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Peter A. Rowe
Kin S. Fan
D. Stuart Gardiner
Stuart G. Macpherson
J. Andrew Bradley
R. Stuart C. Rodger
Brian J. R. Junor
J. Douglas Briggs

Long-term outcome of the use of OKT3 to treat steroid-resistant acute renal allograft rejection

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P. A. Rowe (✉) · K. S. Fan
S. G. Macpherson · J. A. Bradley
R. S. C. Rodger · B. J. R. Junor · J. D. Briggs
Renal Unit, Western Infirmary, Glasgow
G11 6NT, UK
FAX (041) 334-6432

D. S. Gardiner
Department of Pathology, Western
Infirmary, Glasgow G11 6NT, UK

Abstract OKT3 was used to treat steroid-resistant acute renal allograft rejection in 30 of 496 adult patients transplanted over a 6-year period. Rejection was reversed (defined as a fall in serum creatinine by 50% or more within 30 days of treatment with OKT3) in 40% of cases. Successful reversal was significantly more likely when rejection occurred shortly after transplantation (t ratio -2.53; $P = 0.019$). The long-term outcome was disappointing; the actuarial graft survival at 1 year from the start of treatment with OKT3 was 42%, and no grafts have thus far survived longer than 3 years. Graft survival was shorter in older patients (coefficient/standard error 2.226; $P < 0.05$), and no other predictor of long-term outcome was identified. Patient survival at 3 years was 88%. Serious infection occurred in 33% of patients, with two deaths. Our experience suggests that treatment with OKT3 is unlikely to reverse acute renal allograft rejection in more than half of patients where rejection is resistant to steroids. Although long-term graft survival occurred in a few cases, the overall long-term outcome was disappointing, particularly in older patients. Finally, our analysis indicates the difficulty of predicting which patients will derive long-term benefit when OKT3 is used to treat steroid-resistant rejection.

Key words Rejection, acute, OKT3
Steroid-resistant rejection, OKT3
OKT3, steroid-resistant rejection
Kidney transplantation, rejection, OKT3

Introduction

The murine monoclonal antibody muromonab CD3 (OKT3, Ortho-Cilag), which binds to the CD3 cell surface antigen receptor on T lymphocytes, has been widely used in the treatment or prevention of acute solid organ allograft rejection. When employed as initial therapy for acute rejection, it is successful in reversing rejection in more than 90% of cases [9, 14]. It is, however, an expensive agent with the potential for serious adverse effects and is, therefore, reserved in many transplant units for the treatment of rejection unresponsive to conventional therapy with high-dose steroids [3, 4, 10, 13, 20]. When used in this way, its efficacy is less well established and the long-term survival of grafts not well described. We have undertaken an analysis of the treatment of steroid-resistant renal allograft rejection by OKT3 to establish its efficacy when used as "rescue" therapy and to try to identify any factors that could be used to predict outcome.

Materials and methods

The records of all adults receiving renal transplants in the 6 years from January 1986 to December 1991 were searched to identify those given OKT3 following the use of high-dose steroids in the treatment of acute rejection. The standard immunosuppressive protocol employed during this period was cyclosporin and low-dose prednisolone. Cyclosporin was begun at 15 mg/kg once daily, and the dose was progressively reduced, aiming to achieve whole blood trough concentrations that varied from 300 μg/l initially to 100 μg/l at 12 months. The dose of prednisolone was 20 mg per day for the first 3 months,

tapering to 10 mg per day thereafter. Azathioprine was also used in some patients at a dose of 1.0–1.5 mg/kg daily as part of a triple drug regimen intended to minimise cyclosporin nephrotoxicity.

The diagnosis of acute rejection was confirmed by graft biopsy in every case, and initial treatment was with oral prednisolone, starting at 200 mg per day and being tapered by 50 mg every 2 days to reach the maintenance dose after 10 days. OKT3 was used as second line therapy at varying intervals after the beginning of treatment with high-dose prednisolone when it was judged clinically that rejection was resistant to steroids.

The OKT3 was given in accordance with the manufacturer's recommendations, i.e. at a dose of 5 mg/day by bolus intravenous injection for 10 days, after ensuring that there was no evidence of salt and water retention. Latterly, a 500-mg dose of methylprednisolone was given intravenously 1 h before the injection of OKT3 in order to reduce the incidence of the first dose reaction [2]. The dose of cyclosporin was reduced by half during OKT3 treatment in order to minimise the production of antimouse antibodies [8] and the dose of prednisolone was reduced to 20 mg/day.

