A Combined Treatment of Statins and H.E.L.P. apheresis for Treatment of Cardiac Allograft Vasculopathy

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Introduction

Cardiac allograft vasculopathy (CAV) still is a main cause of mortality and morbidity after heart transplantation with poor prognosis (1). Scarcity of donor organs and bad predictions after retransplantation demand a concept to secure success of transplantation. Cardiologic interventional measures are associated with a high rate of reocclusion, and remain symptomatic. Several randomised controlled trials (2, 3) have demonstrated that the preventive use of HMG-CoA reductase inhibitors (=statins) reduces the incidence of CAV and acute rejections, as well.

Besides cholesterol, various kinds of endothelial injuries seem to account for the rapid development and fatal progression of the disease promoting

a persistent prothrombotic activation (4, 5, 6) with ensuing deposition of fibrin in the microvasculature.

We assumed that a therapeutic concept of an aggressive, consistent reduction of plasma fibrinogen and cholesterol could reverse or mitigate the progression of CAV. Such a reduction can be achieved by a combination of heparin-mediated extracorporeal LDL/fibrinogen precipitation (H.E.L.P. apheresis) and statins.

This combined treatment already proved beneficial in the prevention of CAV (7), performing better than statins alone, because the benefit appeared to be mainly related to the drastic fibrinogen reduction. In the present study we analysed the data from eleven centres from Germany and Switzerland including all CAV patients world wide ever being treated with H.E.L.P. apheresis and statins. We will show that the combined treatment strikingly improved survival in 28 patients with manifest CAV.

Methods

Eligibility criteria: Included were 30 patients (age: 38 - 62 yr.) suffering from CAV prior to the onset of H.E.L.P. apheresis treatment. CAV was diagnosed according to the criteria of Gao, or if intravascular ultrasound (IVUS) was available, lesions corresponding to grade IV of the Stanford classification were equally considered to be indicative of CAV. There were no specific exclusion criteria. Two patients had interrupted apheresis treatment for several years, these two cases are described separately in this paper. The remaining 28 patients completed the study.

Settings and locations: Eleven medical H.E.L.P. centres in Germany and Switzerland enrolled patients in this study. They are located at Duisburg, Hamburg, Hof, Hoyerswerda, Kempten, Köln, Marburg, München, Oeynhausen, Stralsund, and Zürich. Standardised questionnaires were sent to each centre. The study was regional observational, and the data of this study were compared with data from the International society of Heart and Lung Transplantation, 18th Official Report (1).

Interventions: HMG-CoA reductase inhibitors (statins) were prescribed according to the routine of the respective centre. The H.E.L.P. procedure has thoroughly been studied and was described in detail elsewhere (for review: 8,9). The principle of the method is a selective precipitation of atherogenic blood compounds by precipitation with heparin: Precipitated are LDL-cholesterol, lipoprotein(a), CRP, fibrinogen, and other clotting factors (8,9) in an extracorporeal system (Plasmat Secura, B. Braun AG, Melsungen, FRG).The plasma levels of the latter compounds are reduced by 60±10 %. Treatment intervals vary between 7 -14 days.

Laboratory analysis: The tests were performed at the respective centres with standard methods in the respective centres.

Objectives: The primary endpoint was all cause mortality, but secondary endpoints included cause specific mortality, the rate of rejections, infections and cancer.

Statistical methods: The actuarial survival was calculated by the life table method for direct comparison of the present data with the data from the official ISHLT registry, and for estimation of the annual survival probability under treatment. Follow-up ended in June 2002.

Results

Baseline characteristics: Immunosuppressive medication and the concurrent medication comprised of the usual prescriptions. Patients displayed a pronounced atherogenic risk constellation (4.8 risk factors/patient), and were overweight, mean BMI was 26.5. Particularly the LDL-cholesterol (185±71 mg/dL), fibrinogen (4.12±0.93 g/L), and lipoprotein(a) concentrations (38±45 mg/dL) were elevated at baseline. The patients were transplanted between 1983-1997. CAV was diagnosed on average 4.0±3.0 years after transplantation. Regular treatment with H.E.L.P. apheresis was begun 1.1±1.4 years after diagnosis of CAV. Statin treatment was continued or begun at the same time as H.E.L.P. treatment.

Efficacy of treatment - Primary end points: The mean observation time was 10.1±3.4 years after transplantation. In total, during the entire follow-up 5 out of 28 patients died.

