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Effect of fluvastatin on acute renal allograft rejection: A randomized multicenter trial

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Background. Statin therapy has been reported to reduce the acute rejection rate following renal transplantation in a pilot study. The present study is the first randomized, double-blind and adequately powered study to examine the effect of statins on acute rejection of renal allografts.

Methods. A total of 364 patients were randomly assigned to receive either fluvastatin 40 mg or placebo in combination with conventional cyclosporine-based immunosuppressive therapy. The primary end point was treated first acute rejection. Secondary end points included biopsy-proven rejection, histological severity of rejection, occurrence of steroid-resistant rejection, and serum creatinine at three months following transplantation.

Results. Fluvastatin was well tolerated; no patients developed myositis or rhabdomyolysis. There was no difference in the acute rejection rate [86 (47.3%) fluvastatin vs. 87 (47.8%) placebo] and no significant difference in the severity of rejection, steroid resistant rejection or mean serum creatinine at three months (160 μmol/L vs. 160 μmol/L). Total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and triglyceride levels increased following renal transplantation. With the exception of the increase in HDL-C, which was augmented, the increases in lipid parameters were significantly reduced by fluvastatin (total cholesterol +17.5% vs. 35.7%; LDL-C +6.3% vs. 46.7%; HDL-C +43.3% vs. 38.1%; triglyceride +52.2% vs 77.6%).

Conclusions. Contrary to the reported effects of statins, fluvastatin had no effect on the incidence or severity of acute rejection following renal transplantation. There were no increases in adverse events. A significant and potentially beneficial alteration in the lipid profile was observed in the early post transplant period. We conclude that fluvastatin may be used safely to correct dyslipidemia in patients with end-stage renal failure through the peri-transplant period.

Key words: kidney transplantation, acute rejection, HMG CoA reductase inhibition, dyslipidemia, end-stage renal failure, cyclosporine A.

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HMG–CoA (3,hydroxy, 3-methylglutaryl coenzyme A) reductase inhibitor (statin) therapy is of proven benefit in reducing cardiovascular morbidity and mortality in patients with or without coronary disease (CVD) [1–6]. However, there is some evidence that certain effects of these drugs, including beneficial effects in patients with osteoporosis [7–10], are independent of cholesterol reduction and may be due to the reduced synthesis of other isoprenoid products of the mevalonate pathway [7, 8]. The putative potential effects on osteoporosis, however, have recently been challenged [11]. Four pilot studies have examined the effects of statin treatment in solid organ transplant populations. In kidney recipients a significant reduction in the rejection rate was observed [12]. Two studies in heart transplant recipients have reported conflicting results. Wencke et al could not demonstrate any significant effect on rejection rates in a four-year follow-up study [13]. In the study of Kobashigawa et al, an effect was only evident for severe rejections with hemodynamic compromise, whereas statin treatment had no effect on mild or moderate rejection episodes [14]. Recently a multicenter placebo-controlled study, including simvastatin in one arm, failed to demonstrate any effect of simvastatin on acute renal allograft rejec-

tion (Kasiske et al, *Transplantation* 69:S225, 2000). Studies in experimental animals also have shown prolongation of islet and cardiac allograft survival associated with statin treatment [15, 16]. The explanation for these observations has focused on the effects of statins on the function of leukocytes and the observation that inhibition of the production of specific isoprenoids—farnesyl and geranylgeranyl—might inhibit proliferation of T lymphocytes and natural killer (NK) cells in vitro [7, 17–20]. Recently, it has been demonstrated that statins might inhibit the inducible expression of the class II major histocompatibility complex and thus repress activation of T cells in the immune response [21]. Preliminary findings in human transplant recipients suggest that statins may also reduce NK cell function in vivo [12, 14, 15]. Taken together, while these studies suggest a potential mechanism for statin-mediated immunosuppression, in the absence of adequately powered studies, it remains uncertain whether this effect is of any clinical relevance.

Hyperlipidemia is common in renal transplant recipients (RTR), with levels of cholesterol and triglyceride increasing in the early post-transplant period, and is likely to contribute to increased cardiovascular risk [22, 23, 24]. Thus, there is considerable interest in the use of statins in this population. Fluvastatin has potential benefits in the treatment of hyperlipidemia in organ transplantation [25, 26, 27] and it does not share a metabolic pathway with the calcineurin inhibitors cyclosporine and tacrolimus. Inhibition of the microsomal enzyme cytochrome P450 3A4 (CyP 3A4) by these immunosuppressive agents inhibits the metabolism of statins. The increase in fluvastatin concentration by calcineurin inhibitors is therefore less than that observed with other statins. Thus, the present study was designed to assess the effects of administration of fluvastatin on acute rejection in RTR receiving cyclosporine-based immunosuppressive regimes.

