The Efficacy and Tolerability of Ezetimibe in Cardiac Transplant Recipients Taking Cyclosporin

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Background. Despite statin treatment, hyperlipidemia remains problematic after cardiac transplantation and is associated with the development of cardiac allograft vasculopathy. The cholesterol absorption inhibitor ezetimibe may offer a viable option for add on therapy; however, questions have been raised regarding the safety of this during concomitant cyclosporin treatment.

Methods. This is the first placebo controlled, randomized double blinded trial assessing the efficacy and tolerability of ezetimibe in cardiac transplant recipients receiving cyclosporin. Sixty-eight cardiac transplant patients were randomized to receive ezetimibe (10 mg) or matching placebo for 6 months in addition to usual treatments. Fasting blood tests were performed at regular time intervals during the study.

Results. Fifty-nine patients completed the study. At 6 months, ezetimibe had reduced total cholesterol by 18% (5.4±1.1 to 4.4±0.7 mmol/L, $P<0.001$), low-density lipoprotein cholesterol by 26% (3.0±1.0 to 2.1±0.7 mmol/L, $P<0.001$), and triglycerides by 13.5% (2.3±1.3 to 1.8±0.9 mmol/L, $P=0.02$). Tolerability was excellent with no patients experiencing predefined safety endpoints. An equal number of patients withdrew consent from each arm of the study because of perceived side effects. Specific analysis confirmed ezetimibe had no significant effect on cyclosporin levels.

Conclusion. We conclude that ezetimibe is both efficacious and tolerable in cardiac transplant recipients taking cyclosporin. It can be safely considered as add on therapy in patients taking statins (or as monotherapy) to further reduce low-density lipoprotein levels, which may in turn reduce the risk of cardiac allograft vasculopathy.

Keywords: Ezetimibe, Transplantation, Vasculopathy, Hyperlipidaemia.

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Hyperlipidemia remains problematic after cardiac transplantation and can affect the long-term outlook of patients by hastening the development of cardiac allograft vasculopathy (CAV) (*1*). Indeed, over a chronic time setting (>5 years from transplant) CAV represents one of the most commonest causes for death in these patients (*2*). The origin is complex but is thought to be multifactorial and includes both immunological and nonimmunological factors as well as circulating hyperlipidemia (*3*).

Hyperlipidemia may develop in the posttransplant population for several reasons. These include inappropriate diet, restricted physical activity, and most importantly, adverse effects from immunosuppressive therapy, such as cyclosporin and corticosteroids (*4*, *5*). 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), have become a mainstay of treatment for cardiac transplant patients and effectively reduce both low-density lipoproteins (LDL) and total cholesterol (TC). Moreover, they have been observed to reduce both the incidence of CAV (*6*, *7*) and all cause mortality (*7*, *8*). However, the prescribed doses are often restricted given that high dose treatment is associated with a greater risk of adverse events (*9*, *10*). In addition, there is a concern over possible interactions with immunosuppressive drugs (*11*) which could increase the risk of myopathy or rhabdomyolysis (*12*). Consequently, the cholesterol levels of many transplant patients may remain elevated and thereby detrimental to long-term prognosis.

Ezetimibe is a cholesterol absorption inhibitor and has been shown outside the transplant setting to significantly reduce TC and LDL cholesterol, as monotherapy (*13*) or in combination with a statin (*14*). Its safety profile is reportedly favorable with previous (nontransplant) studies revealing no statistical increase of adverse events during phase 3 studies, comparing ezetimibe with placebo (*15*). To date, there have been no randomized placebo controlled trials assessing its efficacy and tolerability in cardiac transplant recipients. There have been two recent open label/observational studies that have attempted to report on the safety and efficacy of

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ezetimibe in cardiac transplant patients (*16*, *17*). However, the respective study designs and small cohort sizes limit the conclusions that can be derived. Furthermore, there have been concerns expressed regarding a possible interaction with cyclosporin (*18*, *19*), which necessitates careful investigation. In this study, we formally assessed the efficacy and tolerability of ezetimibe in cardiac transplant recipients taking concomitant cyclosporin.