Details of the clinical course of the patients were extracted from the case records, with particular attention to subsequent adverse events. Serious infection was defined as that which was life-threatening. Follow-up was continued until 31 March 1992, to death or to transfer of the patient to another unit. The response to OKT3 was assessed by serial serum creatinine results and by calculation of graft survival in days from administration of OKT3 using the Kaplan-Meier product limit technique. The time of graft failure was defined as the day of transplant nephrectomy or permanent discontinuation of immunosuppressive therapy. Death with a functioning graft was treated as graft failure.

Two distinct definitions of short-term reversal of acute rejection were used; both were calculated from the serum creatinine concentration at the start of OKT3 treatment compared with the lowest value observed within the subsequent 30 days. Firstly, reversal of rejection was considered to have occurred if the serum creatinine concentration decreased by 20% or more; secondly, reversal was considered to have occurred if the serum creatinine concentration fell by 50% or more.

Histocompatibility match, degree of previous sensitisation to HLA antigens, histological features of rejection in the graft biopsy, timing of the rejection episode and its treatment, and graft function both before and after therapy with OKT3 were correlated with short-term reversal of rejection by multiple regression analysis (Minitab) and with long-term graft survival by Cox proportional hazards regression analysis (BMDP), forcing the entry of all the covariates, to determine factors that might be useful in predicting the outcome.

The HLA match was expressed as a total mismatch score derived from summed mismatches at A, B, and DR loci. Sensitisation was assessed by historical peak panel reactive antibody titre expressed as a percentage. Each graft biopsy was reviewed by a pathologist (DSG) without knowledge of the outcome and scored for the degree of interstitial cellular infiltrate, interstitial haemorrhage, endothelial swelling, glomerular or vascular thrombosis, glomerular tuft or vessel necrosis, and inflammatory cell adherence to endothelium, each graded on a scale from 0 (none), 1 (mild), 2 (moderate) to 3 (severe). These indices were then summed to produce a histology score ranging between 0 and 18 for statistical analysis.

Results

A total of 496 adults received renal allografts during the 6 years from 1986 to 1991 inclusive, and 251 (50.6%) of these required one or more courses of high-dose prednisolone to treat acute rejection (182 patients received a single course, 57 received two courses, 9 received three courses and 3 were given four courses). In 30 of the 335 rejection episodes (9%), high-dose steroids failed to reverse acute rejection and OKT3 was given as rescue therapy.

Twenty-one male and nine female patients were given OKT3; their median age was 40.5 (range 17.3–65) years. Twenty-five had received their first graft, four their second graft and one his third graft. Twenty-seven grafts were from cadaveric donors and three from living related donors, (a proportion – 10%) – comparable to the total unit practice [17]. Ten patients' (33%) grafts failed to function immediately, but primary nonfunction persisted up to the time of treatment with OKT3 in only two cases. Both of these grafts subsequently failed (at 5 and 13 days after OKT3). In the remaining 28 cases with functioning grafts, the lowest serum creatinine recorded prior to treatment with OKT3 ranged between 50 and 884 (median 147) μmol/l. The duration of follow-up measured from the beginning of OKT3 therapy ranged from 1 month to 5 years (median 16.3 months).

The beginning of the acute rejection episode treated with OKT3 occurred at a median of 26 (range 4–521) days after transplantation. All patients were receiving cyclosporin and prednisolone at this time, and three patients were also receiving azathioprine. The graft biopsy scored for statistical analysis was carried out a median of 2 (range 0–9) days before the use of OKT3, and in 13 cases this was a second biopsy performed during treatment with prednisolone. In 22 cases OKT3 was given during the first rejection episode, in 7 cases the second and in 1 case the third.

At the time of first diagnosis of acute rejection, the serum creatinine ranged between 115 and 987 (median 340) μmol/l. The median interval between diagnosis of acute rejection and the use of OKT3 was 6.5 (range 2–43) days, and the serum creatinine on the day that OKT3 was started ranged between 250 and 1007 (median 595) μmol/l. Excluding the 2 patients with persisting primary nonfunction, dialysis was required in 12 patients (43%) during the period of antirejection treatment, and in 5 of these graft function was never regained.