METHODS

Patients

This study was an international, multicenter, randomized, double-blind, placebo controlled trial of fluvastatin 40 mg daily or matched placebo in RTR. All patients aged 18 years or older, receiving cadaveric or living related renal allografts, were eligible. Multiorgan transplant recipients were excluded, but patients receiving a second or subsequent renal allograft were eligible for inclusion. The protocol also excluded patients with malignant disease, serological evidence of HIV or HbsAg, systemic infection, pregnancy, or those using inadequate contraceptive measures. All patients received cyclosporine-based immunosuppressive regimes, including prednisolone with, or without, azathioprine. There were no stipulations on the dosages of immunosuppressive agents used. The use of antibody therapy, mycophenolate or tacrolimus was precluded at the outset, although subsequent changes in therapy for clinical indications, such as acute rejection, were at the discretion of the investigating physician. The protocol was approved by the national and local ethical committees in the participating centers in Norway, Sweden, Finland, United Kingdom and Ireland. The study was carried out according to the Declaration of Helsinki. All patients gave written informed consent to participate, and were recruited prior to, or within 48 hours of transplantation surgery.

Study design

Fluvastatin, 40 mg per day (or placebo), was administered in a double-blind fashion for twelve weeks following transplantation. Blood samples were taken for fasting lipids, serum creatinine and full blood count at recruitment and 2, 6 and 12 weeks after commencement of therapy. A central laboratory (Medinet, Breda, The Netherlands) was assigned to analyze all serum lipids and selective biochemical parameters.

The primary end point was treated acute rejection, defined as a clinically suspected acute rejection episode, during which the patient completed a course of high-dose steroids according to the local protocol. There were no stipulations on the treatment either for subsequent rejection episodes, or for changes in immunosuppressive therapy deemed appropriate following the first acute rejection episode. The study protocol required biopsy confirmation where possible. All biopsies were scored by an experienced renal histopathologist according to the Banff criteria [28]. In addition to the primary end point, secondary end points were studied. These included biopsy-proven rejection, histological severity of rejection, the number of steroid resistant rejection episodes, graft loss, serum creatinine at three months, absolute lipid levels, and lipid sub-fractions. Sequentially numbered sets of study medication were made available to each clinical site. Each medication pack was labeled with a study identification code and randomization number. Randomization was stratified by center and blocked pseudorandomization was performed by the producer centrally (Switzerland). The block size was eight patients. Following randomization, patients were assigned a unique patient identifier consisting of a center number and a patient number. Center numbers were assigned centrally and patient numbers by the investigator. Patients received medication according to randomization number: patients with a cadaveric donor graft were assigned the next available randomization number starting from the beginning, patients with a living donor graft were assigned the next available number starting from the end of the list of available randomized numbers. All study personnel directly involved in the conduct of the study were blinded to treatment until all patients had completed the study

and all data were finalized. Randomization was centrally performed using a validated system that automates the random assignment of treatment groups to randomization numbers. Randomization data were kept strictly confidential, accessible only to authorized persons, until the time of unblinding.

Statistical analysis

The planned sample size was based on the assumption that fluvastatin would reduce the incidence of first-treated rejection episodes by 30%, from 45% in the placebo group to 31.5% in the fluvastatin-treated group. Four-hundred-and-four patients were required without adjustments for drop outs, with 5% alpha level and power = 80%. Due to administrative reasons, the trial was stopped when 364 randomized and evaluable patients were completed. With this number we could detect a 31.5% relative reduction in incidence, still with 80% power. The primary efficacy analyses were based on intention-to-treat for all variables. All patients who received at least one dose of study medication were included. Per protocol analyses also were performed for those patients who completed the trial on study medication. Descriptive statistics are given as mean (SD) for continuous variables and number of cases (%) for the categorized variables. The Chi-square or Fisher exact tests were used to compare such variables between the two treatment groups. The Cochran-Mantel-Haenzel test was used to compare categorical variables.

