 9 women, ranging in age from 15 to 68 years (mean 49). Changes in lipid and lipoprotein values after heart transplantation in these patients are shown in Figures 1 and 2. All changes in these values between baseline (before transplantation) and 3 months after transplantation were significant at $p < 0.05$.

Total cholesterol increased from 168 ± 7 mg/dl at baseline to 211 ± 6 mg/dl at 1 month and to 234 ± 7 mg/dl at 3 months. Triglycerides showed a similar pattern of change, with an increase from 107 ± 6 mg/dl at baseline to 150 ± 7 mg/dl at 1 month and to 195 ± 10 mg/dl at 3 months. High density lipoprotein cholesterol increased from a baseline value of 34 ± 1 mg/dl to a peak of 56 ± 2 mg/dl at 1 month with a decline to 47 ± 1 mg/dl at 3 months. In the subset of 56 patients whose HDL cholesterol level was measured at all

Figure 2. Mean plasma lipoprotein values (±SEM) before and after heart transplantation in the 100 patients. Baseline versus 3-month values are significant at $p < 0.05$ for both high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol.

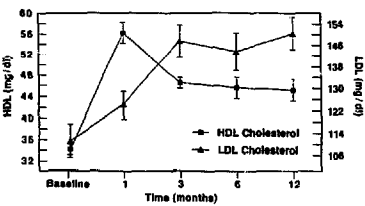

Table 1. Clinical/Laboratory Characteristics of Patients With Unacceptable Toxicity From High Dose (≥40 mg/day) or Combination Lovastatin Therapy (protocol 1, n = 5)

	Patient 1*	Patient 2*	Patient 3	Patient 4
Age (yr)/race/gender	36/W/M	46/W/M	32/W/F	47/W/M
Reason for transplantation	ASCVD	ASCVD	ASCVD	ICM
Lovastatin				
Dose (mg)/schedule	40/b.i.d.	40/b.i.d.	40/q.d.	20/q.d.
Duration (mo)	9	16	8	10
Other medication—dose/schedule				
Cyclosporine (mg/kg)	3/q.d.	3.5/q.d.	4/q.d.	4/q.d.
Azathioprine (mg)				125/q.d.
Prednisone (mg)	10/q.d.	10/q.d.	10/q.d.	15/q.d.
Gemfibrozil (mg)				600/b.i.d.
Nicotinic acid, slow release (mg)			500/t.i.d.	
Erythromycin (g)		2/q.d.		
Serum/plasma values				
TC (mg/dl)—before/on lovastatin	359/237	500/251	368/280	276/217
AST (U/liter)	266	843	397	—
ALP (U/liter)	52	128	155	51
Bili (mg/dl)	0.9	0.5	3.3	0.5
CK (U/liter)	8,920	23,832	1,122	12,000
CR (mg/dl)	9.7	2.8	2.1	9
Cyclosporine† (ng/ml)	1,013	904	908	—

*Previously described (6,7). †Determined 12 h after dose by whole blood radioimmunoassay. ALP = alkaline phosphatase; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; b.i.d. = twice daily; Bili = total bilirubin; CK = creatine kinase; CR = creatinine; F = female; ICM = idiopathic cardiomyopathy; M = male; q.d. = every day; TC = total cholesterol; t.i.d. = three times daily; W = white.

time points, the increase that occurred between baseline and 1 month and the decline that occurred between 1 and 3 months were significant ($p < 0.001$ and $p < 0.005$, respectively). Low density lipoprotein cholesterol increased from 111 ± 6 mg/dl at baseline to 124 ± 5 mg/dl at 1 month and to 148 ± 6 mg/dl at 3 months. No further significant changes in lipid or lipoprotein values occurred after 3 months.

Despite the postoperative instructions given patients regarding the American Heart Association Step One Diet, LDL cholesterol remained ≥130 mg/dl in 64% of patients and ≥160 mg/dl in 22% at 6 months after transplantation. In addition, triglycerides remained ≥200 mg/dl in 41% of patients and >250 mg/dl in 23% at this time.