Using the first definition of reversal of acute rejection (decrease in serum creatinine by more than 20%), OKT3 was successful in 21 of the 30 patients (70%). No significant correlations were found between reversal and any of the variables studied (overall $F = 1.92$; $P = 0.11$). Using the second definition (decrease in creatinine by more than 50%), rejection was successfully reversed in only 12 of the 30 patients (40%). There was a significant correlation (overall $F = 2.67$; $P = 0.034$) between reversal of rejection and the interval between transplantation and onset of acute rejection (t ratio -2.53; $P = 0.019$; Table 1).

The Kaplan-Meier estimates of graft and patient survival from the time of starting OKT3 in all 30 patients are shown in Fig. 1. One-year graft survival was 41% and 2-

Table 1 Correlations of short-term successful reversal of rejection as determined by multiple regression analysis (*PRA* Historical peak panel reactive leucocytotoxic antibody expressed as percentage, *Mismatch score* summed mismatch at A, B, and DR loci (range 0–6), *Tx-Rejection* time interval between transplant operation and administration of high-dose prednisolone for acute rejection in days, *Rejection-OKT3* time interval between administration of high-dose prednisolone and start of OKT3 treatment in days, *Creatinine* serum creatinine value at the start of OKT3 treatment, *RRT* need for temporary or continuing dialysis during treatment with OKT3, *Histology* score representing severity of rejection changes observed before starting OKT3, *NS* not significant)

Variable	Coefficient	Standard deviation	*t* ratio	*P* value
Constant	1.5041	0.4402	3.42	0.003
Age	−0.00860	0.006456	−1.33	NS
PRA	−0.00211	0.002122	−1.00	NS
Mismatch score	0.00589	0.006957	0.08	NS
Tx-Rejection	−0.00183	0.000722	−2.53	0.019
Rejection-OKT3	−0.00040	0.009803	−0.04	NS
Creatinine	−0.00069	0.000566	−1.21	NS
RRT	−0.2594	0.2052	−1.26	NS
Histology	0.04257	0.02936	1.45	NS

Table 2 Summary of survival analysis with covariates using the Cox model (*PRA* historical peak panel reactive leucocytotoxic antibody expressed as percentage, *Mismatch score* summed mismatch at A, B, and DR loci (range 0–6), *% Fall creatinine* percentage fall in serum creatinine calculated from the value at the start of OKT3 treatment and the lowest value observed in the next 30 days, *Tx-Rejection* time interval between transplant operation and administration of high-dose prednisolone for acute rejection in days, *Rejection-OKT3* time interval between administration of high-dose prednisolone and start of OKT3 treatment in days, *Creatinine* serum creatinine value at the start of OKT3 treatment, *RRT* need for temporary or continuing dialysis during treatment with OKT3, *Histology* score representing severity of rejection changes observed before starting OKT3, *NS* not significant). The overall log-likelihood was −40.673 (global chi-square 35.3; 9 degrees of freedom; $P < 0.0001$). The coefficient/standard error value required for significance at the $P = 0.05$ level is that for *t* with 20 degrees of freedom, namely 2.086. Only age and percentage fall in serum creatinine after treatment are significantly related to graft survival.

Variable	Coefficient	Coefficient/SE (*t* ratio)	*P* value	% Change in hazard for unit change in variable
Age	0.0677	2.2258	< 0.05	7.0
PRA	−0.0038	−0.4805	NS	−0.4
Mismatch score	0.0889	0.3352	NS	9.3
% Fall creatinine	−0.0583	−3.7932	< 0.005	−5.6
Tx-Rejection	−0.0006	−0.2106	NS	−0.1
Rejection-OKT3	−0.0407	−1.0004	NS	−4.0
Creatinine	0.0042	1.9321	NS	0.4
RRT	−0.6396	−0.7648	NS	−47.3
Histology	−0.2389	−1.6573	NS	−21.3

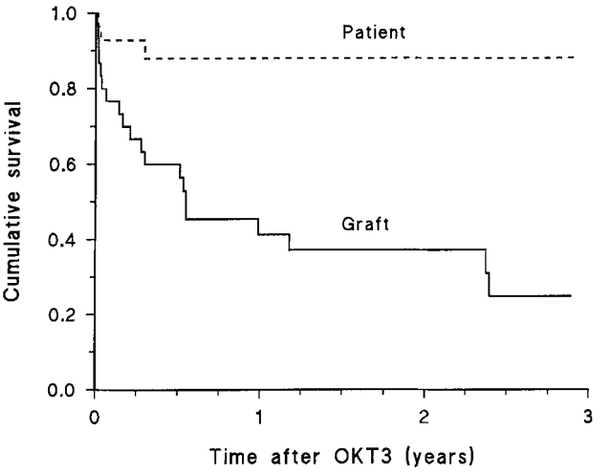

Fig. 1 Kaplan-Meier estimate of graft and patient survival from the time of OKT3 administration to treat steroid-resistant renal allograft rejection

year survival 37%, and no graft has thus far survived for more than 3 years. The median graft survival was 200 (interquartile range 52–874) days. The 3-year patient survival was 88%, and the median patient survival 935 days (study limited to 1057 days).

