Immunosuppression induction with daclizumab and antithymocyte globulin in cardiac transplantation: clinical experience with 8 cases

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Abstract: Objective To review the clinical experience of immunosuppression induction therapy to prevent acute rejection in 8 patients with cardiac transplant. **Methods** Between June, 2000 and May, 2002, 8 patients with end-stage dilated cardiomyopathy undergoing orthotopic cardiac transplantation received induction therapy with two-dose daclizumab (1.0 mg/kg), given intravenously within 12 h before cardiac-transplantation surgery and two weeks thereafter, and with an initial 5-day course of intravenous antithymocyte globulin (100 mg/d) following transplantation. Cyclosporine or tacrolimus, mycophenolate mofetil or azathioprine, and prednisolone were applied for immunosuppression maintenance. **Results** No death occurred during the follow-up. Routine endomyocardial biopsies in all cases performed in the early stage detected only mild rejection, and no acute allograft or renal dysfunction was found. Three patients developed opportunistic infection, and only one had late acute rejection in the 14th post-transplantation month. **Conclusions** Induction therapy with intravenous daclizumab and antithymocyte globulin is effective to prevent acute rejection and alleviate organ dysfunction in cardiac transplantation, but might increase the chance of infections.

Key words: cardiac transplantation; immunosuppression induction; acute rejection; antithymocyte globulin; daclizumab

Acute rejection and acute right heart failure of the allograft and post-transplant opportunistic infections severely affect the short-term survival of the recipients of cardiac transplantation, and the standard triple-drug immunosuppressive therapy with cyclosporine, azathioprine and prednisone often gives rise to high incidence of complications, also likely to result in acute renal dysfunction [1]. We had performed orthotopic cardiac transplantation in 42 patients with end-stage cardiopathy from August, 1995 to June, 2003, and between June, 2000 and May, 2002, 8 recipients received perioperative immunosuppression induction with monoclonal antibody (mAb) daclizumab combined with polyclonal antibody antithymocyte globulin (ATG), and favorable effects were achieved. We therefore conducted a retrospective analysis of the cases to determine t he impacts of the induction therapy on recipient survival, acute rejection episodes, occurrence of infections and the patients' renal function after cardiac transplantation.

MATERIALS AND METHODS

Clinical data

All the 8 patients were male aged 33 to 53 years (mean 44.4 years), weighing 46 to 70 kg (mean 56.0±7.6 kg), who suffered end-stage dilated cardiomyopathy with severe heart failure and heart function of NYHA class Ⅳ. The pulmonary vascular resistance of all patients (2.4-6.7 Wood unit, mean 4.8±2.3 Wood unit) was in acceptable range when measured by right heart catherterization preoperatively. All patients were weaned from maximal medical therapy such as inotropic, diuretic and vasodilator therapy. Six patients had episodes of nonsustained ventricular tachycardia recorded on 24-hour Holter electrocardiography, 3 received no medications for slight elevation of blood urea nitrogen (BUN) and creatinine levels, and 1 suffered pleural effusion.

All the donors were male with their age ranging from 22 to 31 years, matched for ABO and Rh blood types and body weight with the recipients and lymphocyte cross-match revealed positivity rates all below 10% for the lymphocytotoxic antibodies. All the patients underwent standard orthotopic cardiac transplantation procedure. The donor hearts were preserved in 4 ℃ Stanford University solution and protected by cold blood cardioplegia during operation. The warm ischemia time of the donor heart was 3-7 min, with aortic cross-clamp time of 100-153 min and extracorporeal circulation time of 139-237 min.