The primary end point comparison was a pre-planned test for the difference between the Kaplan-Meier estimates of not having a primary event within three months in the two treatment groups. Comparison of changes in the lipid values between baseline and three-month visits was done by calculating the mean of individual absolute and percentage differences with confidence limits.

RESULTS

Study population

A total of 364 patients (260 males) were recruited between January 1998 and June 1999 in 11 centers in four European countries (147 UK, 97 Norway, 68 Sweden, 40 Finland, 12 Ireland). Eighty-seven patients received living donor transplants and 277 cadaveric transplants. Demographic data are shown in Table 1. The mean age was 48.4 (14.1) years, 92.6% of patients were of Caucasian origin and 12% had diabetes. The mean time on renal replacement therapy was around three years, and 8% of patients had previously received a renal transplant. There was no difference in any of these parameters between the two groups. The pattern of primary renal disease, cytomegalovirus (CMV) status, donor age, cold ischaemia and cross-match information also was similar (Table 1).

Eighty-three percent of the patients who commenced the study completed the full protocol, with no difference between groups. The reasons for withdrawal, including seven deaths, are outlined in Table 2, and did not differ between groups.

Efficacy analysis

Acute rejection. In the intention-to-treat analysis, 86 (47.3%) patients had a treated acute rejection episode compared with 87 (47.8%) in the placebo group (P = 0.92; Table 3). There was no difference in the mean time to first acute rejection [19 (17) vs. 18 (12) days]. The first rejection episode was biopsy-confirmed in 70 and 75 patients, respectively, and was deemed steroid resistant (necessitating change to, or addition of, second-line immunosuppression) in 38 (20.9%) patients in the fluvastatin group and 34 (18.7%) in the placebo group (P = 0.44). Eighteen patients (9.9%) in the fluvastatin group, and 19 (10.4%) in the placebo group (P = 0.86) experienced a second acute rejection episode. The corresponding numbers of graft losses (including death with a functioning graft) were 12 and 7, respectively (P = 0.33). The spectrum of histological severity is shown in Table 3. There was a trend towards a smaller number of biopsies with mild rejection in the fluvastatin group, although this failed to achieve statistical significance (P = 0.09). Finally, there was no difference in graft function at three months following transplantation. The serum creatinine was 160 ± 62 μmol/L in the fluvastatin group and 160 ± 83 μmol/L in the placebo group, in those patients whose grafts continued to function at this time point.

Lipid levels. It is well established that levels of total cholesterol TC, low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) rise following transplantation as a result of immunosuppressive therapy and altered diet [22–24]. Thus, the effects of statins must be viewed against the changing background. The absolute levels of TC, LDL-C, triglycerides (TG) and HDL-C are shown in Table 4, and the mean values for LDL-cholesterol throughout the study period in Figure 1. There was a 17.5 (11.5 to 23.4)% increase (mean, 95% confidence interval) in total cholesterol in the fluvastatin group, compared with 35.7 (28.7 to 42.8)% increase in the controls. The final total cholesterol at 12 weeks was 10.0% lower in the active treatment group. LDL-C showed a similar pattern. There was a 6.3 (−0.09, 12.7)% increase in the fluvastatin group and a 46.7 (29.0, 64.5)% increase in the placebo group with the final LDL-C being 18.2 lower in the active treatment group. HDL-C also increased following transplantation; the increase in the treatment group was 43.3 (34.8 to 51.9)% versus 38.1 (29.6 to 46.6)% in the control group. At 12 weeks the HDL-C was 6.1% higher in the active treatment group. Triglyceride levels were higher following transplantation with a trend towards a smaller increase

