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The risk of infection following OKT3 and antilymphocyte globulin treatment for renal transplant rejection: results of a single center prospectively randomized trial

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Abstract. Some 43 of 60 (72%) renal allograft recipients who were prospectively randomized to receive either OKT3 monoclonal antibody ($n = 30$) or ALG (antilymphocyte globulin) polyclonal antibody ($n = 30$) for steroid-resistant rejection suffered from infection, 25 (83%) following OKT3 and 18 (60%) following ALG treatment ($P < 0.05$). Clinically evident herpes infection was most frequently seen (9 and 7, respectively), followed by pneumonia (6 and 1, respectively $P < 0.05$), urinary tract infection and wound infection (2 of each in both groups) fungal *(Candida)* and multibacterial infections. One patient died in each group due to cytomegalovirus (CMV) pneumonia, giving a mortality of 4.3% in each group. Actuarial 1-year graft and patient survival rates were 80% and 97% in both groups, respectively. It is concluded that ALG and OKT3 are equally effective in renal allograft rejection resistant to steroid treatment, however, the risk of infection appears to be higher with OKT3.

Key words: Infection – OKT3 – Antilymphocyte globulin – Rejection

OKT3 monoclonal antibodies have heralded a new era in the treatment of organ transplant rejection. Although the relative advantages of OKT3 monoclonal antibodies in terms of graft survival in steroid-resistant renal allograft rejection has been well documented [4], the relative risk of serious life-threatening infections has not been detailed. Since polyclonal antibodies such as antilymphocyte globulin (ALG) have been used in the pre-OKT3 era as the sole antibody treatment for graft rejection, it was the purpose of this prospectively randomized trial to evaluate various factors associated with the incidence of infections following the treatment with antibodies when graft rejection did not respond to steroid administration.

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Patients and methods

Between 20 July 1987 and 26 June 1991 60 patients aged 41 ± 12 years (mean ± SD; range 17–65) were entered into the study and were followed for a minimum of 3 months up to 51 months. Eighteen (30%) were female and 42 (70%) were male. Two (3.4%) had diabetes. One patient (1.6%) received his graft from a mismatched related donor, and the rest (98.4%) from a cadaver donor. Also, 59 patients (98.4%) underwent transplantation for the first time, while one (1.6%) underwent retransplantation. Half of these 60 patients were randomized to receive OKT3 monoclonal antibodies while the other half received ALG for steroid-resistant rejection.

In the OKT3 group 20 (66.6%) patients were male and 10 (33.4%) female; in the ALG group 22 were male (73.3%) and 8 female (26.7%). Each group had one diabetic patient. Both groups contained 29 patients with primary cadaver transplants. In the ALG group 1 patient had a secondary transplant, and in the OKT3 group 1 patient had a mismatched related graft. The age of the recipients, the presence or absence of diabetes, the number of transplants, the type of donors (cadaver or living related), the number of mismatches (A, B and DR) were statistically insignificantly different (Table 1).

Diagnosis of rejection. The patients only entered in the study had a clinical diagnosis of rejection, involving a rise in serum cratinine level over 0.3 mg/dl, decrease in diuresis of at least 500 ml/day, fever graft tenderness, and histological proof of rejection of the mononuclear interstitial cellular type.

Treatment of rejection. If a steroid bolus therapy of 0.5 g on 2–4 successive days did not lead to graft function improvement, the patients were randomized to receive either OKT3 or ALG for 10 days. Con-

Table 1. Patient demographics of the cohorts receiving OKT3 or antilymphocyte globulin (ALG) for steroid-resistant rejection

	ALG ($n = 30$)	OKT3 ($n = 30$)	P
Age (years)	40.9 ± 12.1	40.2 ± 12.8	n.s.
Sex (m/f)	22/8	20/10	n.s.
Diabetic	1	1	n.s.
HLA-A, -B mismatches	1.8 ± 1.0	1.8 ± 0.8	n.s.
DR mismatches	0.5 ± 0.6	0.7 ± 0.6	n.s.
first transplant	29	30	n.s.
Retransplant	1	0	n.s.
CAD/LRD	30/0	29/1	n.s.
Pres. time (h)	20 ± 5	20 ± 5	n.s.
Donor age (years)	41 ± 13	42 ± 15	n.s.

