Induction Therapy After Cardiac Transplantation: A Comparison of Anti-Thymocyte Globulin and Daclizumab in the Prevention of Acute Rejection

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Background: Induction therapy with antibodies decreases and delays early allograft rejection. We compared the safety and efficacy of daclizumab and anti-thymocyte globulin (ATG) with respect to the frequency and severity of acute cardiac allograft rejection in heart transplant recipients.

Methods: Forty sequential adult patients were retrospectively studied. In the first 20 patients ATG (2.5 mg/kg daily for 3 to 5 days peri-/and post-operatively) was used as induction therapy and, in the remaining 20 patients, daclizumab (1 mg/kg peri-operatively and every 2 weeks thereafter for a total of 5 doses) was used. A standard triple-drug immunosuppression regimen was administered to all patients.

Results: Baseline characteristics and trough levels of cyclosporine in the 2 groups were similar. During the induction period, defined as the first 3 months, 12 acute rejection episodes requiring treatment (ISHLT Grade $\geq$2) occurred in the ATG group and 9 in the daclizumab group ($p > 0.05$). However, the number of biopsies with Grade 1 rejection was increased >2-fold in the daclizumab group ($n = 35$) compared with the ATG group ($n = 17$; $p = 0.04$). The total number of biopsies performed within the first 3 months increased by 26% in the daclizumab group. The number and severity of rejection episodes after 3 months was similar in the 2 groups. The overall occurrence of bacterial infections was significantly higher in the ATG group than in the daclizumab group ($p = 0.05$).

Conclusions: ATG and daclizumab are equally effective in preventing acute rejections requiring treatment (ISHLT Grade $\geq$2). Due to the significantly greater frequency of Grade 1 rejections, daclizumab was found to be associated with an increased number of additional biopsies for monitoring rejection status. This implies additional costs to the transplant program, and the long-term implications of the increased number of low-grade rejection episodes remains to be determined. J Heart Lung Transplant 2005;24:296–302. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

Induction therapy in cardiac transplantation has been used as adjuvant in quadruple-drug immunosuppression regimens for several years. Two different induction regimens are currently being used: one-based on polyclonal antibodies, anti-thymocyte globulin (ATG), and the other based on monoclonal antibodies against either CD3 (OKT3) or the interleukin-2 receptor (daclizumab, basiliximab).

The use of ATG results in a marked depletion of T lymphocytes.[1,2] When ATG is used as induction therapy, early post-operative renal insufficiency is minimized and the number of rejection episodes decreased. Furthermore, a trend toward a lower incidence of coronary atherosclerosis 5 and 10 years after transplantation has been observed in patients receiving ATG.[3,4] In one study a trend toward a higher incidence of rejection episodes was observed with OKT3 prophylaxis and with a smaller risk of infections when compared with ATG prophylaxis.[5]

Daclizumab mediates its action by competitive inhibition of the T-cell interleukin-2 (IL-2) receptor, thereby inhibiting clonal proliferation and differentiation.[6] Although IL-2 plays an important role in graft rejection, interference with the IL-2 pathway alone is not sufficient to prevent graft rejection.[7,8] Both ATG[1,3,9] and daclizumab,[10] when combined with cyclosporine, steroids and azathioprine/mycophenolate mofetil, are

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more effective than standard triple-drug therapy alone in preventing rejections after cardiac transplantation. The polyclonal antibodies may be superior immunosuppressive agents due to their panlymphocytolytic activity. On the other hand, the newer monoclonal antibodies are superior to polyclonal antibodies in their target specificity and the reproducibility of their effects, and they may have a reduced risk of systemic side effects.[2] Furthermore, one may anticipate that the polyclonal antibodies cause an increased frequency of infections due to their panlymphocytolytic activity. To date, no studies has compared ATG (Thymoglobulin) to daclizumab (Zenapax) as induction therapy after cardiac transplantation.

The purpose of this study was to evaluate the efficacy of immunosuppressive induction regimens based on either ATG or daclizumab with respect to the number and severity of rejection episodes during the first year after cardiac transplantation.