METHODS

This trial was registered with the European Clinical Trials Database (EudraCT) under the number 2006-005565-18. Full ethics committee and Medicines and Healthcare products Regulatory Agency approval was obtained before commencement of the study. This was a randomized, placebo controlled investigation using double blinded methods at a single center. Randomization took place by computer. The study medication was provided in individual 6-month packs by Schering Plough, labeled with unique codes that corresponded to sealed envelopes containing the code break. This provided the basis of the double blinding. Statistical powering was incorporated into the study design. This dictated that 68 patients should be recruited, based on a power calculation that assumed a 10% dropout rate (initial sample size calculation of 31 patients in each arm). This was designed to provide a 90% power and 5% significance level to detect a 15% reduction in TC levels and a 15% reduction in LDL levels, assuming a baseline mean (±SD) TC of 5.5±1.0 and a mean (±SD) LDL level of 3.0±0.5 in our transplant population. Follow up was planned for a time of 6 months.

Blood Analysis

Patients underwent routine venepuncture at baseline and at follow-up visits after 1 month, 3 months, and 6 months. Fasting bloods were analyzed at each time interval for TC, LDL, high-density lipoprotein, triglycerides (Trigs), full blood count, urea and electrolytes, liver function tests, creatine kinase (CK), and cyclosporin levels (pretreatment).

Inclusion Criteria

Stable cardiac transplant recipients with concomitant treatment of cyclosporin were recruited from an outpatient setting.

Exclusion Criteria

Derangement of liver function tests (alanine aminotransferase [ALT]>2×upper limit of normal); derangement of muscle enzyme levels (CK levels>2×upper limit of normal); previous intolerance or allergy to ezetimibe; hospital admission or rejection episode within the last 3 months.

Primary Objective

The primary objective of the study was to evaluate the efficacy of ezetimibe in cardiac transplant recipients who were taking cyclosporin. Efficacy was measured by examining the changes (from baseline) of TC and LDL in the peripheral blood, during and at the end of the study period. Patients taking statins were not permitted to change dose during the study, unless clinically required (which would result in their discontinuation).

Secondary Objective

The secondary objective was to assess the tolerability of ezetimibe in cardiac transplant recipients. This was performed by measuring plasma changes in CK, ALT and cyclosporin levels at all intervals throughout the active study period. Changes which defined a secondary endpoint were set as follows: CK>5×the upper limit of normal with symptoms, CK>10×the upper limit of normal with or without symptoms, cyclosporin levels reduced by 50% or increased >2×baseline value, or ALT >3 times upper limit of normal.

Statistics

Analyses were performed on a per protocol basis. Data were assessed for its distribution by means of analysis of skewness and the Kolmogorov Smirnov test. Baseline demographics were assessed for differences using Pearson's chi-squared test for qualitative variable or the independent *t* test for quantitative variables. Changes in analysis parameters (TC, LDL, Trigs, so forth) between the two groups were assessed across the study period using the one-way model of analysis of variance. Analysis between the two groups at specific time points used the independent samples *t* test (for nonparametric data, the Mann-Whitney *U* test was used). *P* values less than 0.05 were considered statistically significant.

RESULTS

A total of 68 patients were recruited into the study of which 34 were randomized to active treatment and 34 to placebo control. The mean age (±SD) of participants was 55±12 years (range 25–78 years) and 83% were men. Mean time (±SD) from transplantation was 7.6±5.6 years (range 0.9–20.1 years) and over 91% were taking concomitant statin treatment (Table 1). Baseline demographics are shown in Table 2. Cyclosporin was administered as cyclosporin A under the trade name of "Neoral." The trough target level for patients was between 100 and 150 μg/L. Secondary immunosuppressants were being used in 52 patients (76%), in the form of mycophenylate sodium, mycophenylate mofetil, or azathioprine. Furthermore, 61 of patients (90%) were receiving prednisolone at an average dose of 6.8 mg daily.

