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Polyclonal versus monoclonal rejection prophylaxis after heart transplantation: a randomised study

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Abstract. Recent studies comparing the effects of induction therapy with polyclonal antilymphocyte globulins (ALG) or with monoclonal T-cell-specific antibodies are not unanimous. Therefore, 55 heart recipients were allocated to either 7-day courses of polyclonal ALG ($n = 28$) or of monoclonal OKT3 ($n = 27$). Additionally, azathioprine and low dose steroids were given. There were no severe side effects after OKT3; the course of ALG, however, had to be discontinued in 20 patients because of extensive flares. No differences between the two groups were found in freedom from rejection or in the incidence of infection. The 1- and 2-year survival was 96% in both groups. Although monoclonal and polyclonal induction therapies are equally effective for rejection prophylaxis, OKT3 may be preferred because of a lack of important side effects. However, the fact that a shorter course of ALG is equally effective may be in favour of ALG.

Key words: Heart transplantation – Rejection prophylaxis – Polyclonal/monoclonal antibodies

Polyclonal antilymphocyte or antithymocyte globulins (ALG, ATG) as well as monoclonal antibodies against T cells have proved to be effective for reversing acute cardiac allograft rejection [5, 7, 10]. Subsequently, various protocols using these antibodies have been developed for rejection prophylaxis in heart transplant recipients [2, 11, 12, 19]. More recently, studies comparing the effects of polyclonal and monoclonal T-cell-specific antibodies have been reported [9, 13, 14, 17]. Their results, however, are not unanimous about the superiority of one antibody preparation with respect to another in terms of rejection prophylaxis, safety and infectious complications.

In an earlier, randomized, controlled study in heart transplant recipients, we demonstrated that OKT3 facilitates patient care by preventing renal failure in the immediate postoperative period but does not reduce the incidence of rejection when compared to cyclosporine given i.v. [2]. Polyclonal anti-T-cell prophylaxis may induce broader immunosuppression resulting in fewer rejection episodes but might also give rise to more infectious complications. The present study was undertaken to compare a polyclonal horse lymphocyte-specific immunoglobulin with monoclonal OKT3 with regard to rejection prophylaxis, safety and infectious complications.

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Materials and methods

All consecutive heart transplant recipients between 1 August 1989 and 1 August 1991 were enrolled into the trial and were subsequently allocated to receive either OKT3 (Ortho Pharmaceutical, Raritan, N.J.) or ALG (horse lymphocyte-specific IgG2, Lymphoglobulin, Institut Merieux). OKT3 was started postoperatively in a dose of 5 mg/day, 1–2 h after arrival at the Intensive Care Unit while still on the ventilator, and continued for 7 days. Similarly, ALG was started 1–2 h after arrival at the Intensive Care Unit, in a dose of 425 lymphocytotoxic units (0.5 ml) per kilogram of bodyweight daily and continued for 7 days. In addition, azathioprine was administered postoperatively, 50 mg/day intravenously for 6 days, and prednisolone was given prior to the operation (20 mg) and 60 mg/day thereafter, in two divided doses, tapering down by 10 mg every 3 days to 20 mg/day and subsequently by 2.5 mg/week until the maintenance dose of 10 mg/day was reached at approximately 8 weeks postoperatively. Half of the daily corticosteroid dose was given shortly before the administration of OKT3 or ALG, in combination with 4 mg clemastine i.v., to alleviate side effects. Oral cyclosporine was initiated on postoperative day 5 in a dose of 8 mg/kg daily in two divided doses and adjusted to the plasma levels.

Cyclosporine levels were measured by specific ^{125}I-CSA radioimmunoassay (Cyclotrac, Incstar, Stillwater, Minn.) to keep plasma 12 h trough levels between 80 and 120 ng/ml in the early postoperative period and between 50 and 100 ng/nl after 9–12 months.

The diagnosis of acute rejection was made by histological examination of endomyocardial biopsies and graded according to Billingham's criteria of none, mild, moderate and severe rejection [3]. For the diagnosis of moderate rejection, the coexistence of mononuclear infiltrates and myocyte necrosis was required.

Treatment of acute rejection was instituted in the case of moderate rejection and consisted of R(abbit)-ATG to keep T cells between

Table 1. Characteristics of the patients who received either monoclonal or polyclonal antibodies for rejection prophylaxis

Induction therapy		ALG	OKT3
Number of patients		28	27
Gender M/F		23/5	22/5
Recipient age (years, range)		45 (18–61)	48 (15–62)
Primary heart disease	CMP	16	14
	IHD	12	10
	VHD	–	3
Donor age (years, range)		26 (14–43)	24 (12–38)
CMV serostatus negative *(n)*		13	9
PRA (%, median, range)		0 (0–20)	0 (0–54)
Donor/recipient gender mismatch *(n)*		9	10
Mismatch HLA-A		1.3 ± 0.5	1.4 ± 0.7
HLA-B		1.6 ± 0.6	1.4 ± 0.6
HLA-A + B		2.9 ± 0.9	2.9 ± 1
HLA-DR		1.2 ± 0.5	1.3 ± 0.7
Mismatch HLA-A + B 0 *(n)*		1	0
1 or 2		8	11
> 2		19	16
Mismatch HLA-DR 0 *(n)*		1	4
1		20*	10*
2		7	13

