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Antilymphocyte globulins versus OKT3 as prophylactic treatment in highly sensitized renal transplant recipients

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Abstract Monoclonal antibodies were proposed as an effective prophylactic immunosuppressive treatment in highly sensitized patients (HSP). In this study we compared the results obtained in HSP treated with OKT3 or antilymphocyte globulins (ALG). From January 1989 to January 1993, 38 transplantations were performed in patients with high panel reactive antibodies (PRA > 50%). The group comprised 22 women and 16 men, mean age 45 ± 2 (23–67) years; ten were second grafts and two were third grafts. Peak PRA was ≧ 80% in 24 sensitized patients and 50–80% in 14 sensitized patients. Patients were randomly assigned to either prophylactic OKT3 ($n = 15$) or ALG ($n = 23$). Oral cyclosporin A (10 mg/kg) was started at day 8 in the OKT3 group and when the serum creatinine level decreased to 200 μmol/l in the ALG group. OKT3 was systematically withdrawn on day 10 but ALG was stopped only when total blood cyclosporin A concentration reached 150–200 ng/ml. In both groups, azathioprine (150 mg/day) and prednisolone were given. During the first months, 6/15 grafts were lost in the OKT3 group (three hyperacute rejections, one renal vein thrombosis, one steroid-resistant rejection, one death); in the ALG group 4/23 grafts were lost (one hyperacute rejection, two steroid-resistant rejections, one death). Side effects were significantly more frequent in the OKT3 group than in the ALG group. After 12 months of follow up, the graft survival was 71% (27/38) and did not significantly differ (log-rank test, NS) between the OKT3 (60%, 9/15) and the ALG group (78%, 18/23). We conclude that the use of the monoclonal antibody OKT3 as a prophylactic agent in HSP does not improve the early graft survival when compared with prophylactic ALG. Polyclonal antibodies, which react with many epitopes and are much better tolerated seem to offer a good strategy for induction therapy in this population.

Key words Kidney transplants
Highly sensitized recipients
OKT3 · Antilymphocyte globulins

Introduction

OKT3 has been proposed as an effective and safe prophylactic immunosuppressive agent for its ability to prevent or delay the onset of the first rejection episode, to offer an alternative therapy to cyclosporine in patients with delayed transplant function and to delay the administration of potentially nephrotoxic cyclosporine in the immediate postoperative period [1, 2, 3]. It has also been suggested that prophylactic OKT3 could improve the early and long-term outcome of renal transplantation in highly sensitized recipients (HSP) [4, 5] but this finding has not been confirmed by others [6, 7, 8]. We designed a study to compare the safety and efficacy of prophylactic OKT3 versus antilymphocyte globulins (ALG) in HSP receiving sequential immunosuppressive therapy.

Patients and methods

Patients and transplantation

From January 1989 to January 1993, 38 transplantations were performed in patients with high panel reactive antibodies (PRA > 50%). The group comprised 22 women and 16 men, mean age 45 ± 2 (23–67) years, of whom ten were second grafts and two third grafts. Anti-HLA-antibodies were detected by complement-dependent microlymphotoxicity at 37 °C on a panel of 17 donors. Peak PRA was ≧ 80% in 24 HSP, and 50–80% in 14 HSP.

All transplantations were performed with a current negative cross-match (CM) against donor T lymphocytes at 37 °C using the complement-dependent microlymphotoxicity technique [9]. CM were performed with or without DTT (Di-Thio-Treitol) in order to remove IgM. We tested both the current sera and all the historical sera with PRA > 50%. Historical cross-matches were negative in all sera in 30 HSP and positive in at least one serum in 8 HSP. HLA (A/B/DR) mismatches were four in 11 HSP, three in 9 HSP, two in 12 and one in 6 HSP.