In total, 59 patients completed the study follow-up protocol, with a mean follow-up duration of 169 days.

Efficacy

Patients randomized to ezetimibe treatment had significant reductions in TC as early as the end of the first month (13.4% reduction, 5.4±1.1 to 4.6±0.9 mmol/L [209±43 to 178±35 mg/dL], $P<0.001$). TC reduction was significant across all time assessments and by 6 months (protocol end), ezetimibe had reduced TC by 17.9% (5.4±1.1 to 4.4±0.7 mmol/L [209±43 to 170±19 mg/dL], $P<0.001$, Fig. 1).

Significant reductions in LDL were also seen in the ezetimibe treatment group at all time assessments. By 6 months there was an average reduction in LDL of 26.1%, (3.0±1.0 to 2.1±0.7 mmol/L [116±39 to 81±19 mg/dL], $P<0.001$, Fig. 2). At the same time point, Trigs had been reduced in the ezetimibe group by 13.5% (2.3±1.3 to 1.8±0.9 mmol/L [89±50 to 70±35 mg/dL], $P=0.02$). No significant change in high-density lipoprotein was seen between the two groups ($P=0.86$).

TABLE 1. Statin treatment

Statin type	All patients		Ezetimibe		Placebo	
	Number of patients (%)	Average daily dose	Number of patients (%)	Average daily dose	Number of patients (%)	Average daily dose
Any statin	62 (91.3)	27.6 mg	29 (85.3)	27.3 mg	33 (97.1)	27.9 mg
No statin	6 (8.7)	n/a	5 (14.7)	n/a	1 (2.9)	n/a
Pravastatin	34 (49.3)	27.7 mg	14 (41.2)	25.0 mg	20 (58.8)	29.5 mg
Simvastatin	5 (7.2)	28.0 mg	4 (11.8)	30.0 mg	1(2.9)	40.0 mg
Atorvastatin	18 (26.1)	26.7 mg	7 (20.6)	28.6 mg	11 (32.4)	25.5 mg
Rosuvastatin	1 (1.4)	10.0 mg	0 (0.0)	n/a	1 (2.9)	10.0 mg
Fluvastatin	4 (5.8)	40.0 mg	4 (11.8)	40.0 mg	0 (0.0)	n/a

The distribution of statin treatment (with average doses) in the total patient cohort, ezetimibe group, and placebo group.

TABLE 2. Baseline demographics

Demographics	Overall (n=68)	Placebo (n=34)	Ezetimibe (n=34)	Comparison *P* values
Mean age (yrs)±SD	55±12	57±10	52±14	0.597
Male (%)	84	85	82	0.525
Mean time from transplant (yrs)±SD	7.6±5.6	7.2±5.6	8.1±5.7	0.512
% taking statin at baseline	91.3	97.1	85.3	0.087
Mean TC at baseline (mmol/L)±SD	5.3±1.2	5.4±1.3	5.3±1.1	0.414
Mean LDL at baseline (mmol/L)±SD	2.9±1.1	2.8±1.2	2.9±1.0	0.223
Mean Trigs at baseline (mmol/L)±SD	2.2±1.2	2.1±1.1	2.2±1.3	0.490
Mean HDL at baseline (mmol/L)±SD	1.6±0.5	1.7±0.6	1.5±0.4	0.258
% taking cyclosporin	100	100	100	1.000
Mean baseline trough level of cyclosporin (μg/L)±SD	133±65	130±64	135±65	0.579

Baseline demographics for the patient cohort are shown. Patients were well matched between the active and placebo groups, with no statistical differences for any of the documented parameters.

TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Trigs, triglycerides.