Immunosuppression therapy

All the cardiac allograft recipients received

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immunosuppression induction with daclizumab (1.0 mg/kg, Zenapax, Roche, Shanghai) administered intravenously over a period of 15 min within 12 h before cardiac transplantation surgery, and two weeks thereafter for a total of two doses. Rabbit antithymocyte globulin (100 mg/d) was also administered intravenously in an initial 5-day course following the transplantation. Intravenous methylpredisolone (MP, 1 000 mg) was given after removal of the cross-clamps during the operation and post-operatively at the dose of 500 mg/d for two doses. Prednisone (Pred) was given orally twice daily on post-operative day 3. Oral cyclosporine A (CsA) or tacrolimus (FK506), and mycophenolate mofetil (MMF) were initiated on post-operative day 6. MMF were replaced by azathioprine (Aza) one or two months after the transplantation. The doses of CsA or FK506 were adjusted to obtain a whole-blood trough level of 300-500 μg/L or 15-20 μg/L after the transplantation, as measured using a monoclonal assay (TDX assay). Pred was tapered over the course of 7 d to 0.2 mg/kg per day on the third month and further tapered to 0.1 mg/kg per day on the sixth month from day 14 postoperatively.

RESULTS

Efficacy

All the 8 recipients survived. The total follow-up time was 15-38 months with a mean of 25.3 ±7.9 months. After the operation the cardiac function of all the recipients was improved to NYHA class 0-Ⅰ, and all the patients returned to work and rehabilitated to an active lifestyle with good quality of life. Only one recipient developed acute rejection 14 month after transplantation, defined as grade 3 according to the criteria of the International Society of Heart and Lung Transplantation (ISHLT) and was successfully managed with a pulse treatment of steroids (intravenous methylprednisone at 1 g/d for 3 d). Routine right ventricular endomyocardial biopsies for surveil- lance of acute rejection and corresponding treatment assessment were repeatedly performed during the first month after transplantation. Only mild rejections of grade 0-1a (in 7 recipients) and grade 1b(in 1 recipient) were detected. Examinations with echocardiography and Doppler were performed during the follow-up period, showing normal left and right ventricular chamber sizes and septa wall motion in all the cases. The cardiac functions were evaluated by ejection fraction (EF) and fractional shortening (FS) and the result showed that EF were between 64% and 81% (mean 69.4±3.7%) and FS between 38% and 51% (mean 41.8 ±3.5%). No ST-segment depression was detected. Coronary arteriography was performed in 3 recipients 2-3 years after the transplantion and no coronary stricture was found.

The peak serum creatinine concentrations and serum BUN concentrations were 148.5±4.2 μmol/L and 8.6 ±0.9 mmol/L in the first week, and 142.4 ±10.6 μmol/L and 11.4 ±1.3 mmol/L in the first month after transplantation, respectively. Opportunistic infection episodes occurred in 3 recipients within the first month, who all developed pulmonary infections with no obvious symptoms, pulmonary physical signs or chest X-ray manifestations, identified only by sputum cultures. One recipient was infected with *Klebsiella pneumoniae*, another with *Klebsiella pneumoniae* and *Flavimonas*, the third with *Klebsiella pneumoniae*, *Candida albicans* and *Aspergillus*, and all the 3 recipients recovered smoothly. None of the 8 cases developed viral infections such as cytomegalovirus, and their peripheral lympho- cyte counts were within the range of (0.1~0.8)×10^9/L [mean (0.48 ±0.18) ×10^9/L] during the first month after transplantation. The clinical effects of immunosuppression induction protocol in cardiac transplant recipients appeared to be superior in comparison with those of standard protocol[1](Tab.1).

Tab. 1 Comparison of the clinical effects of immunosuppression protocols in cardiac transplant recipients

Immunosuppression protocol	*n*	Death	Acute rejection	Allograft dysfunction	Renal dysfunction	Opportunistic infection
Induction protocol	8	0	1	0	0	3
Standard protocol	18	4	7	5	4	12

Adverse effects

The administration of daclizumab and antithymocyte globulin was not associated with any short-term severe adverse reactions except for mild fever. There was no evidence of allergic reaction, hypotension, asthma, myalgias and urticaria. Similarly, no long-term adverse effects such as lymphoma or cancers were observed.

DISCUSSION

We found that induction therapy with two-dose daclizumab and five-dose antithymocyte globulin in addition to the maintenance therapy with triple immunosuppressive agents improved short-term graft survival of the patients, decreased the occurrence of acute rejection and prolonged the first rejection episode in the first three months after cardiac transplantation, and decreased the overall severity of rejection, allograft dysfunction, renal dysfunction and opportunistic infectious complications as compared with generalized immunosuppressive therapy[1,2].