We calculated the actuarial survival in order to get the annual survival probability estimates, and compared them with the official ISHLT data including 52.195 patients being heart transplanted between 1982 - 2000. Notably, the data reflect the survival estimate of all patients, not only CAV patients who have an inferior prognosis. In fact, the CAV patients treated with the combination of H.E.L.P. apheresis and statins performed better than the patients of the general ISHLT registry. To give an example, a H.E.L.P. patient has a 10-year survival probability of 96 %, whereas the general estimate of the ISHLT for 10 years is only 46 %.

Secondary end points: Among the ~~seven~~ five participants of this study who died in total, no autopsies were available. But the clinical course allowed a relatively clear distinction between death due to CAV (n=1), and death due to non-CAV reasons (n=4; patient A-D). The latter patients (A-D) died of multiorgan failure due to metastatic lung cancer (A), multiorgan failure due to metastatic undifferentiated epithelial cancer (B). The third patient died during an urgency cholecystitis operation after extubation (C), the fourth died of right heart failure two days after tricuspidal replacement (D). The one patient who died of CAV (E) was the only one who was retransplanted: He died 6 years after retransplantation of left heart failure due to CAV.

Safety of statins: Basically all patients had received the combined treatment of statins and H.E.L.P. apheresis in order to maximise the cholesterol-lowering effect, and to bridge the interval between two H.E.L.P. sessions. During the follow-up, three out of 28 patients (10.7 %) had to withdraw statin treatment for myalgia. Notably, more than 50 % of the H.E.L.P. patients had reported repeated muscle pain or cramps over the years which gave reason to adapt the dosage to a tolerable level, or to try another statin. Ten patients (35.8 %) tolerated the statins very well.

Safety and efficacy of H.E.L.P. treatment: 92.9 % of the patients tolerated the apheresis very well, two patients (7.1 %) moderately for difficult venipuncture following long-term prednisolone use. Rare side effects were vasovagal reactions or tiredness occurred. With an approximate frequency of 10/1000 treatments (1%). The apheresis did not impede immunosuppressive medication, the levels of which were regularly monitored. Regarding efficacy of apheresis, the reduction of LDL-cholesterol, the clotting factors, lipoprotein(a), and CRP was a constant percentage (60±10 %) independent of the initial concentration. No rebound or loss of efficacy was observed over the years.

Incidence of cardiovascular events: During the entire follow-up 9 out 28 patients (32%) underwent cardiologic interventions, mainly PTCA or stenting (n=8). One patient received coronary artery bypass grafts. Three patients experienced a myocardial infarction. One patient had experienced a syncope in the presence of ventricular fibrillation, but this event was not associated with an infarction. The patient was successfully reanimated.

Incidence of other transplant related complications: As to *acute rejections* we registered merely acute rejections which had to be treated, or were clinically apparent. The frequencies were low: 13 rejections during 10 years follow-up. In this connection it should be mentioned that the plasma levels of the immunosuppressive drugs were monitored at weekly or fortnight intervals prior to every apheresis. As to the incidence of *infections*, there is no evidence for an increased rate. As to the incidence of *cancer*, we observed five cases during the follow-up, i.e. a frequency of 17.8 %.

Discussion

The present contribution clearly demonstrates that CAV patients benefit from an aggressive fibrinogen and cholesterol-lowering treatment. The result for the CAV patients is even more striking if one considers the cause specific mortality: more than half of the patients did not die of CAV, but for other reasons.

Nonetheless, we could not ascertain the early critical perioperative

phase with infections and rejections of the first months after transplantation, amounting to an approximate additional 10% mortality. Deducting this 10% from our result, the outcome still is exciting. As far as we know, there are no recent data available on the actual prognosis of CAV patients. The outcome of CAV decisively depends on timing of diagnosis and consequent application of treatment as outlined by this study. Most likely, the success of the combined treatment studied here is founded on the concept of an *aggressive* fibrinogen, clotting factor, CRP and cholesterol reduction. With regard to the safety of treatment, the apheresis was no problem at all, and thus the compliance of the patients is excellent. There was no evidence that the combined treatment impeded the prevention of infections, rejections, and cancer, respectively. The relatively high frequency of myalgia reported under statin treatment might be explained by the impaired renal function and the known interaction of statins and immunosuppressive agents.

With no suggestion of harmful effects, the present study provides reassuring evidence of the long-term safety and efficacy of the combined treatment of statins and H.E.L.P. apheresis in patients suffering from CAV.

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