Treatment Protocols

Protocol 1. We treated five patients with high dose lovastatin or lovastatin combination therapy. Although initially we reported (5) substantial reductions in levels of LDL cholesterol with lovastatin at a dose of 40 mg orally twice a day, we subsequently encountered severe toxicity rhabdomyolysis (6,7). Relevant clinical and laboratory data on the four patients who experienced unacceptable toxicity while receiving lovastatin at a high dose (40 mg orally either once or twice daily) or as part of combined hypolipidemic therapy are shown in Table 1. Elevations in creatine kinase and measures of liver function are apparent. Two of the patients had acute renal failure. Three of the four were receiving combination hypolipidemic therapy. The second agents used—nicotinic acid, gemfibrozil and the antibiotic erythromycin—are all now known to interact with lovastatin and increase the likelihood of rhabdomyolysis; with respect to nicotinic acid, enhanced hepatic dysfunction may also occur.

Total 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitory activity in plasma was measured at the time of rhabdomyolysis in two of the five patients. In one (Patient 1, Table 1), the activity was 310 ng-equivalents/ml 12 h after the second daily dose of 40 mg on day 1. In the other (Patient 2, Table 1), the activity was 251 ng-equivalents/ml 3 h after the second daily dose of 40 mg of lovastatin given on day 1. Both values are markedly increased compared with the mean maximal inhibitory activity of 19.9 ± 2.3 ng-equivalents/ml seen with high dose lovastatin (20 mg twice daily) in hypercholesterolemic patients not receiving immunosuppressive therapy (8). When the two patients were rechallenged with only a single daily dose of 20 mg of lovastatin, the inhibitory levels decreased to 65 and 87 ng-equivalents/ml, respectively, 4 h after the dose (substantial improvements, but still higher than the published control values with the drug at 40 mg/day [8]).

Protocol 2. Fifteen patients began lovastatin treatment on protocol 2 (monotherapy with lovastatin at 20 mg/day), in 1988 or later. Among the 14 men and 1 woman (mean age 54

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Table 2. Mean Lipid, Lipoprotein and Other Laboratory Values Before and During Treatment With Lovastatin Monotherapy at 20 mg/day (protocol 2, n = 15)

	Baseline	Treatment	Change (%)	p Value
TC (mg/dl)	299	235	−21	<0.001
TG (mg/dl)	297	273	−8	NS
LDL-C (mg/dl)	190	132	−31	<0.001
HDL-C (mg/dl)	39	42	+8	NS
AST (U/liter)	23	21	−9	NS
ALT (U/liter)	23	18	−2	NS
LDH (U/liter)	185	173	−6	NS
ALP (U/liter)	114	115	+0.9	NS
Bili (mg/dl)	0.67	0.85	+27	0.01
CK (U/liter)	—	93		
BUN (mg/dl)	31	35	+13	NS
Cyclo (dose in mg)	263	290	+10	NS
WBC (cells × 10^3/mm^3)	6.4	7.3	+14	NS

ALT = alanine aminotransferase; BUN = blood urea nitrogen; Cyclo = cyclosporine; HDL-C = high density lipoprotein cholesterol; LDH = lactate dehydrogenase; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; WBC = white blood cells; other abbreviations as in Table 1.

years), the cause of heart failure was coronary artery disease in 11 and idiopathic cardiomyopathy in 4. Mean follow-up after the initiation of lovastatin treatment was 13 months (range 6 to 30). All patients were explicitly warned to discontinue lovastatin and to have their serum creatine kinase level determined if muscle soreness developed.

The effects of lovastatin on plasma lipids and lipoproteins and other laboratory values in patients on protocol 2 (mean values determined at 6 to 12 weeks) are shown in Table 2. Total cholesterol decreased from 299 ± 10 mg/dl before treatment to 235 ± 9 mg/dl during treatment (21% reduction, $p < 0.001$). Low density lipoprotein cholesterol was reduced from 190 ± 10 mg/dl before treatment to 132 ± 12 mg/dl during treatment (31% reduction, $p < 0.001$). Favorable but statistically insignificant changes were also noted between baseline and treatment measurements of triglyceride and HDL cholesterol levels.

The increase in total bilirubin was of borderline statistical significance and was not considered to be clinically meaningful. The mean plasma cyclosporine level did not change significantly. The mean creatine kinase value with treatment was 93 U/liter (range 41 to 245; normal 35 to 200). One patient reported muscle soreness and discontinued lovastatin therapy without having the creatine kinase level measured. She was rechallenged with lovastatin at 10 mg/day and again reported vague muscle soreness; the creatine kinase measurement was 56 U/liter (within normal limits) at the 10-mg dose.