In a cyclosporine-based protocol of immunosuppression, induction with thymoglobuline is associated with a lower rate of early acute rejection. Moreover, the risks of infection and cancer development are not increased and the incidence of graft coronary atherosclerosis tends to be lowered 5 and 10 years after transplantation [3]. The safety of thymoglobuline allowed the withholding of oral cyclosporine or tacrolimus until normal hemodynamic and renal functions were achieved, which decreases the incidence of acute renal dysfunction following transplantation. The present observation is in agreement with that by Carrier *et al* [3]. There were no occurrences of acute renal failure in these 8 recipients during the first week following transplantation. Alloantigen-activated T cells express high-affinity interleukin-2 (IL-2) receptor, and specifically blocking this receptor with human IgG1 mAb daclizumab, a genetically engineered human mAb directed against the alpha chain of the IL-2 receptor (CD25), may prevent allograft rejection after cardiac transplantation without inducing global immunosuppression. As its effective serum half-life is 21 days[4], two doses may provide saturation for at least 1 month and a half (as determined by receptor saturation studies[4]), which covers the period when cardiacallograft rejection is most likely to occur. Induction therapy with daclizumab given intravenously within 24 hours after cardiac transplantation and every two weeks thereafter for a total of 5 doses safely reduced the frequency and severity of cardiac allograft rejection during the induction period and did not increase the incidence of infection or cancer during follow-up [5]. The action mechanisms of daclizu- mab are not known, possibly involving its binding to circulating lymphocytes with IL-2 alpha-chain receptors but without activating the receptors, and the cells there- fore have no free IL-2 alpha-chain receptors available for activation by IL-2. Targeting the IL-2/IL-2R pathway with daclizumab induction therapy after organ transplantation does not completely prevent T-cell reactivity, which can be achieved by the combination of daclizumab pretreatment with antithymocyte globulin. Our study showed that the short-term safety profile of this new induction therapy with two-dose daclizumab and five-dose antithymocyte globulin appears to be superior to that of the therapies we implemented pre- viously [1]. The dose of pred can be tapered more rapidly with the new induction therapy than with con- ventional immunosuppressive therapy, and in addition, the administration of daclizumab is not associated with any detectable signs of adverse events.

The benefit of perioperative induction therapy with monoclonal and polyclonal antibodies remains controversial due in part to the significant decrease in the absolute counts of circulating lymophocytes in the peripheral blood with a concomitant increase in infections, which might need more strict isolation procedures, prophylactic measures with antifungal or antiviral agents and etiological tracking and monitoring. Furthermore, the risk of post-transplant lymphoproliferative disorder might increase after treatment of the allograft recipients with these antibodies which result in a higher rate of lymphoma, although none of the recipients developed lymphoma in this observation.

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赛尼哌结合抗胸腺细胞球蛋白免疫诱导在心脏移植中应用的临床经验(附 8 例报告)

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摘要:目的 总结本组 8 例心脏移植受者应用免疫诱导方案治疗的临床经验。方法 8 例终末期扩张型心肌病患者接受同种异体原位心脏移植术,免疫诱导采用术前 12 h 内及术后第 14 天 2 剂赛尼哌 1.0 mg/kg(抗白介素 -2 受体抗体)结合术后前 5 d 5 剂抗胸腺细胞球蛋白(ATG)100 mg/d 的方法,免疫抑制维持治疗采用环孢素 A(或他克莫司)+ 骁悉(或硫唑嘌呤)+ 泼尼松三联方案。结果 全组无死亡,移植后早期心内膜心肌活检无明显急性排斥反应,无移植物功能不全,无明显急性肾功能不全;3 例发生机会性感染,1 例远期发生急性排斥反应。结论 心脏移植围术期采用 2 剂赛尼哌结合 5 剂 ATG 进行免疫诱导治疗方案能有效预防移植心脏急性排斥反应和减少器官功能损害,但可能增加感染的发生率。

关键词:心脏移植;免疫诱导;急性排斥反应;抗胸腺细胞球蛋白;赛尼哌
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