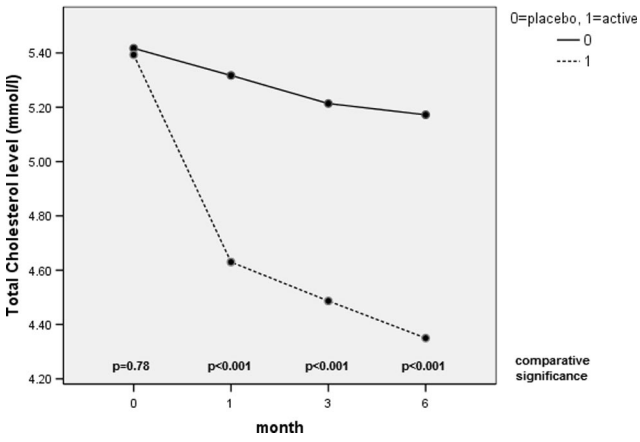

FIGURE 1. Comparisons of the mean total cholesterol level between placebo and active treatment during the follow-up period. A significant reduction in total cholesterol was seen with ezetimibe treatment from 1 month onwards.

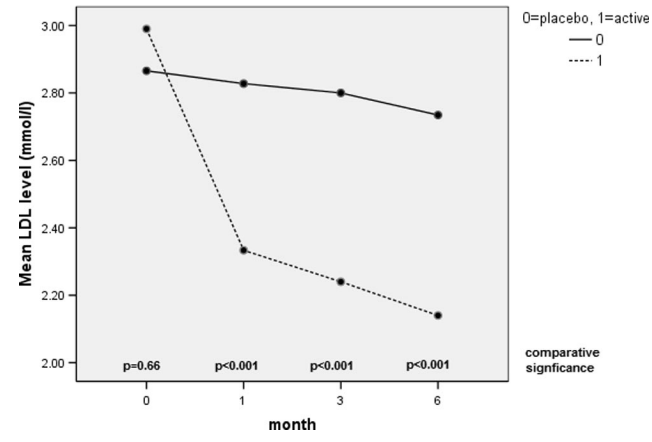

FIGURE 2. Comparisons of the mean low-density lipoprotein level between placebo and active treatment during the follow-up period. A significant reduction in low-density lipoprotein was seen with ezetimibe treatment from 1 month onwards.

Tolerability

In the placebo arm, three patients withdrew consent because of complaints of side effects (nausea and constipation, muscle aching with abdominal cramps, hand cramps, respectively). In the active treatment arm, three patients withdrew consent because of complaints of side effects (abdominal cramps, nausea, neck pain, respectively). One patient died (placebo arm) of noncardiac cause during the trial period and two patients were withdrawn from the study

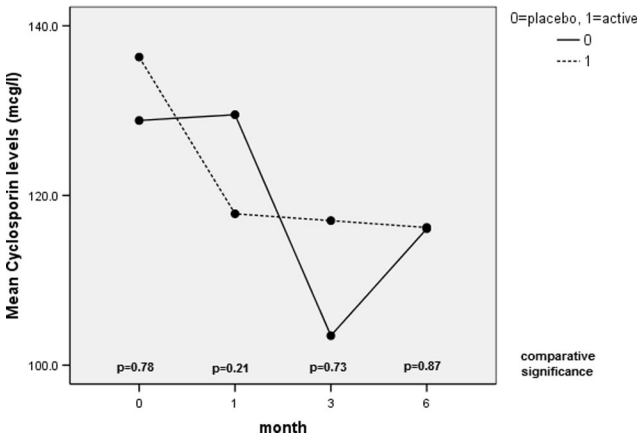

FIGURE 3. Comparisons of the mean trough cyclosporin level between placebo and active treatment during the follow-up period. There was no significant change seen for active treatment.

because of failure to comply with the follow-up schedule. Reported side effects were infrequent and comparable between placebo and active treatment. No patients were withdrawn by the investigating team because of a predefined secondary endpoint. In particular, there was no significant effect of ezetimibe on cyclosporin levels (Fig. 3). We also analyzed the effect of ezetimibe on renal function (urea and creatinine), hemoglobin, platelet count, and white cell count. No significant changes were seen at any time point for all parameters. Further details on the tolerability assessment can be seen in Table 3.