ALG, horse anti-lymphocyte IgG2; CMP, cardiomyopathy; IHD, ischemic heart disease; VHD, valvular heart disease; CMV, cytomegalovirus; PRA, panel reactive activity
* $P < 0.025$

0 and 150/mm³ for 14 days for the first episode of rejection, 1 g methylprednisolone i. v. on 3 consecutive days for the second episode and OKT3 5 mg/day for 10 days in case of ongoing rejection or an early third episode of rejection.

All cytomegalovirus (CMV) seronegative recipients received (CMV seronegative blood products and passive immunization with CMV-specific immunoglobulin (Cytotect, Biotest Pharma, Frankfurt, FRG) for 10 weeks, as reported before [15].

Infections were defined as symptomatic episodes with concurrent demonstration of the causative agent by culture or changes in serological status. CMV infection was defined by a rise of IgM antibodies, demonstration of immediate early antigen (IEA), or isolation of the virus from throat swabs or urine. CMV disease was defined as fever or signs of organ involvement in the presence of CMV infection.

Statistical analysis. Data are expressed as mean values ± 1 SD or medians as appropriate. The significance of differences between means was assessed by the 95% confidence interval. Comparisons of proportions are based on the χ^2 test. Log rank test was used to assess the differences in freedom from rejection. For survival analysis, the Kaplan Meier method was used.

Results

In all, 28 patients received ALG and 27 patients were treated with OKT3. Patient characteristics including the numbers of donor/recipient gender mismatches and numbers of mismatches for HLA-A and -B, as well as the current panel reactive activity (PRA) were similar in both groups, although there was some difference in HLA-DR mismatches (Table 1). All patients received at least one blood transfusion prior to transplantation. Crossmatches of donor lymphocytes with recipient sera, performed in case of more than 5% PRA, were negative.

The scheduled 7-day course of ALG was discontinued in 20 out of 28 patients after 5 days (range 3–6) because of extensive flares. The development of pyrexia (mean highest temperature 39.1 °C) was not different from the fever in the patients from the other treatment group.

The full 7-day course of OKT3 could be completed in all 27 patients. Fever (mean maximal temperature 39.4 °C) occurred in all but 3 patients, a mild rash was noted in 4 patients and diarrhoea in 1 patient.

Median follow-up was 15 months (range 3–25). The 1- and 2-year graft and patient survival was 96% in the OKT3 as well as in the ALG group.

No difference was found in the mean number of acute rejection episodes per patient during follow-up. Actuarial freedom from rejection at 1, 3 and 12 months was 68%, 18% and 13% in the ALG group and 74%, 33% and 20% in the OKT3 group. These differences were not significant (Fig. 1). The numbers of acute rejection episodes per patient were also equally distributed among the two treatment groups: 5, 14, 5 and 3 (ALG) versus 4, 11, 6 and 7 (OKT3) patients with respectively 0, 1, 2 or more than 2 rejection episodes.

A total of 42 patients received 1 (29 patients), 2 (12 patients) or 3 (1 patient) additional courses of polyclonal or monoclonal antibodies after the inductional therapy for the treatment of rejection.

The mean numbers of infections per patient was 0.9 and 0.8 in the ALG and OKT3 groups, respectively. Bacterial infections occurred more frequently than viral infections. There was no difference in the occurrence of bacterial, parasitic and fungus infections between the two treatment groups. CMV disease and herpes zoster were the main virus-induced problems. Again, no difference in the occurrence of viral infections or disease between the ALG and OKT3 groups could be demonstrated (Table 2). In both treatment groups more, but not significantly different, bacterial infections and CMV disease or herpes

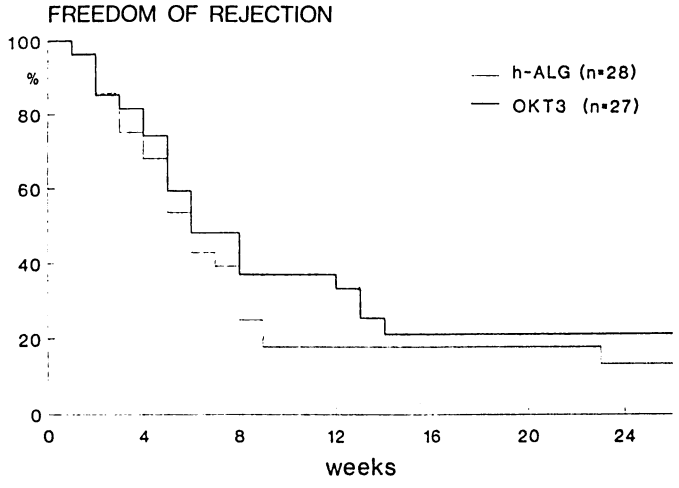

Fig. 1. Comparison of freedom from acute allograft rejection after induction therapy with ALG or OKT3 in 55 heart transplant recipients

