Treatment of Hypercholesterolemia and Prevention of Coronary Artery Disease After Heart Transplantation by Combination of Low-Dose Simvastatin and HELP-LDL-Apheresis

K. Wenke, J. Thiery, N. Arndtz, B.M. Meiser, D. Seidel, and B. Reichart

IN THE long-term follow-up after heart transplantation (HTx), the development of accelerated coronary artery disease remains the major cause of death.[1] The precise pathogenesis of this specific vasculopathy is, however, unknown. Many causative factors may be involved, including elevated serum cholesterol levels after transplantation.[2] In order to minimize the consequences of this postoperative hypercholesterolemia, we initiated a clinical study to prove the beneficial effects and clinical safety of Simvastatin, an inhibitor of cholesterol biosynthesis. For severe hypercholesterolemia we added an extracorporeal low-density lipoprotein (LDL) elimination procedure, the heparin-mediated extracorporeal LDL-cholesterol precipitation (HELP) system (Fig 1). The overall goal of this trial was to determine whether intensive lipid-lowering therapy to less than 110 mg/dL will decrease accelerated coronary artery disease of the graft within a follow-up time of 4 years.

PATIENTS AND METHODS

After HTx, patients were randomized to either a treatment group or a control group. Both groups were maintained on a dietary program for the duration of the trial.

Patients in the treatment group received a dose of 5 to 20 mg of Simvastatin once a day. If the LDL-cholesterol exceeded 135 mg/dL on three consecutive visits in spite of Simvastatin treatment, additional HELP-LDL apheresis was applied. In contrast, the control group received only conventional standard lipid-lowering therapy. Until now, 21 patients have been included in the treatment group and 11 patients in the control group. Average age of the patients (30 men and 2 women) was 45.5 ± 15.5 years. The indication for HTx was either ischemic cardiomyopathy (n = 13) or dilatative cardiomyopathy (n = 19). All patients received standard triple drug immunosuppression (cyclosporine (CyA), azathioprine, corticosteroids). In each patient, a full clinical chemistry panel as well as measurements of immunologic param-

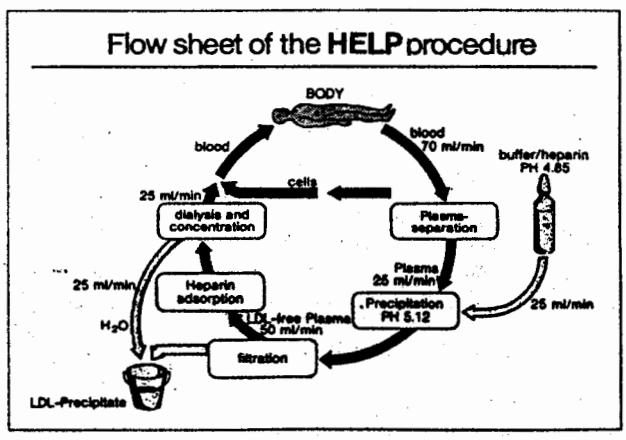

Fig 1. Schematic diagram of HELP procedure.

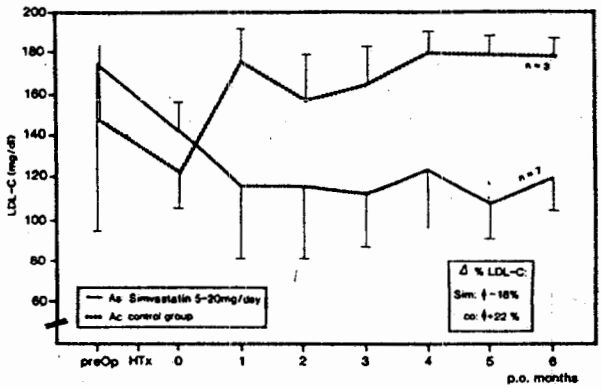

Fig 2. Follow-up of LDL-cholesterol after HTx, Group A (ICMP).

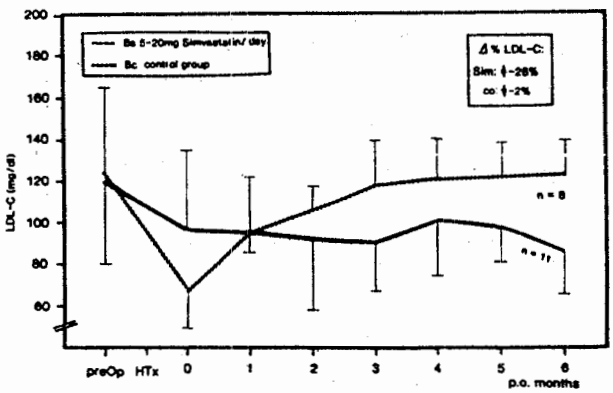

Fig 3. Follow-up of LDL-cholesterol after HTx, Group B (non-ICMP).

From the Department of Cardiac Surgery (K.W., N.A., B.M.M., B.R.) and Institute of Clinical Chemistry (J.T., D.S.), University Hospital Grosshadern, Munich, Germany.

Address reprint requests to Klaus Wenke, MD, Department of Cardiac Surgery, University Hospital Grosshadern, 8000 Munich 70, Marchionstr 15, Germany.

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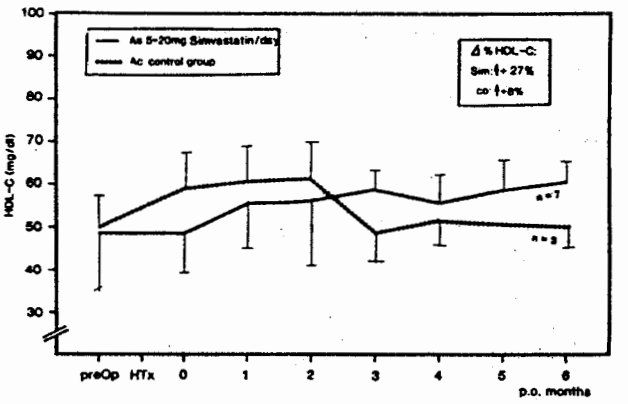

Fig 4. Follow-up of HDL-cholesterol after HTx, Group A (ICMP).