The proportional hazards regression analysis showed that only age and percentage fall in creatinine after treatment were significantly correlated with graft survival (Table 2). Increasing age conferred an increased risk of failure (coefficient/standard error = 2.226, $P < 0.05$), but this effect was small in magnitude (unit increase in age adding 7% to the hazard). The larger the percentage fall in serum creatinine after OKT3, the smaller was the risk of graft failure (coefficient/standard error = −3.793, $P < 0.01$), but graft function at the time of treatment was not significantly related to the risk of failure (coefficient/standard error = 1.932, $0.1 > P > 0.05$), and in contrast to the short-term outcome, the interval between transplantation and the onset of acute rejection was not significantly related to graft survival (coefficient/standard error = −0.2106; $0.5 > P > 0.1$).

Recurrent acute rejection proven by biopsy developed in six patients, a median of 107 (range 20–386) days after treatment with OKT3. All of these episodes were treated with high-dose oral steroids, and three grafts failed between 30 and 54 days later. One patient died with a functioning graft from cardiovascular causes, and the remaining two grafts are still functioning at latest follow-up.

Four of the patients who lost their grafts from rejection despite the use of OKT3 have subsequently been successfully retransplanted. In three cases the follow-up after retransplant ranges between 265 and 511 days, with serum creatinine concentrations between 106 and 168 μmol/l. In the fourth acute rejection at 4 days was unresponsive to high-dose oral prednisolone but was successfully reversed

Table 3 Serious infection after treatment with OKT3

Cause	Time interval from start of OKT3 (days)	Graft status	Final outcome
Peritonitis *(Klebsiella)*	1	Primary nonfunction	Died (11 days)
Pneumonia (organism unknown)	2	Failed (6 days)	Recovered
CMV	8	Failed (11 days)	Died (18 days)
Pneumonia (organism unknown)	8	Failed (23 days)	Recovered
CMV	9	Failed (5 days)	Recovered
Septicaemia *(S. aureus)*	10	Failed (2 days)	Recovered
Septicaemia *(E. coli)*	12	Failed (77 days)	Recovered
Pneumonia *(Pneumocystis)*	12	Function (640 days)	Recovered
CMV	20	Failed (23 days)	Recovered
CMV	26	Failed (101 days)	Recovered
Peritonitis *(S. aureus)*	40	Function (109 days)	Recovered (Died 109 days)

by a second course of OKT3 (the current serum creatinine being 277 μmol/l at 261 days after the transplant).

Persisting anti-OKT3 antibodies developed in two cases, one of whom was the patient who received a second course of OKT3 during a subsequent transplant.

Serious infections occurred in ten patients (33%; Table 3), resulting in the deaths of two patients. These deaths were caused by *Klebsiella* peritonitis complicating CAPD in one case, 5 days after starting OKT3, and by overwhelming CMV infection at 11 days after starting treatment in the other. Grafts were lost in seven of the eight patients who survived serious infection. There were three other deaths after the use of OKT3 in the 30 patients that were from vascular causes and judged to be unrelated to the use of OKT3.

Discussion

This study was designed to assess the short- and long-term efficacy of OKT3 when used to treat acute renal allograft rejection unresponsive to treatment with high-dose oral steroids. Previous studies of the efficacy of OKT3 in steroid-resistant rejection have reported reversal of rejection in between 47% and 96% (median 75%) of cases, but most have not defined the criteria for steroid resistance nor those for successful reversal of rejection, nor has long-term graft survival been examined [3, 4, 5, 7, 10, 13, 15, 20]. The effect of differing criteria for reversal of rejection on quoted success rates is well illustrated in this series where OKT3 reversed 40% or 70% of steroid-resistant acute rejection episodes according to the stringency of the definition of reversal applied. Although no strict criteria for steroid resistance were employed, two-thirds of patients received OKT3 within 10 days of starting high-dose oral prednisolone, and this reflects typical clinical practice.