Table 2. Infections after polyclonal or monoclonal T-cell-specific antibodies

Induction therapy	ALG	OKT3
All infections	26	23
Viral infections	9	6
CMV disease	4	2
Herpes zoster	3	1
Bacterial infections	15	14
Fungus infections (superficial *Candida*)	–	1
Parasitic infections	2	1
Pneumocystis carinii	2	–
Intestinal ascaris	–	1

zoster occurred in patients who received additional anti-T-cell therapy for rejection treatment compared with those without it. Bacterial infections occurred in 21 out of 41 patients with additional therapy versus 8 out of 14 patients without it and CMV disease or herpes zoster in 7 out of 41 patients with versus 3 out of 14 patients without additional anti-T-cell therapy.

Malignancies occurred in 1 patient from the ALG group and in 3 patients in the OKT3 group. The first patient, who received ALG for induction therapy, developed a squamous cell carcinoma of the external acoustic meatus 9 months after transplantation. The second patient died 18 weeks after transplantation from malignant lymphoma. After OKT3 induction therapy he had been treated with R(abbit)-ATG and a second course of OKT3 for intractable rejection. The third patient who received OKT3 initially was operated upon because of adenocarcinoma of the antrum, 7 months after transplantation. In the fourth patient a mucodermoid carcinoma of the palatum was noted, 12 days after transplantation.

Discussion

Although excellent short- and medium-term survival after heart transplantation can be achieved without the use of polyclonal or monoclonal anti-T-cell induction therapy [1], no efforts have been spared to develop an immunosuppressive regimen that would reduce the incidence of rejection as well as the complications of immunosuppression. In our centre the 2-year actuarial survival rates of 91% and 94% were achieved in heart transplant recipients, prior to this study, with and without OKT3 induction therapy, respectively [2]. The fact that OKT3 facilitated the immediate postoperative care, as the administration of cyclosporine could be avoided in the immediate postoperative period, but could not reduce the incidence of rejection made us embark on the present study, comparing the effects of polyclonal and monoclonal antibodies on cardiac allograft rejection. The graft and patient survival in both treatment groups was excellent. No superiority of one regimen over the other could be demonstrated with respect to freedom from rejection or time to detection of the first rejection.

The administration of ALG was hampered by fever and rapidly evolving, giant flares in 20 patients, necessitating premature discontinuation of the medication. No other complications were noted.

As in a previous study, almost all patients developed fever, but none experienced severe side-effects during or after the initial doses of OKT3 [2]. In contrast with the results of others, no haemodynamic deterioration or pulmonary oedema occurred. This may be explained by the fact that the first dose of OKT3 was given immediately postoperatively at the time the patients were still on the ventilator, while isoprenaline and dopamine were administered continuously [4, 8, 16, 18, 20]. Moreover, special care was taken to administer fluids in order to correct the drop of arterial blood pressure and right-sided filling-pressures resulting from the decrease in systemic arterial and venous vascular resistance.

Bacterial and viral infections occurred frequently and were associated with significant morbidity. No difference in the incidence of bacterial and viral infections was observed between the ALG and OKT3 groups despite the more selective action of OKT3. In earlier reports, there is no agreement about a difference in the incidence and nature of infections after monoconal and polyclonal antibodies [9, 13, 17]. However, comparison of the numbers of infections in patients who received additional anti-T-cell therapy with those in patients in whom the induction course was the only antibody therapy revealed that more bacterial as well as viral infections occurred in the patients who received additional antibodies. The difference was not significant.

Malignancy was the cause of death in one patient and appeared to have been treated effectively in two patients. The duration of follow-up is too short to appreciate the final effect of therapy. Although more malignancies occurred in the prophylactic OKT3 group, this difference was not significant. A longer follow-up will be necessary to confirm our earlier findings, in a larger group of patients, that malignancy is not associated with one specific antibody but with the total immunosuppressive load [6].

The data from this randomised trial indicate that polyclonal and monoclonal antibodies are equally effective for rejection prophylaxis after cardiac transplantation. OKT3 induction therapy may be preferred because of a lack of important side-effects. However, the fact that a shorter course of ALG (the scheduled course was discontinued early because of side-effects in the majority of patients). induces a similar freedom from rejection with subsequently similar incidences of the major complications of immunosuppressive therapy may be in favour of ALG.

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