Immunosuppressive treatment

Patients were randomly assigned to either prophylactic OKT3 (5 μmg/day, $n = 18$) or ALG (Merieux Institute, Lyon, France) (3 or 4 vitals/day, $n = 20$). However, three patients initially designated for OKT3 therapy had fluid overload and were treated with ALG (OKT3 group, $n = 15$; ALG group, $n = 23$). Oral cyclosporin A (10 mg/kg) was started on day 8 in the OKT3 group and when serum creatinine level decreased to 200 μmol/l in the ALG group. OKT3 was systematically withdrawn on day 10 but ALG was stopped only when total blood cyclosporin A concentration reached 150–200 ng/ml. The mean duration of ALG was 16 ± 2 (5–32) days. In both groups, azathioprine (150 mg/day) and prednisolone (20 mg/day) were given.

Rejection episodes were treated by i.v. methylprednisolone 500 mg/day for 3 days.

Statistical analysis

The results are expressed as mean ± SEM. The two groups were compared using Wilcoxon's signed ranks test for quantitative values and with the Chi-squared test for qualitative values. Statistical significance was set at $P < 0.05$.

Results

Demographic data

Patient demographics are shown in Table 1. There was no statistically significant difference in age, sex, transplant number, PRA, donor age, cold ischaemia time or vascular anastomosis time between the ALG and OKT3 groups (Table 1).

Transplantation outcome

During the first 3 months, 6/14 grafts were lost in the OKT3 group (three accelerated rejections, one renal vein thrombosis, one steroid-resistant rejection, one death); in the ALG group 4/23 grafts were lost (one hyperacute rejection, two steroid-resistant rejections, one death). After 12 months of follow up, the overall graft survival was 71% (27/38) and did not significantly differ (log-rank test, NS) between the OKT3 group (60%, 9/15) and the ALG group (78%, 18/23) (Fig. 1). Moreover, renal function, as measured by the creatinine level, was similar in patients treated with OKT3 or with ALG (Fig. 1).

Table 1 Demographic comparison of the 38 highly sensitized recipients according to immunosuppressive treatment. There were no significant differences between the groups with Wilcoxon's signed ranks test or the Chi-squared test

	ALG group ($n = 23$)	OKT3 group ($n = 15$)
Age (Years)	48 ± 2	42 ± 3
Sex	11 M/12 F	5 M/10 F
PRA (%)	82 ± 4	79 ± 4
HLA (B/DR) MM		
A/B/DR: 1–2	14 (61%)	6 (40%)
A/B/DR: 3–4	9 (39%)	9 (60%)
Multiple transplantations	9 (39%)	3 (20%)
Positive historical CM	4 (17%)	4 (27%)
Cold ischaemia time (h)	27 ± 1	28 ± 1
Donor age (years)	35 ± 3	33 ± 12
Anastomosis time (min)	36 ± 2	39 ± 2

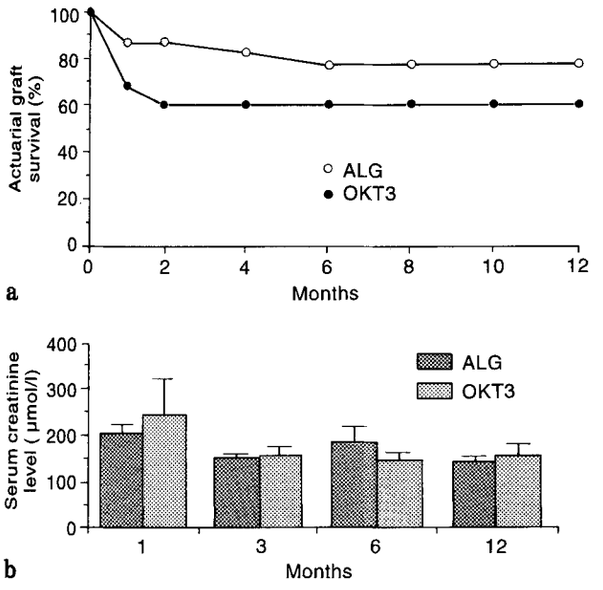

Fig. 1 a, b Graft survival rate (**a**) and serum creatinine level (**b**) in highly sensitized recipients treated with monoclonal antibody (OKT3) or with antilymphocyte globulins (ALG). Statistical significance was not reached when the survival rate of the two groups was compared using the log-rank test

Initial graft function and rejection episodes

Posttransplant renal failure was observed more frequently in the OKT3 group (7/15; 47%) than in the ALG group (6/23, 26%). However, this difference did not reach statistical significance.

