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Reduced dose OKT3 prophylaxis in sensitised kidney recipients

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Abstract Prophylactic use of the monoclonal antibody OKT3 has been studied for the prevention of rejection in sensitised renal transplant recipients. Patients receiving a full dose (FD) regimen were compared to a subsequent consecutive group of patients receiving a reduced dose (RD) regimen. The characteristics of the two groups were not significantly different with regard to age, HLA mismatch and panel-reactive antibody (PRA) status. The number of days that OKT3 was given was 12.9 ± 1.8 for the FD regimen and 11.3 ± 2.8 for the RD regimen. The total dose of OKT3 given was 64.4 ± 9 mg (FD) and 38.3 ± 8.5 mg (RD). Patient survival at 12 months was 8/8 for FD and 17/17 for RD. Graft survival at 12 months was 7/8 for FD and 17/17 for RD. Creatinine at 24 months was 185 ± 68 and 201 ± 81 μmol/l for FD and RD, respectively. A reduced dose regimen of OKT3 produced excellent and comparable results to the standard recommended full-dose regimen. The cost per patient was reduced 40 % from £5676 for FD to £3344 for RD.

Key words OKT3, kidney transplantation · Kidney transplantation, OKT3 · Sensitization, OKT3, kidney transplantation

Introduction

OKT3 monoclonal antibody, which has been in use clinically since 1979, is a mouse anti-human CD3 monoclonal antibody with powerful immunosuppressant potential via its action on T cells [9, 21]. OKT3 has been shown to be efficacious for both treatment of [9, 10, 18] and prophylaxis against allograft rejection [1, 3, 16].

However, OKT3 is a relatively expensive immunosuppressive agent and there are concerns that its use may lead to over-immunosuppression and consequent morbidity and mortality. Thus, we have compared a conventional dose regimen of OKT3 with a lowered dose regimen as induction therapy for renal transplantation in sensitised recipients. The objective of the study was to observe whether the lower dose regimen was equally as effective as the full-dose regimen in terms of patient and graft outcome whilst utilising a lower total dose and, hence, reduced cost. Moreover, it was anticipated that the lower total immunosuppressive load should be beneficial in terms of long-term sequelae.

Methods

Renal allograft recipients received OKT3 if they were 'sensitised', as defined by current or historical non-IgM panel-reactive antibodies (PRA) greater than 75 % for first grafts and greater than 50 % for second or third grafts.

All patients who had received OKT3 monoclonal antibody were identified and the notes reviewed retrospectively. Patients were not randomised between the two regimens. Hence, a consecutive group of patients who received the full-dose regimen of OKT3 was compared to subsequent consecutive patients receiving the reduced dose regimen.

Full-dose OKT3 consisted of 5 mg OKT3 intravenously (i.v.) over 10–14 days. The first dose was given during anaesthesia (day 1) with 0.5 g methylprednisolone i.v. and 10 mg chlorpheniramine

i.v. The second and third doses were given on days 2 and 3 with 100 mg hydrocortisone and 10 mg chlorpheniramine i.v. Subsequent doses were given without these additional agents. Paracetamol was given for pyrexia. Patients receiving the reduced dose regimen were given 5 mg OKT3 on day 1 and day 2, as above, with identical prophylaxis against the cytokine release syndrome [8, 11, 13]. However, from day 3 onwards the dose was reduced to 2.5 mg. The count of $CD3^+$ T cells was estimated by flow cytometry of peripheral blood lymphocytes. The intention of treatment was to maintain the $CD3^+$ count below 0.05 (50 cells/μl). If this target was not achieved after the first two doses, the OKT3 was maintained at 5 mg until the target was met. If the target CD3 count was achieved initially but rose subsequently above 0.05, the dose was increased back up to 5 mg.

All patients received an immunosuppressive regimen consisting of steroids, azathioprine and cyclosporin. Prednisolone was given starting from day 2 at 0.3 mg/kg per day orally. The steroid dose was reduced in a step-wise fashion starting at 1 month in those without rejection or 1 month after an episode of early rejection, aiming for a baseline of 10 mg after approximately 3 months. All patients received azathioprine at a dose of 1.5 mg/kg, with the first dose orally prior to surgery. Cyclosporin was withheld until 4 days before the end of the course of OKT3 and commenced at 10 mg/kg per day in divided doses 12 h apart. Levels were measured by radio-immunoassay as a 12-h trough, aiming at the range 200–250 ng/ml.

Patient details recorded were age, sex, PRA, cytomegalovirus (CMV) status and recipient and donor HLA type by serology.