Treatment with the low dose lovastatin protocol did not require significant alterations in daily doses of cyclosporine, prednisone or azathioprine. No other side effects were observed with protocol 2.

Discussion

Postulated mechanisms of hyperlipidemia after transplantation. The high prevalence of hyperlipidemia observed in our patients is consistent with data in previous studies (5,9–13) examining the natural history of lipid changes after heart transplantation. One mechanism that has been proposed to account for the high incidence of dyslipidemia after heart transplantation is correction of severe congestive heart failure in patients with preexisting lipid abnormalities. In many of our patients with severe congestive heart failure and a history of hyperlipidemia, total cholesterol values were depressed before transplantation.

A second proposed mechanism is the use of immunosuppressive drugs. Several series (14–16) have demonstrated increased levels of total cholesterol after the administration of cyclosporine. The total cholesterol elevations were primarily the result of elevations of LDL cholesterol (5). Prednisone has been shown to increase both total and HDL cholesterol values in heart transplant recipients (17,18). In our series, HDL cholesterol was significantly increased at 1 month after transplantation and the decline at 3 months coincided with tapering of prednisone dosage. Taylor et al. (19) observed that heart transplant patients who received only azathioprine plus cyclosporine as immunosuppressive therapy did not show an increase in HDL cholesterol. The increase in HDL cholesterol is primarily the result of an increase in the HDL_2 subfraction, including an increase in apolipoprotein A-I (20,21). Lipoprotein lipase activity was inversely related to cyclosporine levels in one study (22) of heart transplant recipients, and low levels of lipoprotein lipase activity may lead to increases in plasma triglycerides. The posttransplantation increase in plasma triglycerides in our patients may also be related to the administration of cyclosporine.

Indications for treatment. The sequence of the lipid changes observed in our patients suggests that clinical assessment for hyperlipidemia should be performed 3 to 6 months after transplantation. Lipid values did not significantly change during the 3 months in which the patients were asked to comply with the American Heart Association Step One Diet as recommended by the National Cholesterol Education Program (1). The algorithm of the National Cholesterol Education Program for deciding to pharmacologically treat elevated cholesterol is based on both the LDL cholesterol value and the total risk for developing coronary artery disease. Accelerated coronary artery disease is the most common cause of graft failure in long-term survivors of heart transplantation and is present in 30% of patients by 28 months (23,24); therefore, any heart transplant recipient regardless of gender or traditional risk factors should be considered to be at high risk for developing coronary artery disease. The National Cholesterol Education Program guidelines (1) suggest that drug treatment be considered in high risk patients when the LDL cholesterol value remains ≥160 mg/dl after 6 months of dietary therapy. By that

Table 3. Special Considerations in the Use of Lipid-Lowering Drugs After Heart Transplantation

Drug	Possible Side Effects	Interactions With Immunosuppressants
Bile acid sequestrant (cholestyramine, colestipol)	May prevent absorption of fat-soluble drugs; poor compliance because of constipation and bloating	May inhibit absorption of cyclosporine, which is extremely fat soluble
Nicotinic acid	Elevation of liver function tests; increased uric acid levels; decreased glucose tolerance; exacerbation of peptic ulcer disease	Cyclosporine may cause elevations of liver function tests and uric acid levels; prednisone decreases glucose tolerance and may predispose to peptic ulcer disease
Fibric acid derivative (gemfibrozil)	Gallstones; myositis; nausea; potentiation of warfarin	Increased myositis with concomitant lovastatin + immunosuppressive drugs; decreased metabolism in renal failure
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (lovastatin)	Elevation of transaminase levels; myositis; sleep disturbances	Cyclosporine may increase liver function tests; greatly increased myositis risk with lovastatin + immunosuppressive drugs (cyclosporine)

criterion, 22% of the patients in our natural history series would be considered eligible for pharmacologic intervention. In addition to the high frequency of LDL cholesterol elevation among our patients (64% had LDL cholesterol ≥130 mg/dl at 6 months), we noted a high incidence of elevated triglyceride levels (41% had triglyceride values ≥200 mg/dl at 6 months).