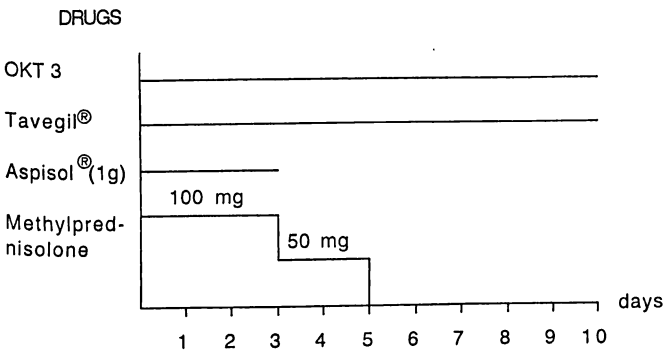

Fig. 1. Concurrent medication with OKT3 to prevent first-dose reactions

currently, the basic immunosuppression was continued with cyclosporin A (Sandoz), (up to 300–400 mg/ml TDX), azathioprine (Wellcome), and steroids as scheduled. The dosage of antilymphocyte globulin (Merieux) was 5 ml/10 kg body weight (maximum 30 ml/day) given via a central venous line. The dosage of OKT3 (Ortho) was 5 ml/day administered intravenously. In addition, methylprednisolone, 1 ampulla of Tavegil, and 1 g of Aspisol were given to the patients to prevent first-dose reactions (Fig. 1).

Basic immunosuppression. The induction and basic immunosuppression following transplantation were identical in all patients. ALG was administered for at least 7 days in a dosage of 5 ml/10 kg bodyweight with a maximum of 30 ml/kg daily. Cyclosporin A was given the first day postoperatively in a dose of 3 mg/kg intravenously and subsequently orally in a dose of 10 mg/kg daily and then reduced in steps as determined by TDX while trying to keep the level between 300 and 400 ng/ml. Prednisolone was given in a dose of 250 mg/day reduced in increments of 25 mg per day to 100 mg and then twice daily in 5-mg increments to a maintenance dose of 10 to 15 mg/day. Between 1 and 5 mg/kg azathioprine was given daily to the patients. For prophylaxis, a cephalosporin antibiotic was administered just prior to surgery. Every patient received a 3-day course of hyperimmunoglobulin 2 ml/kg body weight.

Diagnostic methods. All patients underwent chest roentgenograms on a regular basis (every 3–4 days). Sputum cultures were obtained, and if indicated, fiberoptic bronchoscopy with lavage or brushing was performed. The specimens were cultured and examined with special stains for bacteria, viruses, and fungi. A diagnosis of cytomegalic (CMV) inclusion disease was confirmed when the clinical picture was compatible and there was either serologic (a greater than four fold increase in complement fixing or indirect fluorescent antibody levels to CMV) and/or culture evidence of active CMV infection [5].

Treatment. Infections were treated with antibiotics, either empirically or according to sensitivity testing when cultures were available. Acyclovir was administered for CMV and herpes virus infections. Hyperimmunoglobulin was given to all patients with evidence of CMV infection.

Data retrieval. Each transplant patient completed a scheduled follow-up form at 1, 3 and 6 months following transplantation and every 6 months subsequently until 13 September 1991, loss of function, or death. Detailed information was collected for every week that a patient was hospitalized from the time of transplant until 13 September 1991, loss of function, or death. Computerized information included chest roentgenogram results, a code for infections, culture results, and clinical symptoms such as fever or white blood cell count, and causes of death.

Statistical evaluation. Fisher's exact test was used for comparing small groups of patients, and the χ^2 method was used for comparing larger groups. The graft survival rates were calculated by actuarial techniques. The P values were calculated over the entire period using Gehan's test [2]. In all tests the values were considered statistically significant when P was less than 0.05.

Results

The actuarial graft and patient survival rates are given in Fig. 2. There was no statistically significant difference in graft function or patient survival between those receiving OKT3 and those receiving ALG for steroid-resistant rejection.

