Aggressive Lowering of Fibrinogen and Cholesterol in the Prevention of Graft Vessel Disease After Heart Transplantation

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Background A combined treatment of statins and extracorporeal H.E.L.P.-apheresis (*H*eparin-mediated *E*xtracorporeal *L*DL/fibrinogen *P*recipitation) has already been shown to be beneficial for coronary artery disease (CAD). Presumably high levels of LDL cholesterol, Lp(a), and fibrinogen also increase the risk for graft vessel disease (GVD). Therefore, we studied whether this concept can be applied in GVD, based on the hypothesis that GVD is an accelerated form of CAD.

Methods and Results For comparison of statin treatment alone with the combined treatment, two matched groups of 10 cardiac transplant recipients were studied during a mean period of 3.6±1.0 years. Both groups were comparable in clinical characteristics, immunosuppressive medication, baseline plasma Lp(a), and high fibrinogen levels. Group I had normal LDL-C levels (3.36±0.60 mmol/L). Simvastatin alone was administered in this group to counteract the LDL-increasing effect of the immunosuppressive medication. Group II had marked hypercholesterolemia (LDL-C, 6.07±1.89 mmol/L), which was treated, in addition to simvastatin, with H.E.L.P.-apheresis weekly. GVD was assessed by coronary angiography. Simvastatin alone kept LDL-C levels within baseline limits but could not prevent GVD in 7 of 10 patients. In contrast, the combined treatment prevented GVD in 9 of 10 patients (P=.006) by simultaneous and drastic reduction of 48% LDL-C (P=.006), 35% fibrinogen (P=.002), and 47% Lp(a) (P=.006) below baseline. Both treatments were well tolerated and did not affect prevention of graft rejection and infections.

Conclusions A strategy of early, drastic lowering of fibrinogen, LDL-C, and Lp(a) helps to prevent GVD. (***Circulation.* 1997;96[suppl II]:II-154-II-158.**)

Key Words • graft vasculopathy • hypercholesterolemia • fibrinogen • simvastatin • angiography • transplantation

GVD is still a major cause of mortality after HTX, and to date, there is no effective prevention or therapy.[1,2] Scarcity of donor organs and poor outcome after retransplantation require a treatment to prevent GVD.

The therapeutic approach in the present study is based on the hypothesis that GVD can be considered as an accelerated form of CAD.[1,3-5] This hypothesis is supported by three lines of evidence. Coronary plaques in GVD contain high amounts of cholesterol, fibrin, and lipid-rich foam cells[6-8] similar to atherosclerotic CAD.[9] Plaques in GVD[6-8] differ from CAD[9] in their more diffuse and concentric distribution, which may reflect the rapid development under the immunosuppressive therapy.

CAD normally needs decades to develop,[9] but GVD may develop fast.[1,10] Early signs of GVD can be detected angiographically in almost all patients as soon as 3 years after HTX.[10] The coronary risk factors, plasma LDL-C, fibrinogen, and Lp(a) also increase the risk for GVD.[3,4,11,12]

On the basis of these findings, we conducted a pilot study for the prevention of GVD in HTX patients, following a strategy that has been shown to be beneficial in CAD patients. The treatment is based on a combination of statins with H.E.L.P.-apheresis,[13-15] which drastically lowers LDL cholesterol, Lp(a), and fibrinogen levels.[13] The aim of our study was to investigate whether early and drastic reduction of these compounds can curtail the accelerated process of GVD.

Methods

Patients

Two groups of patients (n=20) with hyperfibrinogenemia, partly associated with hypercholesterolemia, were included in a long-term observation study (mean follow-up, 3.6±1 years) after orthotopic HTX.

The groups were divided according to their plasma LDL-C levels. Group I had a baseline LDL-C <4.14 mmol/L. Simvastatin (15 mg/d) was administered to counteract the cholesterol-increasing effects of the immunosuppressive medication. Group II had LDL-C levels >4.14 mmol/L and was treated, in addition to simvastatin (15 mg/d), with extracorporeal H.E.L.P.-apheresis at weekly or biweekly intervals.

Both groups were matched in pairs for plasma fibrinogen and Lp(a) concentration, original cardiac disease, time of observation after HTX, gender and mean age of recipient and donor, cardioplegic solution, number of acute rejections within the first 6 months after HTX, and duration of treatment. Details are given in Table 1. There were no statistically relevant differences between both groups regarding their clinical char-

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Selected Abbreviations and Acronyms

CAD = coronary artery disease
GVD = graft vessel disease
H.E.L.P. = heparin-mediated extracorporeal LDL/fibrinogen precipitation
HTX = heart transplantation

acteristics, including the incidence of hypertension, diabetes, smoking status, blood pressure, and body mass index (Table 1), except for plasma LDL-C. For ethical reasons, we decided not to include a placebo group, because the immunosuppressive medication increases the LDL-C levels and thereby the risk for GVD. The patients gave informed consent to the study design.