Table 1. Demographic details by treatment group

Demographic variable	Fluvastatin	Placebo	Total	*P* value
N	182	182	364	
Age *years*	49.1 (13.5)	47.7 (14.8)	48.4 (14.1)	0.366
Sex				1.000
Male	130 (71.4%)	130 (71.4%)	260 (71.4%)	
Female	52 (28.6%)	52 (28.6%)	104 (28.6%)	
Race				0.548
Caucasian	167 (91.8%)	170 (93.4%)	337 (92.6%)	
Black	5 (2.7%)	6 (3.3%)	11 (3.0%)	
Asian/Oriental	5 (2.7%)	2 (1.1%)	7 (1.9%)	
Other	5 (2.7%)	4 (2.2%)	9 (2.5%)	
Weight *kg*	74.7 (13.6)	73.6 (14.3)	74.1 (14.0)	0.458
Primary cause of end-stage renal failure				
Glomerulonephritis	46 (25.3%)	60 (33.0%)	106 (29.1%)	
Chronic pyelonephritis	7 (3.8%)	7 (3.8%)	14 (3.8%)	
Reflux/obstructive nephropathy	7 (3.8%)	11 (6.0%)	18 (4.9%)	
Polycystic disease	35 (19.2%)	28 (15.4%)	63 (17.3%)	
Hypertensive nephrosclerosis	23 (12.6%)	13 (7.1%)	36 (9.9%)	
Diabetic nephropathy	18 (9.9%)	18 (9.9%)	36 (9.9%)	
Other	46 (25.2%)	43 (23.5%)	89 (24.4%)	
Total time on renal replacement therapy *days*	786 (881)	1018 (1609)	905 (1310)	
Previous renal transplant	12 (6.6%)	17 (9.3%)	29 (8.0%)	
Diabetes	20 (11.0%)	25 (13.7%)	45 (12.4%)	
Donor age *years*	44.5 (15.8)	45.9 (15.0)	45.2 (15.4)	0.647
Donor recipient cytomegalovirus status				
Positive Positive	83 (45.6%)	77 (42.3%)	160 (44.0%)	0.314
Positive Negative	30 (16.5%)	36 (19.8%)	66 (18.1%)	
Negative Positive	43 (23.6%)	33 (18.1%)	76 (20.9%)	
Negative Negative	23 (12.6%)	32 (17.6%)	55 (15.1%)	
Donor recipients HLA-DR mismatches				0.594
0	59 (32.4%)	59 (32.4%)	118 (32.4)	
1	96 (52.7%)	97 (53.3%)	193 (53.0%)	
2	25 (13.7%)	18 (9.9%)	43 (11.8%)	
Status of panel reactive antibodies				0.624
Positive	21 (11.5%)	18 (9.9%)	39 (10.7%)	
Negative	161 (88.5%)	163 (89.6%)	324 (89.0%)	
Donor specific B-cell crossmatch (Fisher test)				0.214
Positive	5 (2.7%)	1 (0.5%)	6 (1.6%)	
Negative	157 (86.3%)	160 (87.9%)	317 (87.1%)	
Donor specific T-cell crossmatch (Fisher test)				1.000
Positive	2 (1.1%)	1 (0.5%)	3 (0.8%)	
Negative	180 (98.9%)	180 (98.9%)	360 (98.9%)	
Cold ischemia time *hours*	18.9 (6.2)	20.2 (7.0)	19.5 (6.6)	0.170

Data are shown as number (% total). Continuous variable data are shown as mean (SD). See text for details.

Table 2. Patient disposition

	Fluvastatin	Placebo
Intent-to-treat	182 (100%)	182 (100%)
Completed	151 (83.0%)	150 (82.4%)
Discontinued	30 (16.5%)	32 (17.6%)
Death	5 (2.7%)	2 (1.1%)
Adverse event	5 (2.7%)	6 (3.3%)
Withdrawn consent	3 (1.6%)	7 (3.8%)
Failure to return for scheduled visits	1 (0.5%)	0 (0.0%)
Other	16 (8.8%)	16 (8.8%)

in the fluvastatin group. The increase was 52.2 (37.0 to 67.4)% in the active group compared with 77.6 (57.7 to 97.5)%, the levels at 12 weeks being 8.5% lower in the active treatment group.

Adverse events. There was a high incidence of adverse events in both groups consistent with the expected clinical course in the early post-transplant period (Table 5).

Table 3. End points by treatment group

End point	Fluvastatin (*N* = 182)	Placebo (*N* = 182)	*P* value
First treated rejection	86 (47.3%)	87 (47.8%)	0.916
Time to first treated rejection *days*	19.0 (17.2)	17.8 (12.1)	0.556
First steroid-resistant rejection	38 (20.9%)	34 (18.7%)	0.442
First biopsy-confirmed rejection	70 (38.5%)	75 (41.2%)	0.579
Second rejection episode	18 (9.9%)	19 (10.4%)	0.861
Graft loss or death	12 (6.6%)	7 (3.8%)	0.220
Biopsy-confirmed rejection, graft loss or death	77 (42.3%)	80 (44.0%)	0.741
Severity of rejection (BANFF)			0.091
Mild (I)	26 (14.3%)	42 (23.1%)	
Moderate (II)	36 (19.8%)	27 (14.8%)	
Severe (III)	8 (4.4%)	6 (3.3%)	
Serum creatinine at week 12	159.6 (62.2)	160.2 (83.0)	0.947

Data are shown as number (% total). Continuous variable data are shown as mean (SD).