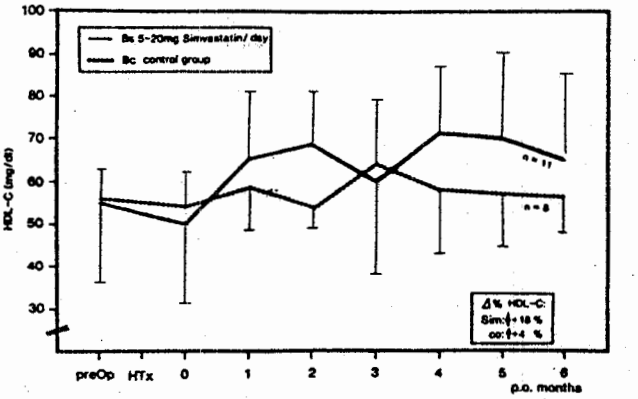

Fig 5. Follow-up of HDL-cholesterol after HTx, Group B (non-ICMP).

eters, specific lipids, and lipid proteins were obtained regularly. In order to monitor drug therapy and its interaction with CyA, CyA and Simvastatin plasma concentrations were recorded.

RESULTS

Before HTx, patients with diagnosis of ischemic coronary artery disease had significantly higher LDL-cholesterol levels than patients with dilatative cardiomyopathy. Six months after HTx, control group patients with ischemic cardiomyopathy showed an increase of LDL by more than 20% while patients with dilatative cardiomyopathy showed no change in LDL-cholesterol concentrations (Figs 2 and 3, respectively). However, in patients with either diagnosis, Simvastatin treatment resulted in a significant decrease of plasma cholesterol concentrations.

High plasma levels of high-density lipidoproteins (HDL) protect against arteriosclerosis while low HDL plasma levels are considered to be a risk factor for coronary artery disease.[3] In our control patients, HDL-cholesterol levels after HTx were in a normal range. However, Simvastatin therapy in the treatment group caused a significant increase of HDL in patients with both ischemic and dilatative cardiomyopathy (Figs 4 and 5).

Five patients in the treatment group suffered from severe familial hypercholesterolemia with baseline LDL values above 280 mg/dL. Drug treatment resulted in an impressive reduction of LDL-cholesterol by approximately 40%. However, after HTx, even under treatment with 20 mg of Simvastatin per day, these patients had pathologic LDL-C concentrations above 170 mg/dL. In these cases, Simvastatin therapy was combined with an extracorporeal procedure to eliminate LDL, that is, HELP.[4] Combination of these two treatment strategies reduced LDL-cholesterol concentrations by approximately 60%, resulting in LDL-cholesterol levels of less than 125 mg/dL (Fig 6).

The overall treatment tolerance of the patients has been

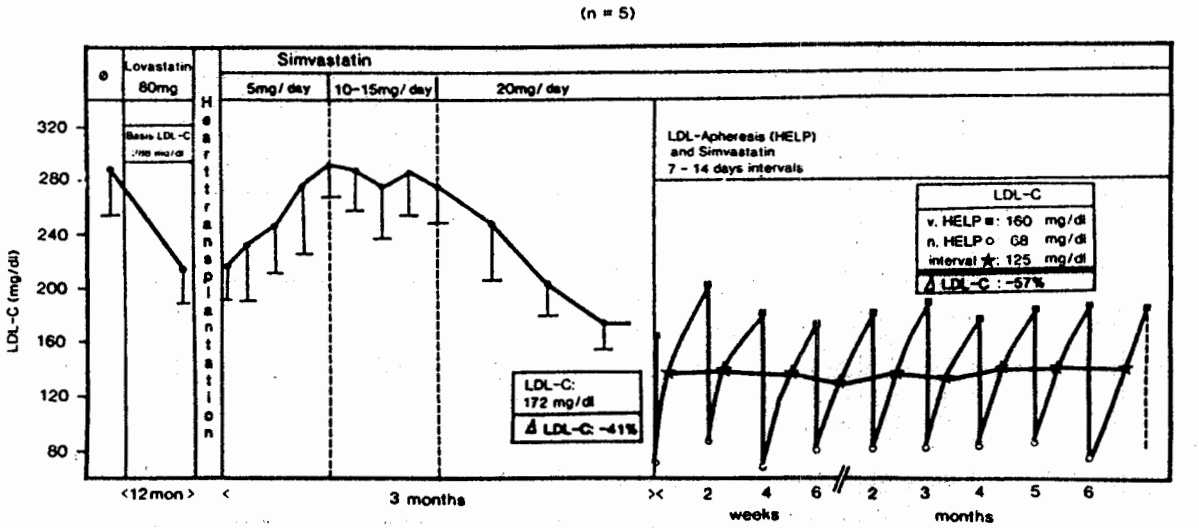

Fig 6. Simvastatin combined with extracorporeal HELP procedure to eliminate LDL.

extremely good. No major complications or clinically relevant adverse effects have been observed after approximately 100 HELP treatment courses.

CONCLUSIONS

The increase of plasma LDL-cholesterol concentrations after HTx can be avoided in most patients by low-dose Simvastatin treatment. In cases of severe hypercholesteremia, in which LDL-cholesterol cannot be decreased below 135 mg/dL by diet and drug therapy, additional HELP-plasmapheresis should be considered.

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