All patients were treated with standard triple drug immunosuppression, consisting of cyclosporine A, azathioprine, and prednisone. Cyclosporine A was controlled regularly and adjusted to 150 to 200 ng/mL blood levels. In case of acute rejection, high-dose cortisol was administered alone. All patients received acetylsalicylic acid, ACE inhibitors, and diuretics. Both groups were surveyed every 6 months in the postoperative years. There were no dropouts.

H.E.L.P.-Apheresis

The H.E.L.P. system is a method for selective removal of LDL-C, Lp(a), and fibrinogen. The system has been in clinical use since 1984 for treatment of patients with familial hypercholesterolemia and advanced CAD. The safety and long-term applicability of the H.E.L.P. system has been proved in more than 100,000 treatments; serious complications have never been observed.

The technique operates at low pH in the presence of heparin and has been described in detail by Seidel et al.[16,17] On average, each session with a Plasmat-Secura apparatus (Braun, Melsungen, Germany) lasts 2 hours, which allows treatment of 3 L of plasma and a mean interval reduction of approximately 51% for LDL-C, 46% fibrinogen, and 45% Lp(a), respectively.[16,17] If combined with statins, one session every fortnight is sufficient for most patients to maintain desired target blood levels. The cost per patient of extracorporeal apheresis is comparable to hemodialysis. For clinical use, time and quantity (blood flow rate) can be controlled separately for individual requirements, which permits treatment of patients with heart failure as well as patients undergoing chronic anticoagulation therapy. Patients with acute bleeding ulcers or severe inborn coagulation defects should not be treated with H.E.L.P.-apheresis.

TABLE 1. Clinical Characteristics of Patients

	Group I (Simvastatin)	Group II (Simvastatin +Apheresis)
Age of recipient, y	55±7	52±8
Age of donor, y	32±13	30±13
Sex of recipient, M/F	8/2	8/2
Sex of donor, M/F	8/2	8/2
Cardioplegic solution (Bretschneider/UW)	3/7	3/7
Original cardiac disease, n		
Ischemic cardiomyopathy	8	8
Dilated cardiomyopathy	2	2
Mean blood pressure before HTX*	120/79	127/77
Body mass index (recipient)	24.8±2.3	24.7±2.7
Smokers before HTX, n	1	5†
Smokers after HTX, n	0	0
Diabetes before HTX, n	3	1
New diabetes after HTX, n	1	3
Acute graft rejections per patient within 6 mo after HTX	1.1	1.2
CMV infections during the follow-up, n	3	4

There were no statistically relevant differences between both groups according to the Wilcoxon test or the Mantel-Haenzel test.

*Mean blood pressure before HTX was measured under treatment with ACE inhibitors and diuretics.

†The difference in smoking habits before HTX showed a trend (P=.051).

Coronary Angiography

To exclude preexisting CAD, only patients with a normal coronary angiogram (immediately after HTX) were included, and coronary angiograms were repeated annually, which is standard practice in the Department of Cardiac Surgery. GVD was classified according to the criteria of Gao et al,[1] who distinguish two types of coronary arterial lesions: type A shows typically tubular or discrete stenoses of proximal or midportions of major graft vessels similar to lesions in CAD, and type B has diffuse, concentric narrowing of the whole vessels including their branches.[1]

Laboratory Studies

Baseline blood samples were taken directly before HTX. Plasma concentrations after apheresis were adjusted by hematocrit.[18] Interval concentrations between two H.E.L.P. sessions were calculated as the arithmetic average of the value taken before the following session and the value obtained after the last session.

LDL-C were quantified by the enzymatic CHOD-PAP method (Boehringer, Mannheim, Germany) after precipitation of LDL from cholesterol with dextran sulfate (Immuno GmbH, Heidelberg, Germany). Lp(a) was assayed by nephelometry (Immuno AG, Heidelberg, Germany), and fibrinogen was measured according to Clauss.[19] Cyclosporine A was determined by a monospecific enzyme multiplied immunotechnique (EMIT; Syva, Evergreen, Calif.) and by a polyspecific fluorescence polarization immunoassay (Abbott, Chicago, Ill.), which quantifies cyclosporine A and its metabolites.