Deciding whether to apply the National Cholesterol Education Program guidelines to heart transplant recipients hinges on whether the benefits of lowering lipids are greater than the toxicity of treatment. The role of hyperlipidemia in the development of accelerated coronary artery disease remains controversial (9,23–26). The diffuse intimal proliferation that occurs after heart transplantation is pathologically unique and is believed to be an immunologically mediated form of chronic rejection. Although lipoproteins probably do not play a primary role in the development of this disorder, both clinical and animal studies (9,25,26) suggest that hyperlipoproteinemia may accelerate the process. Prospective clinical trials to examine whether the treatment of hyperlipidemia will indeed slow the process of posttransplantation intimal proliferation have not been performed.

Dietary modification is the safest form of treatment for hyperlipidemia. All the patients in our series received dietary counseling to follow the American Heart Association Step One Diet. Dietary intervention has been shown to have beneficial effects on blood lipid levels after renal transplantation (27–30), but the reductions have been modest and many of the patients have had persistent elevations of LDL cholesterol and triglycerides. This was also the characteristic pattern in our heart transplant recipients. Because both thiazide diuretics and nonselective beta-adrenergic blockers may elevate lipid values, we avoid prescribing these agents as antihypertensive therapy after heart transplantation. Discontinuing prednisone or reducing its dose may also ameliorate hyperlipidemia (17–19), but with the possibility of increasing the risk of allograft rejection. Therefore, despite dietary intervention and optimization of medical management, many patients will still have elevated cholesterol or triglyceride levels and require pharmacologic intervention.

Drug Treatment of Hyperlipidemia After Heart Transplantation

The potential side effects and drug interactions of lipid-lowering agents must be weighed carefully in the setting of heart transplantation (Table 3).

Bile acid sequestrants (cholestyramine and colestipol in the U.S.). These are considered first-line drugs for treatment of elevated cholesterol by the National Cholesterol Education Program Expert Panel (1) because they have been shown to reduce the incidence of coronary artery disease end points with a low incidence of toxicity. In addition to causing constipation, bile acid resins may interfere with the absorption of lipid-soluble drugs such as cyclosporine. Keogh et al. (31) used cholestyramine in five patients after heart transplantation and achieved a modest (14%) reduction in total cholesterol. Pharmacokinetic studies measuring the area under the whole blood cyclosporine concentration time curve in this study showed variable results, from a 23% decrease to a 55% increase from baseline. Bile acid-binding resins may raise triglyceride levels, which frequently are already elevated after heart transplantation. Because of the potential adverse effects on the absorption of immunosuppressive drugs and on triglyceride metabolism, we do not use bile acid-binding resins as first-choice monotherapy after cardiac transplantation. However, in reduced doses and given either 1 h after or 4 h before the administration of other medications, these agents may be useful in combination with other lipid-lowering drugs.

Nicotinic acid. This agent is also considered a first-line drug for the treatment of high cholesterol by the National Cholesterol Education Program because of documented benefit on coronary artery disease reduction and an acceptable rate of side effects. Nicotinic acid has the advantage of beneficial effects in the mixed hyperlipidemia pattern that is frequently seen after heart transplantation. Unfortunately, nicotinic acid entails numerous side effects potentially exacerbated by immunosuppressive therapy. Both nicotinic acid and cyclosporine can lead to increased values in liver function tests and elevations of uric acid levels (32,33). Both

nicotinic acid and prednisone are associated with abnormalities of glucose tolerance and exacerbation of peptic ulcer disease. Because of the potential increase in side effects in heart transplant recipients, we believe that nicotinic acid may not be a first-line agent and should be used with caution in these patients.

Gemfibrozil, a fibric acid derivative. This is another drug that has been shown to reduce the incidence of coronary artery disease end points (34). Fibric acid derivatives reduce triglyceride levels, with more modest effects on LDL cholesterol. We have used gemfibrozil as a single hypolipidemic agent in a small series of heart transplant patients and achieved marked reductions in triglycerides and more modest reductions in total and LDL cholesterol levels (data not shown). The drug is well tolerated in transplant patients and has not been noted to interfere with immunosuppressive therapy. Fibric acid derivatives have been associated with an increased risk of gallstones, a finding of particular concern because of the high incidence of cholelithiasis requiring cholecystectomy among transplant recipients (35). In addition, the modest LDL cholesterol-reducing effects of gemfibrozil limit its utility for treating severe hypercholesterolemia after heart transplantation.