Onset of treatment for rejections

The ALG treatement started a mean of 23.7 ± 15.7 days following transplantation, while OKT3 treatment was started 19.9 ± 13.2 days following transplantation. Each treatment was performed for 8.2 ± 1.8 and 9.1 ± 2.1 days, respectively. Neither difference was statistically significant (Table 2). A second rejection had to be treated in

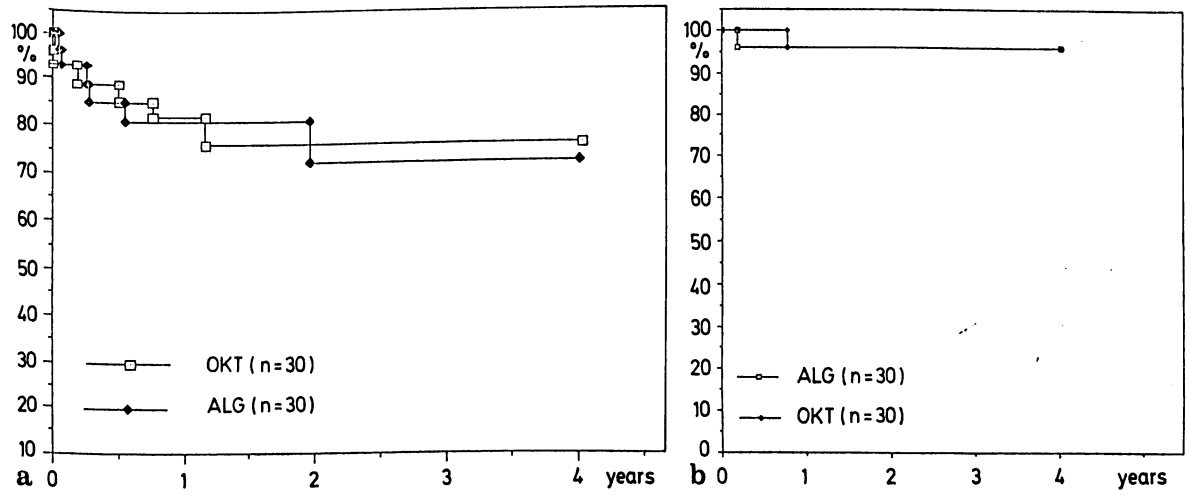

Fig. 2a, b. Actuarial graft (**a**) and patient (**b**) survival rates following OKT3 or ALG treatment for steroid-resistant rejection (P = n.s.)

Table 2. Onset and duration of primary rejection treatment

	ALG (days)	OKT3 (days)	*P*
Onset (mean ± SD)	21 ± 13	19 ± 9	n.s.
Range	6–61	7–74	n.s.
Duration (mean ± SD)	8.2 ± 1.8	9.1 ± 2.1	n.s.

Table 3. Character of first infection following OKT3 and ALG treatment for steroid-resistant rejection

	ALG ($n = 30$)	OKT3 ($n = 30$)	*P*
Pneumonia (CMV)	1 (1)	6 (4)	< 0.05
UTI	2	2	n.s.
Wound	2	2	n.s.
Meningitis	1	1	n.s.
Throat	2	2	n.s.
Sepsis (fungal)	0	1	n.s.
(virus)	7	9	n.s.
(bacteria)	3	2	n.s.
Total	18	25	< 0.05

CMV, cytomegalovirus

12 patients (40%) of the ALG group at a mean ± SD of 118 ± 82 days after transplantation (range 42–327). In the OKT3 group, 12 patients had to be retreated for rejection at a mean ± SD of 285 ± 396 days after transplantation (range 42–1240; Fig. 3). In each group, two patients had to be treated for a third rejection episode.

Incidence of infection

Out of these 60 patients, 43 (72%) contracted an infection requiring intensive antibiotic or chemotherapeutic therapy. Also, 12 (20%); 6 in each group) lost graft function due to causes unrelated to infection. The incidence of infection was 83.3% in the OKT3 group and 60% for the ALG group ($P < 0.05$).

The particular infections according to each group are listed in Table 3.

Ten (33%) patients in the OKT3 group had two episodes of infection 15 ± 17 and 17 ± 16 days (mean ± SD) following treatment. Only 3 patients (10%) in the ALG group suffered from a second infection (*P* vs OKT3 0.05) 21 ± 35 days and 9 ± 4.5 days, respectively (Fig. 4).