Statistics

Values for LDL-C and fibrinogen are expressed as mean±SD and Lp(a) as median with range. The results for group II refer to interval concentrations between two H.E.L.P. sessions. Comparisons between groups included matching criteria and results, which were analyzed by use of two tests. Discrete variables were determined by the Mantel-Haenszel χ^2 statistics[20] for matched data, and continuous variables were determined by Wilcoxon test. Changes in the continuous variables within each group during the time course were compared with Wilcoxon matched-pair signed-rank statistics. Kaplan-Meier life tables[21] were used for a log-rank test to compare corresponding values under consideration of the individual observation times. $P<.05$ was considered to indicate statistical significance. Statistical analyses were performed with PC-SAS version 6.03.[22]

Results

Seven of 10 patients in group I (simvastatin), but only 1 of 10 patients in group II (H.E.L.P.-apheresis and simvastatin) showed angiographic signs of GVD during the 3.6 years of follow-up. The probability that the difference was a random event amounts to P=.006 and P=.014 according to Mantel-Haenszel and Kaplan-Meier, respectively. Thus, the difference is significant. Detailed angiographic findings are given in Table 2.

In group I, the seven patients with GVD developed early angiographic signs after a mean period of 2.2 years. The overall degree was moderate. Only one patient (patient 7, Table 2) developed a stenosis of hemodynam-

TABLE 2. Coronary Angiographic Findings After HTX for Group I (Simvastatin) and Group II (Simvastatin+H.E.L.P.-Apheresis)

Patient	Group I Angiographic Findings	GVD, y*	HTX, y†	Patient	Group II Angiographic Findings	GVD, y*	HTX, y†
1	Normal	No	5.5	1	75%-80% stenoses of RCA, RCX, LCA tapering of side branches, LIMA, RCA-bypasses normal (type A/B)	1.0	5.5
2	Distal occlusion RCX, dilated vessels (type A)	2.2	3.9	2	Normal	No	3.9
3	Tapering of side branches, plaques in all vessels (type B)	0.9	3.7	3	Normal	No	3.7
4	30% RCA stenosis, irregular contoures, plaques (type A)	3.0	4.4	4	Normal	No	4.0
5	Normal	No	2.1	5	Normal	No	2.4
6	Normal	No	2.9	6	Normal	No	3.0
7	50% RCA restenosis, 30% LCA stenosis (type A)	1.3	2.5	7	Normal	No	2.6
8	30% RCX stenosis (type A)	2.2	3.0	8	Normal	No	3.0
9	Tapering and occlusion of side branches, plaques irregular contoures and plaques in all vessels (type B)	4.0	5.6	9	Normal	No	5.6
10	Irregular contoures and plaques in all vessels (type B)	0.5	2.6	10	Normal	No	2.6

*First detection of GVD (years after HTX).
†Observation period (years after HTX).

ic relevance during the follow-up, thus requiring percutaneous transluminal coronary angioplasty.

In marked contrast, in group II, only one patient (patient 1, Table 2) who had an extremely high plasma LDL-C level (8.66 mmol/L) from the beginning and very high fibrinogen levels (>7 g/L) developed GVD 1 year after HTX. Coronary artery bypass surgery became necessary. However, with H.E.L.P. treatment, the patency of all bypass grafts was maintained to date.

Two patients in each group underwent transplantation because of dilated cardiomyopathy, whereas the remaining patients underwent transplantation for ischemic cardiomyopathy. When comparing the small subset of dilated cardiomyopathy patients in relation to the incidence of GVD, there was one patient in the simvastatin group who developed a GVD, whereas both patients who received H.E.L.P. treatment were free of angiographically detectable signs of GVD.

Changes in plasma levels of LDL-C, fibrinogen, and Lp(a) were compared for groups I and II (Table 3). In group I, simvastatin treatment (15 mg/d) alone kept plasma LDL-C levels within baseline limits during the follow-up period. Mean fibrinogen levels remained high. Median Lp(a) levels tended to increase (P=.03, Wilcoxon matched-pairs signed-rank test).

By contrast, group II was characterized by a decrease of 48% LDL-C (P=.006), 35% fibrinogen (P=.002), and 47% Lp(a) (P=.006), when comparing baseline and interval values at the end of the follow-up (P values, Wilcoxon matched-pairs signed-rank test). On average, 3.0±1.0 g cholesterol from the LDL fraction, 0.45±0.33 g Lp(a), and 6.0±1.0 g fibrinogen were eliminated during each apheresis session (arithmetic mean, 467 sessions).

Comparing the plasma levels of both groups at the end of the follow-up, both groups were comparable in their LDL-C (P=NS) and Lp(a) concentrations (P=NS), but a striking difference was observed in the fibrinogen levels (P=.0013, Wilcoxon test).