All patients received amphotericin lozenges orally for the duration of the OKT3 regimen to protect against gastrointestinal candida. Patients who were CMV-negative and who received kidneys from CMV-positive donors were given a prophylactic regimen of i.v. Sandoglobulin. No attempt was made to match donors and recipients for CMV. All patients received cotrimoxazole, 480 mg twice daily for 3 months, as prophylaxis against pneumocystis.

Rejection episodes were established by biopsy after clinical or biochemical evidence of a deterioration in graft function. Rejection episodes were treated by 0.5 g methylprednisolone on 3 consecutive days. Further episodes were treated by a repeat course of steroids or antithymocyte globulin (2 mg/kg per day for 7–14 days). Two possible outcomes from each episode of rejection were defined: reversal of rejection, as a fall in creatinine from a peak for the episode and a return of the creatinine to within 20% of the baseline creatinine prior to the episode, and resistant rejection, as continuing biochemical and histological evidence of rejection.

CMV infection was defined as evidence in asymptomatic patients of seroconversion from pretransplant CMV IgG-negative to post-transplant IgG-positive (primary infection) or conversion of pretransplant IgG-positive IgM-negative to post-transplant IgG-positive and IgM-positive (reactivation). CMV disease was defined as symptomatic clinical evidence of disease associated with serological conversion as above and the detection of virus in a buffy coat preparation of whole blood.

Differences between the two treatment groups were compared by a two-tailed, unpaired Student's *t*-test where appropriate.

Results

Comprehensive data were available on all patients receiving OKT3 within the unit. Eight patients received full-dose (FD) OKT3 prophylaxis between January 1990 and September 1991, followed by 17 patients who received reduced dose (RD) OKT3 from this date to the end of the study in January 1994. One further patient received a single dose of OKT3 but suffered a renal vein thrombosis at 24 h, leading to loss of the graft, and was excluded from the study.

Table 1 Demography, number of previous grafts, HLA mismatch and panel-reactive antibody (PRA) status

	Full dose	Reduced dose
Number	8	17
Sex (M/F)	2/6	8/9
Age (years)	46 ± 17.3	42 ± 9.7
Graft number: First	0	5
Second	7	9
Third	1	3
HLA A mismatch	0.62 ± 0.74	0.68 ± 0.79
HLA B mismatch	0.75 ± 0.94	0.94 ± 0.57
HLA DR mismatch	0.50 ± 0.76	0.44 ± 0.63
All HLA mismatch	1.57 ± 1.7	2.06 ± 1.4
PRA peak (%)	91.7 ± 13.8	80.8 ± 20.4
PRA current (%)	83.8 ± 24.6	53.5 ± 35.6

Details of the demography, number of previous transplants, HLA mismatching of donor and recipient and the non-IgM PRA status of the recipients is shown in Table 1. The groups receiving FD and RD OKT3 were well matched for age and number of previous grafts (P = NS). There was no significant difference in the degree of HLA A, B and DR mismatching between the two groups ($P = 0.63$). Current non-IgM PRA status for all patients was negative for their cytotoxic crossmatch test prior to transplantation. However, two patients receiving RD OKT3 had current non-IgM-negative but historical non-IgM-positive PRA status on crossmatch. Historical PRA status of the two treatment groups did not differ ($P = 0.25$); however current PRA status tended to be lower in the RD group, although this difference was not significant ($P = 0.07$).

Full-dose OKT3 was given for 12.9 ± 1.8 days versus 11.3 ± 2.8 days for RD patients (P = NS). The total dose of OKT3 given to FD patients was 64.4 ± 9.0 mg versus 38.3 ± 8.5 mg for RD patients ($P < 0.0001$). Ten RD patients received the two 5-mg doses followed by 2.5-mg doses thereafter. However, in the other seven RD patients on the basis of the $CD3^+$ count, the OKT3 dosage was continued at 5 mg or had to be returned to a dose of 5 mg after initially being dropped at day 3 to 2.5 mg. All patients suffered typical symptoms of cytokine release syndrome. As both treatment groups received 5 mg of OKT3 on the first 2 days post transplant, the severity of this syndrome was very similar.

Details of patient and graft survival and creatinine at 7 days and at 1, 3, 12, 24 and 36 months are shown in Table 2. Minimum follow-up was 2 years for RD and 3 years for FD patients. There were no deaths in either group of patients in these periods. However, subse-

Table 2 Patient survival, graft survival and graft function in the 1st year after transplantation

	Full dose	Reduced dose
Patient survival at 2 years	8/8	17/17
Graft survival at 2 years	7/8	17/17
Serum creatinine (μmol/l) at 1 week	275 ± 276.7	321 ± 307.1
Serum creatinine 1 month	208 ± 107.1	191.9 ± 77.3
Serum creatinine 3 months	158 ± 52.2	184.9 ± 52.2
Serum creatinine 12 months	150.7 ± 42.7	185.3 ± 72.5
Serum creatinine 24 months	185.6 ± 68.3 (n = 7/8)	201.5 ± 80.7 (n = 17/17)
Serum creatinine 36 months	183.7 ± 56 (n = 7/8)	220.6 ± 100.7 (n = 9/17)
Creatinine range 12 months	83–208	80–382