Probucol. This agent causes a modest reduction in total and LDL cholesterol values, but it has not been proved to be effective in reducing coronary artery disease end points in clinical trials. When used by Anderson and Schroeder (36) in heart transplant recipients, probucol was well tolerated and yielded a 15% reduction in both LDL and HDL cholesterol values but no significant change in the ratio of LDL to HDL cholesterol. The investigators noted no adverse clinical or laboratory effects or interference with immunosuppressive therapy. Probucol is unique among available lipid-lowering agents in that it inhibits the oxidation of LDL particles. Although this action theoretically can decrease LDL uptake in the arterial wall, there are no published clinical trials to confirm the benefit. We do not consider probucol to be first-line therapy, primarily because of its modest effects on lipids.

Lovastatin. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors as monotherapy have not yet been shown to reduce the incidence of coronary artery disease end points. In clinical studies (37–40), lovastatin therapy has resulted in marked reductions in LDL cholesterol, ranging from 24% to 40%, as well as reductions in triglycerides and increases in HDL cholesterol. Its major side effects are dose dependent, including low rates of myositis (0.5%) and serum transaminase elevation (1.5%) at the highest dose of 80 mg/day (37).

As reported here, we initially used up to 80 mg/day of lovastatin. At these high doses, our heart transplant recipients, who were receiving cyclosporine and prednisone, had an unacceptable incidence of myositis, as has been the experience of other groups (41,42). The increased toxicity in transplant recipients may be explained by a marked increase in plasma 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitory activity, an effect noted in our two patients in whom inhibitory levels were measured after the occurrence of rhabdomyolysis. Although reduction of the daily dose to 20 mg reduced the enzyme inhibitory levels in these two patients, the values were still greater than those that would be expected in control subjects receiving the same dose of drug. Similar findings were reported by Kobashigawa et al. (43).

Our treatment of 15 patients with a single daily 20-mg dose of lovastatin resulted in a 21% reduction in total cholesterol and a 31% reduction in LDL cholesterol. These reductions are similar to those seen by others (42,43) using low dose lovastatin after heart transplantation. Lovastatin at 20 mg/day was well tolerated by our patients, without significant change in the mean level of cyclosporine in the blood or in the doses given of cyclosporine, prednisone or azathioprine. The medication was discontinued in only 1 of the 15 patients. Our patients did not have the significant increase in white blood cell count noted by Kasiske et al. (44) in their lovastatin-treated kidney transplant recipients, but the count did increase by 14% (from 6,400 ± 600 cells/mm^3 at baseline to 7,300 ± 500 cells/mm^3 with lovastatin, p = NS).

Recommendations. Lovastatin at a dose of 20 mg/day is a well tolerated and effective treatment for hypercholesterolemia after heart transplantation. The dose should not exceed 20 mg/day—even if the desired level of LDL cholesterol is not reached—because of increased drug toxicity in heart transplant recipients. Combining lovastatin with gemfibrozil or nicotinic acid should be avoided because this approach is associated with enhanced toxicity.

Because of the increased toxicity of lipid-lowering drugs in heart transplant recipients and the uncertain role of lipids in the development of accelerated coronary artery disease in the allograft, we believe that the National Cholesterol Education Program treatment guidelines are not entirely appropriate for the heart transplant recipient with regard to drug selection and treatment goals. Lovastatin in a low dose (≤20 mg/day), with careful patient instruction and follow-up, appears to be more effective and potentially safer than high dose cholestyramine or nicotinic acid for treatment of elevated LDL cholesterol in these patients. Gemfibrozil is a well tolerated and effective option for treatment of hypertriglyceridemia in these patients. The National Cholesterol Education Program goal of an LDL cholesterol level <130 mg/dl may be difficult to achieve with monotherapy, and the data are insufficient to warrant aggressive combination therapy to reach this goal. Prospective clinical trials are needed to examine whether appropriate treatment of hyperlipidemia after heart transplantation can slow the development of accelerated coronary artery disease in the allograft.

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