TABLE 3. Changes in Plasma Concentrations of LDL-C, Fibrinogen, and Lp(a) in Group I (Simvastatin) and Group II (Simvastatin and H.E.L.P.-Apheresis) During the Follow-up

	Group I	Group II	Differences Between Groups (Wilcoxon Test) *P* Value
Plasma LDL-C at baseline (mmol/L)	3.36±0.60	6.07±1.89	.0046
Plasma LDL-C at end of study (mmol/L)	3.52±0.65	3.15±0.44*	NS
Change to baseline in each group (Wilcoxon matched-pairs test): *P* value	NS	.006	-
Plasma fibrinogen at baseline (g/L)	3.90±0.84	4.28±1.33	NS
Plasma fibrinogen at end of study (g/L)	3.90±0.56	2.77±0.41*	.0013
Change to baseline in each group (Wilcoxon matched-pairs test): *P* value	NS	.002	-
Plasma Lp(a) at baseline (mg/dL)	7 (5-91)	16 (7-52)	NS
Plasma Lp(a) at end of study (mg/dL)	17 (5-122)	9 (6-27)*	NS
Change to baseline in each group (Wilcoxon matched-pairs test): *P* value	.03	.006	-

Plasma LDL-C and fibrinogen are presented as mean±SD. Plasma Lp(a) is expressed as median and range. NS=not significant.

Baseline plasma concentrations of LDL-C, Lp(a), and fibrinogen were measured immediately before HTX.

*In group II, concentrations at the end of study refer to the interval plasma concentration of LDL-C, Lp(a), and fibrinogen, which is the average reduction obtained between two H.E.L.P. sessions.

In both groups, the treatment was well tolerated in long-term application without adversely affecting prevention of graft rejection or infections. Cyclosporine A blood levels were not affected by the H.E.L.P. treatment.

Discussion

This pilot study demonstrates the clinical benefit of the combined treatment of simvastatin with H.E.L.P.-apheresis in the prevention of GVD by early and drastic reduction of plasma LDL-C and fibrinogen levels.

The immunosuppressive medication markedly increases plasma cholesterol levels[3,11,23,24] and thus endothelial dysfunction, which is presumably the first step in atherogenesis.[25] Kobashigawa et al[11] showed recently that lowering cholesterol with pravastatin (40 mg/d) reduces mortality and slows development of GVD in the first year after HTX. Nontreated HTX patients showed a mean increase in cholesterol of 42% within 1 year after transplantation and a significantly higher mortality rate.[11]

In the present long-term study, simvastatin was useful in counteracting the cholesterol-increasing effects of the immunosuppressive medication and in inhibiting clinical complications of GVD. However, simvastatin (15 mg/d) alone could not prevent development of GVD in 7 of 10 HTX patients. In our experience, higher doses of simvastatin are not tolerated in most cases. They may increase the risk for myopathia and can interact with elimination of cyclosporine A as previously reported.[26]

Although the overall degree of GVD in the simvastatin group was moderate and might be detected only with careful angiographic assessment, the high incidence of GVD in the simvastatin group was troubling and is probably not explained by insufficient LDL-C reduction in the simvastatin group, because both groups were comparable in their LDL-C levels under treatment. Moreover, there was no evidence for relevant differences in the baseline clinical characteristics of both groups that could have accounted for the difference in outcome.

As the statistical analysis of our data has revealed, a striking difference between both groups was observed in the plasma fibrinogen concentrations at the end of study, a reduction of which cannot be achieved with simvastatin. Most probably, the persistent high levels in group I have contributed to the higher incidence of GVD, and efficient fibrinogen lowering may be important to prevent GVD.

Experimental studies have provided evidence that high plasma fibrinogen levels are associated with disturbed microcirculation, plaque formation, and thrombosis.[27,28] Hunt et al[4] reported significantly higher levels of fibrinogen in HTX patients, which are highest in patients with GVD or in those who underwent transplantation because of ischemic cardiomyopathy. High fibrinogen and Lp(a) levels are independent risk factors of atherogenesis.[28] There is no efficient drug treatment available for those to date. Extracorporeal H.E.L.P.-apheresis may improve the general equilibrium of lipid metabolism, hemorheology, vascular tone, and endothelial function after HTX.

The H.E.L.P.-apheresis system has already been shown to be of clinical benefit in patients with CAD and severe hypercholesterolemia.[13-15] The simultaneous and efficient elimination of LDL-C, Lp(a), and fibrinogen, which is unique to this apheresis system, leads to regression of coronary stenoses and reduces the incidence of myocardial infarctions.[13,14,16]

In our opinion, it is primarily the time factor, the marked acceleration process of GVD, which makes it necessary to eliminate important risk factors as early and efficiently as possible. The data from this report suggest that a therapeutic concept for CAD can be applied in GVD as well, because incompatibilities with prevention of graft rejection and infections did not arise.

Based on the observations of this intention-to-treat study, we are now initiating a controlled, randomized, multicenter trial to investigate whether the combined therapy with H.E.L.P.-apheresis and statins provides a suitable alternative to retransplantation in high-risk patients with GVD.

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