Table 4. Lipid effects by treatment group

Parameter	Baseline		12 weeks		Difference Fluvastatin − Placebo	Difference % Fluvastatin − Placebo
	Fluvastatin	Placebo	Fluvastatin	Placebo		
TC *mmol/L*	4.77 ± 0.10	4.74 ± 0.11	5.47 ± 0.11	6.08 ± 0.11	−0.73 (−1.08, −0.37) $P < 0.001$	−18.3 (−27.4, −9.11) $P < 0.001$
LDL-C *mmol/L*	2.99 ± 0.08	2.96 ± 0.09	3.06 ± 0.08	3.74 ± 0.10	−0.84 (−1.12, −0.56) $P < 0.001$	−40.5 (−59.0, −21.9) $P < 0.001$
HDL-C *mmol/L*	1.02 ± 0.03	1.02 ± 0.04	1.40 ± 0.04	1.32 ± 0.03	0.08 (−0.03, 0.19) $P = NS$	5.23 (−6.75, 17.2) $P = NS$
TG *mmol/L*	1.68 ± 0.08	1.55 ± 0.07	2.04 ± 0.09	2.24 ± 0.09	−0.30 (−0.57, −0.02) $P = 0.034$	−25.4 (−50.2, −0.53) $P = 0.046$

Abbreviations are: TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides.

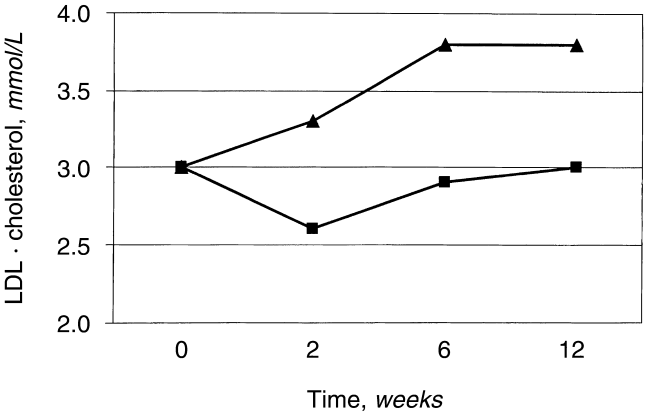

Fig. 1. Low-density lipoprotein-cholesterol (LDL-C) at 0, 2, 6 and 12 weeks. Symbols are (■) fluvastatin group; (▲) control group. Data are shown as mean values. Significant differences ($P < 0.001$) between the groups from week 2.

There were no differences between treatment groups and, specifically, there were no episodes of rhabdomyolysis. There were 16 reports of an elevation of creatinine kinase (CK) levels to more than five times the upper limit of normal, nine in the fluvastatin and seven in the placebo group, respectively. There were also 31 reported increases in transaminase levels to more than three times the upper limit of normal, 11 of which were in the fluvastatin group. These biochemical abnormalities required cessation of therapy in some cases. However, the number of discontinuations due to drug-related side effects was similar in both groups.

Basal immunosuppression. There were no differences between groups for cyclosporine A (CsA), prednisolone or azathioprine dose throughout the study (Table 6).

Blood pressure. Blood pressure values were similar in both groups. At 12 weeks the mean systolic blood pressure was 145 ± 18 versus 146 ± 19 mm Hg (fluvastatin vs. placebo, $P = 0.33$) and the diastolic blood pressure showed a similar pattern (85 ± 11 vs. 86 ± 13 mm Hg). Mean weight also showed no difference between groups, 76.0 ± 11.5 vs. 74 ± 12.9 kg at 12 weeks.

Table 5. Adverse events by treatment group

Event	Fluvastatin ($N = 182$)	Placebo ($N = 182$)
Any adverse events	165 (90.7%)	156 (85.7%)
Any infections	95 (52.2%)	93 (51.1%)
Any drug-related adverse events	19 (10.4%)	21 (11.5%)
Any drug-related infections		1 (0.5%)
Any serious adverse events	43 (23.6%)	45 (24.7%)
Any serious infections	11 (6.0%)	10 (5.5%)

Data are shown as number (% total).