METHODS

Patient Selection

This study included consecutive adult patients receiving heart transplantation from July 1997 to December 2000 at the University Hospital of Copenhagen (Rigshospitalet), Denmark. All patients were ≥18 years of age receiving their first orthotopic heart transplant and still alive 4 weeks after the transplant. Forty patients fulfilled these inclusion criteria. The first 20 patients received ATG (thymoglobulin, Imtix-Sangstat, Merieux) 2.5 mg/kg/day for 3 to 5 days peri- and post-operatively as induction therapy, whereas the remaining 20 patients received daclizumab (Zenapax, Roche) 1 mg/kg/day on the day of transplantation and every second week thereafter for a total of 5 doses. Apart from this change in induction therapy, all patients were treated using the same protocol. A total of 9 patients were excluded: 3 due to age <18 years; 2 due to death within the first 24 hours of transplantation; and 2 due to death from multi-organ failure within the first 3 weeks. Two patients receiving a combined heart and liver transplantation were excluded. None of the patients excluded had an acute rejection episode as the underlying cause of death.

Immunosuppressive Therapy

All patients received triple-drug immunosuppression consisting of cyclosporine, azathioprine and steroids. Cyclosporine administration was performed according to a standard schedule. The intended serum cyclosporine level was 400 μg/liter (range 300 to 400) for Weeks 1 to 6 300 μg/liter (range 240 to 300) for Weeks 6 to 24 and 200 μg/liter (range 180 to 240) for Week 24 onward. Azathioprine was given at a starting dose of 4 mg/kg, and 2 mg/kg at follow-up, tailored by leukocyte counts. Prednisolone was started at 0.2 mg/kg and, after 4 to 6 weeks, reduced to 0.1 mg/kg as maintenance therapy. None of the patients were weaned off completely.

Biopsy Schedule, Histologic Grading and Treatment of Rejection

All patients underwent endomyocardial biopsies to diagnose and evaluate the severity of rejection episodes. Standard biopsies were taken weekly for the first 6 weeks after transplantation, every second week for the next 6 weeks, monthly for 3 months and every third month thereafter. Rejection was assessed according to the classification of the International Society for Heart and Lung Transplantation (ISHLT).[11] If a biopsy showed any signs of rejection (Grade ≥1), supplementary biopsies were taken once a week during the subsequent weeks until no signs of rejection were found on 2 consecutive biopsies. Three consecutive Grade 1 biopsies led to pulse therapy consisting of intravenous methylprednisolone (Solumedrol, 1 g/day for 3 days). The same treatment was used in all cases of Grade ≥2 rejection and, in cases of Grade 3B or 4 rejection, a rescue dose of 2.5 mg ATG was added for 3 to 5 days.

Standard Prophylactic Anti-Microbial Chemotherapy

All patients received standard treatment consisting of intravenous ceftriazone (Rocephaline) 3 g/day for 1 to 2 days as anti-bacterial prophylaxis. *Pneumocystis carinii* prophylaxis consisted of oral sulfamethizole and trimethoprim 400 mg/80 mg/per day. As cytomegalovirus (CMV) prophylaxis, patients received intravenous gancyclovir (Cymevene), initially 5 mg/kg twice daily for 10 days, then oral gancyclovir 3 g/day for a total treatment period of 3 months.

Definition of Infection

Viral infection with CMV was surveyed by serology based on IgG anti-CMV seroconversion or IgM anti-CMV in the blood.[12] If anti-bacterial therapy was initiated based on the clinical situation in addition to the standard prophylactic treatment, then we considered the patient to have had a bacterial infection.

Statistical Analysis

Patients were followed up for 12 months after transplantation or censored at the time of death. If several consecutive biopsies showed rejection, we considered this as 1 episode of rejection until a biopsy appeared without signs of rejection. Differences in categoric variables between the 2 groups were evaluated by chi-square analysis. Continuous variables were compared between groups with an unpaired Student's *t*-test. Kaplan–Meier plots with log-rank analysis were used to compare the time to a first rejection episode. All