The incidence of acute rejection episodes during the first 3 months was the same in the two groups (52% in the ALG group, 53% in the OKT3 group). There was no significant difference in the day of onset of the first rejection episode (15 ± 4 days in the OKT3 group, 28 ± 11 days in the ALG group).

Viral infections

The occurrence of viral infection was similar in the OKT3 group (5/15, 33%) and in the ALG group (12/23, 52%) (chi-squared test, NS). Of the 12 HSP who suffered CMV disease, 8 were given ALG for more than 15 days.

Side effects

The clinical manifestations of the cytokine release syndrome observed in OKT3-treated patients included fever (100%), gastrointestinal symptoms (53%), headaches (33%), tachycardia (27%) and dyspnoea (20%). The incidence of side effects was significantly higher in the OKT3 group than in the ALG group (Table 2). We did not observe meningitis or pulmonary oedema. However, rash was observed in five cases (22%) in the ALG group.

Table 2 Side effects observed with OKT3 and ALG

	ALG group ($n=23$)	OKT3 group ($n=15$)
Fever	3 (13%)	15 (100%)
Gastrointestinal symptoms	0	8 (53%)
Headaches	0	5 (33%)
Tachycardia	1 (4%)	4 (27%)
Dyspnoea	0	3 (20%)
Meningitis	0	0
Pulmonary oedema	0	0
Rash	5 (22%)	0
Acute renal failure	6 (26%)	7 (47%)

Discussion

Hyperimmunization remains a problem in kidney transplantation because of its prolonged waiting time and higher risk of graft loss. In these immunologically high-risk recipients different immunosuppressive strategies have been used in clinical studies to prevent rejection. This study shows that successful transplantation in HSP (actuarial survival rate > 70%) was obtained with a triple immunosuppressive regimen including ALG, azathioprine and prednisolone. These results are similar to those obtained by different groups with a quadruple immunosuppression [8]. When compared with prophylactic ALG, the use of the monoclonal antibody OKT3 in our sequential protocol did not improve the early graft survival or the incidence of acute rejection episodes. Moreover, side effects were significantly more frequent in the OKT3 group when compared with the ALG group.

Clinical features of cytokine release syndrome characterized by fever, nausea, vomiting and tachycardia were noted in almost all patients receiving OKT3. However, we did not observe any pulmonary oedema. It has been suggested [10, 11] that OKT3 may be associated with an increased occurrence of delayed graft function as a consequence of the cytokine-induced nephropathy [12]. Indeed, in our study, OKT3 tended to increase the incidence of early posttransplant acute renal failure as no difference in other pre-or perioperative risk factors for ARF was observed between the two groups (Table 2).

Viral infection were observed with the same frequency with the two therapeutic protocols. However, when ALG was given for more than 15 days, it was associated with an increased occurrence of CMV diseases.

We conclude that the use of the monoclonal antibody OKT3 as prophylactic agent in HSP does not improve early graft survival when compared with prophylactic ALG, and increases the incidence of side effects including early acute renal failure, which makes the management of these patients more complicated. Polyclonal antibodies, which react with many epitopes on the lymphocyte membrane and are much better tolerated than OKT3 seem to offer a good strategy for induction therapy in HSP. Thus, we suggest that ALG be used as a prophylactic regimen and OKT3 be reserved for treatment of rejection.

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