Table 3 Incidence, mode of treatment and outcome of rejection episodes with full and reduced-dose OKT3 (*Rx*, treatment given; *MP*, methylprednisolone; *Rev*, reversed; *Res*, resistant; *ATG*, antithymocyte globulin)

	No.	Rejection 1	Rejection 2	Rejection 3
Full dose	8	7/8 Rx MP (n = 7) Rev 6/7 Res 1/7 Rx ATG Rev 1/1	0	0
Reduced dose	17	9/17 Rx MP (n = 9) Rev 8/9 Res 1/9 Rx ATG Rev 1/1	4 Rx MP (n = 4) Rev 3/4 Res 1/4 Rx ATG Rev 1/1	1 Rx MP (n = 1) Rev 1/1

Table 4 CMV status of donor and recipient pairings and subsequent incidence of CMV infection and disease (*Pos*, positive; *Neg*, negative)

	Full dose (n = 8)	Reduced dose (n = 17)
CMV status	Pos/Pos 4 Pos/Neg 2 Neg/Pos 1 Neg/Neg 1	Pos/Pos 7 Pos/Neg 1 Neg/Pos 5 Neg/Neg 4
Infection	5/8	1/17
Disease	0/8	2/17

quently, there have been two deaths with functioning grafts. One patient (FD) died at 4.5 years with osteomyelitis and pneumonia and a second (RD) at 3.5 years with cirrhosis. All 17 of the 17 grafts were functioning at 24 months in the RD group. One of eight grafts was lost in the FD regimen group in the first 3 years. This patient suffered a secondary haemorrhage at day 29 post-transplant from an infected renal vein to iliac vein anastomosis. The renal function at that time was creatinine 216 μmol/l, but the graft had to be sacrificed.

Immediate graft function was seen in 7 out of 8 FD and 12 out of 17 RD (P = NS) patients with dialysis dependence at the end of the OKT3 course in 1 out of 8 FD and 3 out of 17 RD patients. Creatinine at 1, 3, 12 and 24 months was not significantly different between the two treatment regimens ($P > 0.2$; Table 2).

The number of rejection episodes and the outcome of treatment were compared and contrasted for the two treatment groups. Rejection was seen in 6 out of 8 FD patients and in 9 out of 17 RD patients (P = NS; Table 3). The median time to first rejection after the end of the OKT3 treatment was + 9 (range −3 to + 946) days for FD patients versus 32 (range + 1 to + 414) days for RD patients. All first rejections were confirmed by biopsy and treated with methylprednisolone. Only four patients suffered more than one episode of rejection. The details of the treatment and outcome of second and third rejections are shown in Table 3.

The donor/recipient CMV status was recorded and the presence or absence of evidence of CMV infection and disease was studied (Table 4).

Discussion

This study reports a consecutive series of highly sensitised cadaveric renal transplant recipients receiving prophylactic OKT3. It has been shown elsewhere that induction therapy with a reduced dose regimen of OKT3 can be effective in carefully selected non-sensitised patients [17, 19]. However, in most practice in the United Kingdom, these patients would not have received antibody therapy. It has also been shown that full-dose OKT3 is beneficial in the transplantation of sensitised recipients [7, 22]. However, this is the first study with

sensitised patients that demonstrates that a dose of OKT3 below that recommended by the manufacturers (5 mg daily for 10–14 days) can be used effectively.

The most striking finding of the study was the graft survival at 2 years. Remarkably, no grafts were lost to rejection in the study period. Rejection was seen commonly with both treatment regimens (Table 3). In the FD regimen, six of seven patients had a single rejection episode that was fully sensitive to steroids. Only in one patient was the rejection steroid-resistant and required ATG. Interestingly, it was this patient who, despite successful rescue of the graft from rejection, lost the graft from potentially fatal haemorrhage from an infected venous suture line. It is likely that the profound immunosuppression would have played a major role in this unusual technical failure. In contrast, there were four patients who also received RD OKT3 who suffered more than one episode of acute rejection. Most of these were successfully reversed by pulsed steroids, with only one patient requiring ATG. These results support the contention that most rejection episodes after OKT3 are steroid-sensitive [3]. The increased incidence of recurrent rejection episodes with the RD regimen might lead to an increase in chronic rejection [4, 6]; yet, this has not become evident after 2 years of follow-up.

