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High or low dose steroid therapy for acute renal transplant rejection after prophylactic OKT3 treatment: a prospective randomized study

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Abstract. In this prospective randomized study, acute renal transplant rejections occurring in patients who received prophylactic OKT3 therapy were treated with either 3 pulses of 8 mg/kg methylprednisolone (MPS) in an alternate-day regimen (total dose 25 mg/kg in 1 week, H group, $n = 24$) or 5 daily pulses of 3 mg/kg MPS (total dose 17 mg/kg, L group, $n = 22$). Acute rejection was proven by biopsy in more than 85% of cases in both groups. No difference was observed in rejection reversal (H 88%, L 91%), graft losses in the following 3 months (H 11%, L 4%) or the time evolution of the serum creatinine levels. The number (H 14, L 21) as well as the nature and severity of infections were similar in both groups. Only one death occurred in a patient who received OKT3 rescue therapy for corticoresistant rejections and developed Epstein-Barr virus (EBV)-related lymphoma. In conclusion, low dose MPS pulses appear as effective and safe as a higher dose to reverse acute rejection occurring after OKT3 prophylaxis. Thus, we favour the use of the low dose regimen in these patients.

Key words: Steroid therapy for rejection – Acute renal rejection – OKT3

Steroid pulses therapy has been the cornerstone of acute kidney graft rejection treatment for more than 3 decades [3, 5]. The optimal dose of steroids in patients who received polyclonal lymphocyte-specific antibodies (ALG), azathioprine (AZA), and cyclosporin A (CsA) as primary immunosuppression still remains a controversial issue [2, 6–8, 11, 13, 16]. Recently, it was found that primary immunosuppression with a 2-week course of prophylactic OKT3 resulted in a reduced incidence of early rejection episodes [4, 12, 15, 17]. More importantly, a significant long-term increase in kidney graft survival was observed in OKT3-treated recipients (Abramowicz et al., manuscript submitted) as compared with those receiving a triple-drug regimen (CsA, AZA, prednisone). Although patient survival was similar in both groups, OKT3 prophylaxis was associated with an increased incidence of infectious episodes. It is therefore important to investigate the effectiveness in rejection reversal and the possible decrease in infectious complications of low steroid doses for acute rejection therapy in patients who received OKT3 prophylaxis as primary immunosuppression.

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Patients and methods

All patients included in this study received a 2-week course of prophylactic OKT3, with AZA, prednisone and CsA being introduced on postoperative day 11. From July 1989 to November 1990, 45 episodes of acute renal graft rejection occurring in 38 patients (19 in each group) were randomly assigned to receive a methylprednisolone (MPS) dose of either 8 mg/kg · day, 3 times in an alternate-day regimen (high dose group) or 3 mg/kg daily over 5 consecutive days (low dose group). The 7 days' cumulative dose of MPS was 25 mg/kg in the high dose group and 17 mg/kg in the low dose group.

Both groups were identical as regards the age of the donors and recipients, cold and warm ischaemia times, number of human leucocyte antigen (HLA)-A, -B and -DR incompatibilities and the incidence and intensity of HLA-specific immunisation.

More than two-thirds of rejections occurred within 6 months after transplantation in both groups. Acute rejection was diagnosed

Table 1. Rejection episodes

	High dose ($n = 24$)	Low dose ($n = 22$)	P value
Corticosensitive	21 (88%)	20 (91%)	NS
Corticoresistant	3 (12%)	2 (10%)	NS
Rescued by OKT3	2 (8%)	1 (5%)	NS
ALG	–	1 (5%)	NS
Graft losses after OKT3 course	1 (4%)	–	NS
Re-rejection[a]	5 (24%)	5 (25%)	
Graft losses	2 (8%)	2[b] (8%)	

[a] Rejection occurring within 45 days after steroid pulses
[b] This patient died of a lymphoma after a second OKT3 course