DISCUSSION

In this trial of heart transplant recipients taking cyclosporin, the addition of the cholesterol absorption inhibitor ezetimibe to usual treatment (the majority of patients were already taking a statin) significantly reduced TC, LDL, and Trigs. Furthermore, the tolerability of ezetimibe in this setting was excellent. No serious adverse events occurred with ezetimibe treatment, whereas one death was observed in the placebo group. Reported side effects were infrequent and an equal number of participants withdrew from the study for this reason between both study groups.

Our results would support the finding of two recent observational studies, assessing similar parameters. In the first study by Konstandin et al. (*16*) (n=25), a significant 13% reduction in TC was observed by 4 months, which extended to 17% by 1 year. LDL was also observed to be reduced in the magnitude of 15% and 25%, respectively. Tolerability was also reported to be satisfactory, given only two patients withdrew from treatment because of side effects. It was also reported that blood cyclosporin levels remained unchanged. However, the absence of a placebo control limits a true tolerability assessment. In the second study (*17*) (n=25), significant reductions of TC and LDL were also observed in the magnitude of 22% and 28%, respectively, over a 6-month period. Collectively, these two studies in combination with our findings provide good evidence to support the efficacy and tolerability of ezetimibe for lipid lowering in cardiac transplant patients (including those taking cyclosporin).

The study was not designed to assess the direct impact of ezetimibe treatment on mortality or morbidity after cardiac transplantation. The benefit of LDL lowering by ezetimibe has recently been brought under question following the results of the ENHANCE study (*20*). In this imaging study which compared Simvastatin against a combination of Simvastatin and ezetimibe, no significant differences were found in the changes of carotid intima-media thickness after 24 months of treatment. The failure of a positive result has created much confusion and debate over current methods of

TABLE 3. Tolerability assessments

Assessment parameters	Unit of measurement	Analysis time point	Placebo	Ezetimibe	Significance	Comments
ALT	Mean values (U/L)	Baseline	23.4	22.8		No patients met safety endpoint of ALT>3×ULN
		Month 1	19.7	25.7	$P=0.147$	
		Month 3	22.0	26.0	$P=0.589$	
		Month 6	20.0	23.6	$P=0.653$	
CK	Mean values (U/L)	Baseline	98.2	99.3		No patients met safety endpoint of CK>5×ULN with symptoms or CK>10×ULN without symptoms
		Month 1	101.0	102.9	$P=0.927$	
		Month 3	102.5	118.2	$P=0.384$	
		Month 6	109.2	124.1	$P=0.319$	
BIL	Mean values (U/L)	Baseline	12.2	11.5		
		Month 1	11.9	12.3	$P=0.228$	
		Month 3	11.1	11.4	$P=0.241$	
		Month 6	12.1	11.9	$P=0.622$	
Cyclosporin	Mean trough level (μg/L)	Baseline	128.8	134.0		No patients met safety endpoint of Cyclosporin level <50% baseline or >2×baseline
		Month 1	129.5	115.9	$P=0.213$	
		Month 3	103.5	116.0	$P=0.730$	
		Month 6	116.1	114.6	$P=0.869$	

No significant differences between active and placebo groups were shown for any safety parameter (at any time point) during the study.
ALT, alanine aminotransferase; CK, creatine kinase; BIL, Bilirubin; ULN, upper limit of normal.

LDL cholesterol lowering. However, it should be noted that several aspects of the ENHANCE study design, limits its ability to translate changes into clinical practice. This was a surrogate endpoint study and, therefore, does not provide clear data about ezetimibe's effect on mortality and morbidity. In addition, most of the patients had already been pretreated with a statin before inclusion. This could clearly explain the lack of effect. Most importantly, the study cohort (familial hypercholesterolaemia) was a different population to cardiac transplant recipients.

In conclusion, ezetimibe is both safe and effective at lowering TC and LDL levels (and triglycerides) after a heart transplant. It may be used alone or in addition to a statin while patients are taking concomitant cyclosporin.

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