Patients receiving both FD and RD OKT3 were well matched for HLA (Table 1). This followed the need to avoid mismatches to obtain a negative crossmatch prior to transplantation. This degree of matching may have contributed to the good results in this study, and many kidneys were obtained as "beneficial" matches from the national organ sharing system (UKTSA).

It was not the primary purpose of this study to compare and contrast side effects between the two regimens. Both treatment groups received identical first and second doses of OKT3 and there was, not surprisingly, no difference in early cytokine-induced side effects. The incidence of CMV infection was monitored for the two treatment regimens (Table 4) and tended to be lower for the RD group. However, this reduced incidence of infection may be explained by the lower proportion of CMV-positive donors (8/17) for RD patients than for FD patients (6/8). If an induction regimen with an antibody preparation is to be used, OKT3 has been shown, in one recent study, to confer a significantly reduced incidence of CMV compared to induction with ALG [12]. This advantage might therefore be extended further by the use of RD OKT3, as it is possible that a RD regimen might lead to less CMV disease [15, 17]. Furthermore, an association between CMV infection and the incidence of rejection has been shown [20]. Therefore, the low incidence of rejection seen in this study may also have been influenced by the low incidence of CMV infection and disease.

Immediate graft function, as defined by the passage of urine and the absence of the requirement for dialysis, was seen in 7 of 8 FD and 12 of 17 RD patients. This compares favourably with the delayed graft function seen with patients on cyclosporin who are not receiving OKT3. It has been suggested that the cytokines released by OKT3 might contribute to delayed graft function [5]. If this is so, it was not seen in our patients, probably as any effect on delayed function was outweighed by the benefit of the deferred introduction of cyclosporin. A detrimental effect on long-term graft survival has been noted by others in patients with delayed graft function. There was a raised incidence of delayed graft function in RD (5/17) patients compared to FD (1/8) patients. Furthermore, creatinine at 3 years was higher, but not significantly so, in the RD group (Table 2), and this may be an early warning of a greater incidence of chronic rejection. However, serial biopsies in this group have not been performed to address this question.

There was no significant difference in the duration of OKT3 prophylaxis between the two treatment regimens. The rationale of retaining the initial two 5-mg doses with the RD regimen was to avoid immunological stimulation due to cytokine release without sufficient OKT3 to induce significant lysis. It is not clear if there is any clinical basis for this widely held assumption.

In this series, for the RD patients, if required we increased the dose of OKT3 back to 5 mg daily to maintain the $CD3^+$ count below 0.05 cells/μl for as long as possible. However, with a policy of returning a RD regimen of OKT3 to a full dosage when the $CD3^+$ count falls outside the target range, it could be argued that the immunosuppressive load would be the same with the two regimens. This follows as the $CD3^+$ counts would not be significantly different between the two regimens. Hence a RD regimen simply avoids wastage of OKT3 when there is little receptor available to bind to. Following the good clinical results reported here, we would now not increase the dose of 2.5 mg back to 5 mg even if the $CD3^+$ count rose above the target range as long as the 5-mg loading doses initially had produced the desired reduction. With this policy the degree of suppression of the CD3 count over the full period of treatment is less and should reduce the total immunosuppressive load and, hence, possibly reduce detrimental sequelae. Further studies continue to address this question.

The use of OKT3 in our patients did not lead to any early mortality after a minimum follow-up of 2 years after transplantation (Table 2). Early deaths from sequelae of the cytokine release syndrome have been avoided by use of prophylactic agents as described with special attention to the avoidance of fluid overload and intensive monitoring [11]. Subsequently, there have been two late deaths (3.5 and 4.5 years post-transplant) with functioning grafts, neither of which appeared directly linked to OKT3 usage. Post-transplant lymphoproliferative disorder (PTLD) has thus far not been

seen in any of these patients [2, 13]. With FD OKT3, PTLD has only been seen in less than 0.4 % of greater than 35,000 patients treated world-wide [14]. However, we would hope that the lower total exposure to the OKT3 antibody in the RD regimen might be helpful in this respect, as has been suggested previously [15].

With the RD regimen reported here, total usage of OKT3 was significantly reduced (64 mg FD versus 38 mg RD). The cost per patient has been calculated at £5676 for the FD regimen and £3344 for the RD regimen. If the RD patients had all been treated with the FD regimen, this would have cost an additional £40,000. Clearly, there are major cost savings from using a RD regimen and this study shows that there is no adverse impact on clinical efficacy.

In conclusion, it has been confirmed that sensitised renal transplant recipients can be transplanted successfully under the cover of OKT3 monoclonal antibody. Furthermore, there was no detrimental effect from the introduction of a regimen using a 40 % reduction in the dose of OKT3 monoclonal antibody than that recommended currently. This regimen therefore combines clinical benefit and considerable cost advantages.

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