Table 2. Creatinine evolution with treatment

	Methylprednisolone dose					
	High		Low		*P* value	
	Creatinine[a]	Day[b]	Creatinine	Day	Creatinine	Day
Rejection	3.1 ± 0.4	0	3.6 ± 0.7	0	NS	–
Peak	3.5 ± 0.4	1.8 ± 0.4	4.0 ± 0.7	1.5 ± 0.5	NS	NS
Nadir	1.7 ± 0.1	19.6 ± 1.8	1.6 ± 0.2	20.1 ± 1.6	NS	NS

[a] Serum creatinine, mg/dl (mean ± SEM)
[b] Mean ± SEM

when the serum creatinine level rose or failed to decrease in a recently transplanted patient without evidence of other causes of allograft dysfunction. Rejections were proven by biopsy in more than 85% of cases. The rejection was considered corticoresistant if the serum creatinine level continued to rise at the end of the MPS pulses. Some corticoresistant rejections were further treated with OKT3 or ALG according to clinical criteria. Infectious complications were recorded if they occurred within 3 months after steroid pulse therapy.

Results

Rejection episodes were corticosensitive in 90% of cases in both groups (Table 1). In these patients, the serum creatinine levels before treatment, at peak and at nadir were similar in both groups, as was the day of occurrence of peak and nadir (Table 2).

Corticoresistant rejections were successfully rescued by OKT3 or ALG (used in a patient immunized against OKT3) in 2 patients in both groups. One patient lost his graft from renal graft artery thrombosis after the second OKT3 injection given as rescue therapy (Table 1).

Re-rejection occurred within the next 45 days in about 20% of patients. Steroid pulses were effective in two-thirds. One patient who received OKT3 for re-rejection died of lymphoma.

Infections occurred within 3 months of steroid pulses in about 40% of cases (Table 3). Most were bacterial urinary tract infections, as well as benign herpetic and candida stomatitis.

The incidence of more severe infections [bacterial sepsis, lung infections due to cytomegalovirus (CMV) and aspergillosis and disseminated Epstein-Barr virus (EBV) infection] was similar in both groups.

Table 3. Infectious episodes

	High dose ($n = 24$)	Low dose ($n = 22$)	*P* value
Number of rejection with infections	9 (38%)	10 (45%)	NS
Proportion infected per rejection episode	0.58	0.95[a]	$P < 0.05$
Number of infections	14	21	
Bacterial	10 (71%)	10 (48%)	NS
– With septicaemia	2 (14%)	1 (5%)	NS
Viral	3 (21%)	7 (33%)	NS
– HSV	2	4	NS
– CMV	1	2	NS
– EBV	0	1[b]	NS
Fungal			
– Oral candidosis	0	4 (19%)	NS
– Aspergillosis	1 (7%)	0	NS

[a] Seven infection episodes in a single patient
[b] Death from EBV-associated lymphoma
HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus

Discussion

The main conclusion of this prospective randomized study is that acute kidney graft rejection occurring after OKT3 prophylaxis was very efficiently treated by low dose steroid pulses. The reversal rate, the evolution of renal function and the incidence of re-rejection were similar for both steroid doses. This is in agreement with all five previous randomized studies, which found no benefit in increasing the steroid dose [7, 8, 10, 11, 13].

Interestingly, the percentage of corticosensitive rejections in our patients who received OKT3 prophylaxis was substantially higher than the commonly observed 70% rate. This is in accordance with the results of our prospective randomized study demonstrating a higher proportion of cortico-sensitive rejections after prophylactic OKT3 as compared with CsA.

The small number of corticoresistant episodes could usually be rescued by a second OKT3 (or ALG) course. However, the dangers of giving multiple courses of OKT3 over short periods of time should be emphasized. Indeed, this strategy is associated with an unacceptable incidence of Epstein-Barr virus (EBV)-associated lymphomas [1, 14].

Decreasing the steroid dose was not followed by a reduced incidence of infection. Infections were only recorded during the first 3 months following rejection. On the other hand, the difference between the 2 groups in the cumulative dose of corticosteroids was rather limited in the long term if only one episode of rejection was treated.

In conclusion, low dose MPS pulses appear as effective and safe as high dose pulses to reverse acute rejection occurring after OKT3 prophylaxis. We thus favour the use of the low dose regimen in these patients.

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