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OKT3 Therapy in Addition to Tacrolimus Is Associated with Improved Long-Term Function in Patients with Steroid Refractory Renal Allograft Rejection

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Key Words
OKT3 · Renal transplantation · Steroid refractory rejection · Tacrolimus

Abstract
Background/Aims: The aim of this study was to evaluate long-term allograft salvage rates of patients with steroid refractory allograft rejection after kidney transplantation and to identify factors indicating a successful outcome. ***Patients and Methods:*** Fifty patients with continuing rejection after high-dose steroids were included in the study. Baseline immunosuppression was switched from cyclosporine to tacrolimus in all patients. Twenty patients additionally received OKT3 as antirejection therapy. Patients having received a cadaveric renal transplant in 1995, excluding patients with steroid resistant rejection, were chosen as a control cohort. ***Results:*** Patient survival rates were 96% (n = 48) and 90% (n = 45) and allograft survival rates were 66% (n = 33) and 62% (n = 31) after 5 and 7 years following steroid refractory renal allograft rejection. Graft survival within the control cohort was 73% after 5 years and 69% after 7 years. Creatinine clearance increased from 20 ± 15 ml/min/1.73 m^2 at the start of tacrolimus therapy to 37 ± 29 ml/min/1.73 m^2 and to 32 ± 26 ml/min/1.73 m^2 after 5 and 7 years. OKT3 treatment predicted successful rescue therapy ($p = 0.005$ and $p = 0.04$ after 5 and 7 years). ***Conclusion:*** Our data indicate a reasonable graft survival in steroid refractory renal allograft rejection using tacrolimus. OKT3 treatment in addition to tacrolimus therapy may be beneficial for long-term allograft survival.

Introduction

Acute renal allograft rejection has decreased survival rates of transplants since the early days of human kidney transplantation. Although its overall rate has decreased during recent years, acute renal allograft rejection continues to be a serious problem impacting on long-term allograft survival by increasing the rate of chronic rejection [1]. Acute rejection is usually treated by glucocorticoid ('steroid') pulse therapy, the overall reversal rate ranges between 74 and 100% [2]. Reversal rates may be lower if acute cellular rejection is accompanied by vascular and/or chronic rejection [3, 4]. The term 'refractory' rejection describes ongoing rejection despite treatment with pulse steroids. The time period before a rejection is considered to be steroid resistant ranges from 3 to 7 days [5, 6].

Traditionally, antilymphocyte preparations [polyclonal antithymocyte globulins (ATG), monoclonal antibody (OKT3)] are the first-line therapeutics in steroid-

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resistant rejection. Most of the studies compared OKT3 with ATG in induction protocols. Only few data are available comparing the two drugs in the *treatment* of steroid refractory rejection [7]. The success rates of OKT3 therapy reported in the literature range between 50 and 96% [9–11].

A different concept is to treat refractory rejection with the calcineurin-inhibitor tacrolimus. This concept was first presented in the mid 1990's [12]. Renal function could be restored by switching the immunosuppressive long-term medication from cyclosporine to tacrolimus in 74% of patients (tacrolimus 'rescue' treatment). Meanwhile, the effectiveness of this therapeutic regimen for reversing rejection has also been proven in other studies [13].

Newer, more experimental approaches (plasmapheresis, intravenous administration of immunoglobulins) have been used in cases of refractory humoral rejection [14–16]. The best strategy for achieving an optimal outcome in steroid-resistant rejections is not clear as there are only few very limited studies which included a follow-up of more than 3 years [13, 17–20]. As there are only very few data available in patient cohorts with complete follow-up, predictive parameters for successful long-term treatment of refractory rejections have not been identified. In particular, it is not clear which patients may profit from antibody therapy and which patients can be sufficiently treated switching them to tacrolimus.

It was the aim of this study to prospectively investigate the long-term outcome of patients with refractory renal allograft rejection and to identify factors predicting a successful outcome.

Patients and Methods

Patients

Data from patients having received a cadaveric renal transplant between 1993 and 1997 and having suffered steroid-resistant acute allograft rejection during the first year after surgery were prospectively collected. The time frame 1993–1997 was chosen because immunosuppressive therapy during this period consisted of cyclosporine A as the primary therapy in nearly all patients. Patients were included in our database at the time of rejection. Data of follow-ups were collected at yearly intervals.

Inclusion Criteria

Patients with steroid-resistant acute renal allograft rejection during the first year after cadaveric kidney transplantation were included into the study. All patients had a negative cross-match before transplantation. Acute allograft rejection had been diagnosed by renal biopsy in all patients. Treatment of acute rejection was performed using intravenous prednisolone pulse therapy for at least 3 consecutive days. Refractory rejection was defined as one or more of the following criteria: persistent rejection in renal biopsy, dependence on hemodialysis therapy and failure of the serum creatinine to decrease below 125% of the baseline before rejection within 5 days after the start of antirejection therapy [6]. In case of a steroid-resistant rejection, patients were switched to tacrolimus as baseline immunosuppression. Some patients had additionally been treated with OKT3 before conversion to tacrolimus. The switch of basic immunosuppression from cyclosporine to tacrolimus for steroid-resistant rejection was mandatory for inclusion in the study. The minimal observation period for all patients was 7 years after the switch to tacrolimus.