There are several other factors that could account for the disparate rates of reversal reported. Varying steroid regimens have been employed to treat acute rejection and the criteria used to judge resistance to steroids before use of OKT3 are rarely described. In the study with the highest immediate success rate [20], the interval between use of prednisolone and OKT3 was very short (median 1 day) and in some instances OKT3 appeared to be used as initial treatment rather than as rescue therapy. In contrast, OKT3 was given a mean of 10.5 days after diagnosing acute rejection in the study with the lowest immediate success rate [4]. We began treatment with OKT3 between 2 and 43 (median 6.5) days after high-dose steroids, but could not demonstrate any significant correlation between reversal and the time interval before resorting to OKT3.

The response to OKT3 is usually judged by its effect on graft function as assessed by serum creatinine concentration, but the use of the peak value of serum creatinine during OKT3 treatment as the basis for calculation of subsequent changes will lead to an overestimation of success. This is because the administration of OKT3 often causes a transient rise in serum creatinine, unrelated to its effect on the rejection process, that has been attributed to cytokine-related reductions in renal blood flow [1, 6]. The definition of a successful response to OKT3 that was used in the study with the lowest reversal rate was a reduction in creatinine concentration to below the pretreatment value for at least 3 days [4], whereas the study reporting the highest reversal stated only that a progressive fall in serum creatinine from the peak during OKT3 therapy was used [20].

The long-term outcome of OKT3 rescue therapy is more important than immediate reversal of rejection, and half of the patients reported here were back on dialysis or dead within a year of transplantation. The median graft survival after treatment with OKT3 was 200 days, and only 42% of grafts survived for 1 year. No graft has yet survived 3 years. The only other centre to report long-term outcome quotes a 2-year graft survival of 55% in cadaveric kidney recipients [11] and a 4-year graft survival of 66% in cases where acute rejection occurred within 90 days of transplantation but only 20% where rejection occurred later than this [12]. This striking difference was not tested for statistical significance, and in our series there was no relation between long-term outcome and the

time interval between transplantation and the need for OKT3, though there was a significant correlation between this time interval and immediate reversal of rejection.

All of our patients experienced the well-known immediate adverse effects that include fever, headache, gastrointestinal disturbance, and malaise during OKT3 therapy [9], but these were less severe in the patients who were pretreated with methylprednisolone, as described by Chatenoud et al. [2]. The potentially more serious effect of an increase in capillary permeability with pulmonary oedema [16] was prevented by correction of fluid overload before treatment. However, a third of the patients developed serious infections, two of which were fatal. This infection rate is higher than that generally associated with OKT3 use [9] but may be related to the risks of cumulative immunosuppression when OKT3 is used as rescue therapy. There is an increased risk of lymphoma in patients given large doses of OKT3, which is probably related to cumulative immunosuppression rather than specifically to the use of OKT3 [9, 19], but no patient in this series has developed any type of tumour so far.

Since long-term graft survival after OKT3 rescue therapy is poor and the risk of infection is high, it is important to establish if the likelihood of success can be predicted at the time therapy is started. Successful initial reversal of rejection by the more stringent definition was more likely if rejection occurred shortly after transplantation, but we could not identify a time interval that could be useful clinically to discriminate between success and failure. Furthermore, the Cox analysis failed to show any useful way of predicting which patients will respond to OKT3 other than age. Older patients are also at increased risk of dying from infection, and the two patients who died from infection in this series were aged 50 and 61 years. The correlation between fall in serum creatinine and long-term outcome is to be expected since such a fall indicates a response to treatment. It is of interest that graft function at the start of OKT3 was not significantly related to long-term outcome, though it came closest of the covariates tested. The severity of rejection as assessed histologically was not helpful in predicting graft survival in our patients, as has been found useful by others [18], perhaps because all of the patients included in this study had, by definition, severe rejection. Though the sample size was small, the lack of any correlation between outcome and the other covariates tested suggests that these factors have little clinically significant influence on outcome.

In conclusion, we have found that only a small proportion of patients with steroid-resistant rejection derive long-term benefit from treatment with OKT3 and that such treatment carries a significant risk of infection, particularly in older patients. While OKT3 undoubtedly has a useful role as a rescue treatment, these results are disappointing. Although long-term graft survival can sometimes be achieved, our experience suggests that the only useful pointer to help decide which patients will benefit is age.

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