DISCUSSION

This is the first study of adequate power to address whether statin therapy is associated with a reduced acute rejection rate following solid organ transplantation. The results demonstrate that whilst fluvastatin 40 mg per day is effective in reducing total cholesterol and LDL-C, the drug has no effect on the acute rejection rate, severity of rejection or graft function during the first three months after renal transplantation.

The study design was based on the results of two studies in heart [13, 14] and one pilot study in renal [12] transplant recipients. The renal study showed a marked reduction (57%) in rejection episodes [12]. Of the two heart transplant studies, one showed no significant effect on rejection rates [13], and the other only an effect on severe, but not mild-to-moderate rejection episodes or the overall rejection rate [14]. While the results of the two studies indicating an effect suggest that statins may have a role in preventing acute rejection in solid organ transplantation [12, 14], the studies were small and only one was designed to assess rejection rates [12]. Indeed, none of the studies were adequately powered to detect a significant reduction in this end point. There are number of possible explanations for the discrepancy between the result of our study and those previously published. First, the published studies may be spuriously positive due to small sample size and the differences reported may reflect other aspects of the study design or patient population. Second, the dose of fluvastatin used may not be comparable to the doses of pravastatin used in

Table 6. Basal immunosuppression

	Baseline		Week 2		Week 6		Week 12	
	F	P	F	P	F	P	F	P
CsA *mg/day*	464 ± 192	475 ± 197	437 ± 185	426 ± 167	292 ± 161	304 ± 148	244 ± 131	243 ± 113
Prednisolone *mg/day*	36 ± 41	33 ± 37	20 ± 13	20 ± 18	17 ± 6	18 ± 16	12 ± 5	12 ± 5
Azathioprine *mg/day*	116 ± 62	114 ± 57	81 ± 51	82 ± 45	64 ± 51	71 ± 49	65 ± 48	67 ± 49

Abbreviations are: CsA, cyclosporine A; F, fluvastatin; P, placebo.

previous studies. Finally, it is clearly possible that immunosuppressive actions are not common to all statins (fluvastatin, simvastatin), but specific to certain drugs of that class (pravastatin).

Study size and design

The single-center report by Katznelson et al in 48 renal transplant patients, half were randomized to pravastatin 20 mg treatment [12]. The study did not have adequate statistical power to detect a reduction in rejection episodes, and the very high rejection rate in the placebo group (58%) suggests that this was not a representative study population. In contrast, the acute rejection rate in our study is similar to that reported in other studies using conventional cyclosporine-based double or triple therapy. Moreover, although the number of rejection episodes (6 vs. 14) was significant at a 5% level in the study of Katznelson et al [12], had a single additional rejection episode occurred in the active treatment group (7 vs. 13) the findings would not have achieved statistical significance. Thus, the failure of our present study, which has greater statistical power to detect a reduction in acute rejection rates, to confirm the earlier report in kidney transplant recipients is likely to reflect the small size in the previous report.

The reported study of cardiac transplant recipients demonstrating a significant reduction in rejections included fewer than 100 patients [14]. The improvement in rejection in this study was confined to severe, or hemodynamically significant, rejection episodes with no effect on mild, moderate or focal moderate rejection episodes. Furthermore, it was designed to study regression of accelerated graft vascular disease (GVD) and not the incidence of rejection episodes. However, the authors demonstrated a significant reduction in intimal proliferation in the statin treatment group in accordance with the study of Wenke et al [13]. Cardiac allograft rejection is more likely to have hemodynamic sequelae in the presence of severe GVD and thus, the non-immunological effects of statins on GVD, rather than any immunosuppressive effects may offer an explanation for the effects on rejection severity and patient survival.