Discussion

This ongoing analysis of our prospectively randomized trial has been reported on several occasions [3, 7]. It is important to see that there are no statistically significant differences in patient or graft survival rates using both protocols for therapy, while the risk factors in the two groups were the same at the onset of the study. A very important finding of the study was that despite the use of ALG for induction therapy and prophylaxis of rejection, there was no disadvantage to reinstituting ALG for the treatment of rejection in terms of graft survival and incidence of infection. A low sensitization to ALG has been reported by others [6] due to the polyclonal character of the serum. Since the 1-year graft survival rates are compatible in both groups, differences in morbidity become more important. There was a statistically lower incidence of infection, in particular of pneumonia, in the ALG group; however, the two patients who died of CMV pneumonia belonged one to each group. This might be due to the additional application of steroids which was administered to prevent first-dose reactions in the OKT3 group.

The course of each of the patients who died was complicated by one or more aggravating factors, while the patients in whom the pneumonia resolved experienced milder courses. Generally [1], there is an increased incidence of infection with rejection episodes and the ensuing treatment; however, according to our findings the incidence of infection was indeed higher with OKT3 than with ALG. We failed to find any particular predisposition for a specific etiologic microbe. CMV was the only viral pathogen (except for herpes virus), appearing by itself or in concert with other pathogens.

Thus, kidney recipients treated for steroid-resistant rejection can be subjected to ALG treatment without an in-

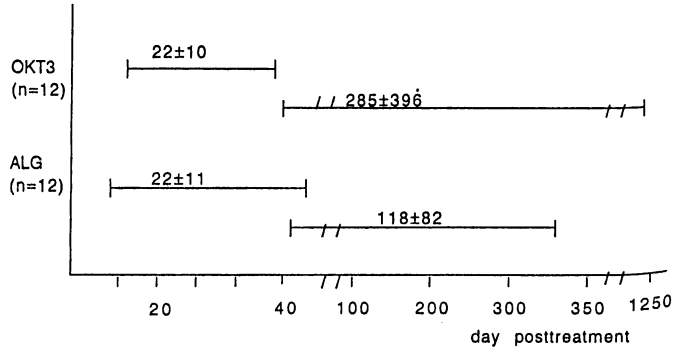

Fig. 3. Onset (mean ± SD) of primary and secondary rejection in patients with two rejection episodes

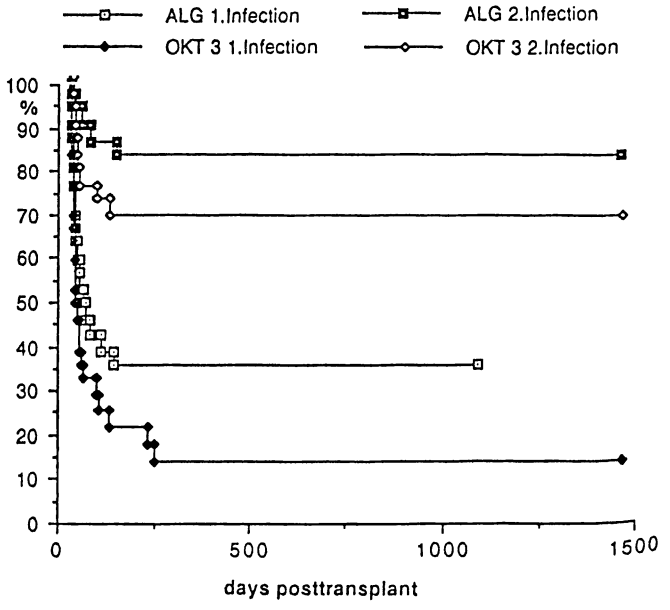

Fig. 4. Percentage of infection-free patients (primary and secondary) following ALG and OKT3 for steroid-resistant rejection

creased risk of infection and with similar graft survival rates when compared with OKT3 treatment, even if ALG is used as an induction therapy. This should allow us to reserve OKT3 for rescue occasions when steroids or a repeated course of polyclonal antibodies is unsuccessful in reversing rejection. The mortality was similar in patients receiving ALG or OKT3 treatment. There is certainly no evidence that ALG renders patients more susceptible to CMV infection than OKT3 treatment; in contrast, OKT3 treatment is accompanied by a higher incidence of CMV infection, which might be due to the increased amount of steroids given.

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