Statin type and dosage

The choice of statin and dose equivalence may offer alternative explanations for the discrepancy between the present and previous studies [12–14]. Although cyclosporine interacts with the metabolism of fluvastatin, the area under the curve for fluvastatin is increased only about twofold during cyclosporine therapy [26]. In contrast, concomitant cyclosporine increases the area under the curve several-fold for other statins [27]. The results of this study confirm the predicted beneficial effects on the lipid profile in the post-transplant period. However, these data are difficult to compare with outcome studies of statin therapy in the general population because of the pattern of increasing levels of total cholesterol, LDL-C, and HDL-C and triglycerides that follow transplantation. The key findings, based on the intention-to-treat analysis, show that LDL-C was 40.5% lower in the fluvastatin group, compared with 26.3% [13] and 26.4% [14] in the studies in cardiac transplantation and 27.8% in the pilot study in renal transplant recipients [12] in which beneficial effects on acute rejection were reported. The comparison with other published studies is limited by the fact that previous studies reported the time-averaged lipid levels during the follow-up period and these are likely to decrease with reduction in immunosuppressive therapy beyond three months, Thus, overall, fluvastatin appears to have had a similar effect on LDL-C to that observed in the other studies and the achieved level of mean LDL-C of around 3.1 mmol/L was similar to that reported in the previous studies (2.8 to 3.0 mmol/L; [12–14]). Other lipid parameters also were modified by active treatment. HDL-C was 5.2% higher, total cholesterol was 18.3% lower and triglyceride 25.4% lower in the fluvastatin group at three months post-transplant. Moreover, the efficacy of fluvastatin in the present study is diluted by the patients who failed to take therapy for the three-month follow-up period (Table 2). The achieved levels of TC, HDL-C and TG show a similar pattern in comparison with other studies and are slightly less than those reported for this dose of fluvastatin in carefully controlled single-center studies in stable renal transplant recipients [25, 27]. Thus, it seems unlikely a higher dose would have unmasked a significant effect on rejection when none was apparent in the presence of a significant benefit on plasma lipids.

Is immunosuppression unique to other statins?

In vitro and in vivo studies have shown a variety of effects of statins that appear to be mediated by interme-

diates in the mevalonate pathway including the isoprenoids, farnesyl and geranylgeranyl. These effects include inhibition of proliferation of vascular smooth muscle cells [7, 8, 29] and T lymphocytes [18–21] and are similar between the individual statins. The reported observation that pravastatin reduces rejection is consistent with the in vitro effects of this drug on immune effector cells. However, both simvastatin and fluvastatin exert an immunomodulatory effect in vitro [27], implying that they should also have similar actions in vivo. It follows that fluvastatin and simvastatin would be expected to have an effect on transplant rejection, should such an effect genuinely exist. An alternative explanation for the immunosuppressive effects of statins is that an increase in free levels of CsA (a consequence of reduced levels of LDL-C, to which CsA is bound in the circulation) may enhance the immunosuppressive effects of immunosuppressive agents [30]. However, the levels of both CsA and LDL-C in the present study are similar to previous reports making this an unlikely explanation for differences in acute rejection rates.

Conclusion

This study demonstrates that fluvastatin does not reduce the acute rejection rates in renal transplant patients. This finding is at variance with a previous published pilot study [12], but is consistent with the lack of an effect in mild-to-moderate rejection rates in one short-term [14] and one long-term study in heart transplant recipients [13]. Overall, the absence of immunosuppressive actions in this study is consistent with the absence of increased infections or malignant complications in any of the large-scale outcome studies of statin therapy [1–5]. In our view, the previous reports on allograft rejection are likely to reflect the influence of GVD on rejection severity in cardiac transplantation [14], and the small size and design of the published renal study [12]. However, the use of statins in transplant recipients is quite common, despite no data from prospective large multi-center studies are available to demonstrate any beneficial effect for acute rejections or long-term cardiovascular protection in this population.

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REFERENCES

1. Sacks FM, Pfeffer MA, Moye LA, *et al*: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 335:1001–1009, 1996
2. Shepherd J, Cobbe SM, Ford I, *et al*: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 333:1301–1307, 1995
3. The Scandinavian Simvastatin Survival Study: (4S). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study Group. *Lancet* 344:1383–1389, 1994
4. Pedersen TR, Wilhelmsen L, Faergeman O, *et al*: Follow-up study of patients randomized in the Scandinavian simvastatin survival study (4S) of cholesterol lowering. *Am J Cardiol* 86:257–262, 2000
5. Downs JR, Clearfield M: Weis S for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS study. *JAMA* 279:1615–1621, 1998
6. White HD, Simes RJ, Anderson NE, *et al*: Pravastatin therapy and the risk of stroke. *N Engl J Med* 343:317–326, 2000
7. Kwaja A, Connolly JO, Hendry BM: Prenylation inhibitors in renal disease. *Lancet* 355:741–744, 2000
8. Massy ZA, Keane WF, Kasiske BL: Inhibition of the mevalonate pathway: Benefits beyond cholesterol reduction? *Lancet* 347:102–103, 1996
9. Wang PS, Solomon DH, Mogun H, Avorn J: HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 283:3211–3216, 2000
10. Chan KA, Andrade SE, Boles M, *et al*: Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 355:2185–2188, 2000
11. Reid IR, Hague W, Emberson J, LIPID Study Goup, *et al*: Effects of pravastatin on frequency of fracture in the LIPID study: Secondary analysis of a randomised controlled trial. *Lancet* 357:509–512, 2001
12. Katznelson S, Wilkinson AH, Kobashigawa JA: The effect of pravastatin on acute rejection after kidney transplantation—A pilot study. *Transplantation* 61:1469–1474, 1996
13. Wenke K, Meiser B, Thiery J, *et al*: Simvastatin reduces graft vessel disease and mortality after heart transplantation: A four-year randomized trial. *Circulation* 96:1398–1402, 1997
14. Kobashigawa JA, Katznelson S, Laks H, *et al*: Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 333:621–627, 1995
15. Katznelson S: Effect of HMG-CoA reductase inhibitors on chronic allograft rejection. *Kidney Int* 56(Suppl 71):S117–S121, 1999
16. Maggard MA, Ke B, Wang T, *et al*: Effects of Pravastatin on chronic rejection of rat cardiac allografts. *Transplantation* 65:149–155, 1998
17. Romano M, Diomede L, Sironi M, *et al*: Inhibition of monocyte chemotactic protein-1 synthesis by statins. *Lab Invest* 80:1095–1100, 2000
18. McPershon R, Tsoukas C, Baines MG: Effects of lovastatin on natural killer cell function and other immunological parameters in man. *J Clin Immunol* 38:513–519, 1993
19. Chakrabarti R, Engleman EG: Interrelationships between mevalonate metabolism and the mitogenic signalling pathway in T lymphocyte proliferation. *J Biol Chem* 266:12216–12220, 1991
20. Cutts JL, Scallen TJ, Watson J, Bankhurst: Role of mevalonic acid in the regulation of natural killer cell cytotoxicity. *J Cell Physiol* 145:550–557, 1989
21. Kwak B, Mulhaupt F, Myit S, Mach F: Statins as a newly recognized type of immunomodulator. *Nat Med* 6:1399–1402, 2000
22. Kasiske BL, Tortorice KL, Heim-Duthoy KL, *et al*: The adverse impact of cyclosporine on serum lipids in renal transplant recipients. *Am J Kidney Dis* 17:700–707, 1991
23. Vathsala A, Weinberg RB, Schoenberg L, *et al*: Lipid abnormalities in cyclosporine-prednisone-treated renal transplant recipients. *Transplantation* 48:37–43, 1989
24. Aakhus S, Dahl K, Widerøe TE: Cardiovascular morbidity and risk factors in renal transplant patients. *Nephrol Dial Transplant* 14:648–654, 1999

25. Holdaas H, Hartmann A, Stenstrøm J, *et al*: Effect of fluvastatin for safely lowering atherogenic lipids in renal transplant patients receiving cyclosporine. *Am J Cardiol* 76:102A–106A, 1995
26. Goldberg R, Roth D: Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 62:1559–1564, 1996
27. Jardine AG, Holdaas H: Fluvastatin in combination with cyclosporin in renal transplant recipients: A review of the clinical and safety experience. *J Clin Pharmacy Ther* 24:397–408, 1999
28. Solez K, Hansen HE, Kornerup HJ, *et al*: Clinical validation and reproducibility of the Banff Schema for renal allograft pathology. *Transplant Proc* 1:1009–1011, 1995
29. Gulanikar AC, MacDonald AS, Sungurtekin U, Belitsky P: The incidence and impact of early rejection episodes on graft outcome in recipients of first cadaver kidney transplants. *Transplantation* 53:323–328, 1992
30. Klaghi F, McLachlan AJ, Keogh AM, Brown KF: Effect of simvastatin on cyclosporine unbound fraction and apparent blood clearance in heart transplant recipiets. *Br J Clin Pharmacol* 44:537–542, 1997