Control Cohort

Adult patients having received a cadaveric renal transplant in 1995, excluding patients with steroid-resistant rejection and early graft loss due to technical failure, were chosen as a cohort for comparison of graft survival (n = 49, 27 male, 22 female, mean age 43 ± 15 years, mean donor age 44 ± 14 years).

Immunosuppressive Medication and Monitoring of Treatment

Prednisolone (500 mg) was given during transplant surgery and standard long-term immunosuppression consisted of cyclosporine and prednisone. Prednisone was started after transplantation at 30 mg/day for the first week, the dose being tapered 5 mg every week to 10 mg/day. Basic immunosuppression consisted of cyclosporine in all patients. The cyclosporine trough levels were adjusted to 200–300 ng/ml. Thirty-one patients received azathioprine and 10 patients received mycophenolate mofetile in addition to cyclosporine and prednisone.

Antirejection Therapy after Failure of Steroid Bolus Therapy

Antibody treatment with OKT3 (Biotech®, USA) was used in a subgroup of patients as anti-rejection therapy. OKT3 treatment was performed for 10 days in a dosage of 5 mg per day. Prednisolone was infused 1 h before the first OKT3 dose at a dosage of 250–500 mg. Basic immunosuppression was switched from cyclosporine to tacrolimus in all patients. Tacrolimus was given twice a day using an initial dosage of approximately 0.2 mg/kg/day to achieve tacrolimus trough concentrations of 6–10 ng/ml initially and 5–8 ng/ml for long-term maintenance therapy. Therapy was monitored by measuring the blood tacrolimus trough levels by a microparticle enzyme immunoassay.

Monitoring of Renal Function

Serum creatinine was used to monitor renal function. Patients were monitored at least twice a week during the first month after conversion, then at least once a week during the following 5 months. Thereafter, creatinine measurements were performed every 6 months. Creatinine clearance was calculated according to the method of Cockroft and Gault [21]: 140 – age × body weight (kg)/72 × blood creatinine level (mg/dl). Creatinine clearance was estimated as 5 ml/min/1.73 m^2 for patients on dialysis.

Diagnosis of Rejection

Rejection was diagnosed by renal biopsy. Grade of rejection was defined as either cellular (interstitial) or vascular as the 'Banff' classification was not routinely used at this time and tissue samples were not generally available for a retrospective pathological analysis.

Statistics

To identify predictive factors of graft survival, variables obtained before antirejection therapy were evaluated with the Cox proportional hazard model. All continuous predictors or 'covariates' were categorized according to the median of the distribution. The risk ratios (and their confidence limits) were computed as exponential functions of the parameters. Candidate variables that were significantly associated with survival time were evaluated in a multivariable Cox proportional hazards model to identify independent predictors of survival time. A p value of <0.05 was considered statistically significant. Data are given as mean ± SD.

Results

Patients' Characteristics

Fifty patients were included in the study (29 male, 21 female; mean age 42 ± 23 years). Fifty-two percent (n = 26) of the donors were female, 48% (n = 24) were male. The mean donor age was 44 ± 16 years. Causes of end-stage renal disease were glomerulonephritis (n = 20), diabetes (n = 8), pyelonephritis (n = 8), polycystic disease (n = 5), Alport's syndrome (n = 2), uric acid nephropathy (n = 2), nephrolithiasis (n = 2), reflux nephropathy (n = 1), Henoch-Schönlein purpura (n = 1) and Goodpasture's syndrome (n = 1). Forty-four patients had received the first, 4 patients the second and 2 patients the third renal transplant. Simultaneous kidney-pancreas transplantation was performed in 5 patients. Data for renal function, patient and graft survival were available for each patient and none of the patients was lost to follow-up.

Tacrolimus was introduced 33 ± 43 days after the beginning of a first steroid bolus regimen (n = 50). Twelve patients received a second course of steroid bolus therapy before switching baseline immunosuppression from cyclosporine to tacrolimus. OKT3 therapy was started in 20 patients 26 ± 44 days before the switch to tacrolimus.

Survival Rates

Patient survival rates after 5 and 7 years following the change of baseline immunosuppression from cyclosporine to tacrolimus were 96% (n = 48) and 90% (n = 45), respectively. Causes of death were myocardial ischemia in 6% (n = 3) and breast cancer and ileus in 2% (n = 1, each). Allograft survival rates after 5 and 7 years were 66% (n = 33) and 62% (n = 31), respectively (fig. 1). Graft survival within the control cohort transplanted in 1995 was 73% after 5 years and 69% after 7 years (n = 34). In the patient cohort with steroid-resistant rejection, creatinine-clearance increased from 20 (± 15) ml/min/1.73m^2 to 37 (± 29) ml/min/1.73 m^2 at year 5 after change to tacrolimus and to 32 (± 26) ml/min/1.73 m^2 after 7 years.

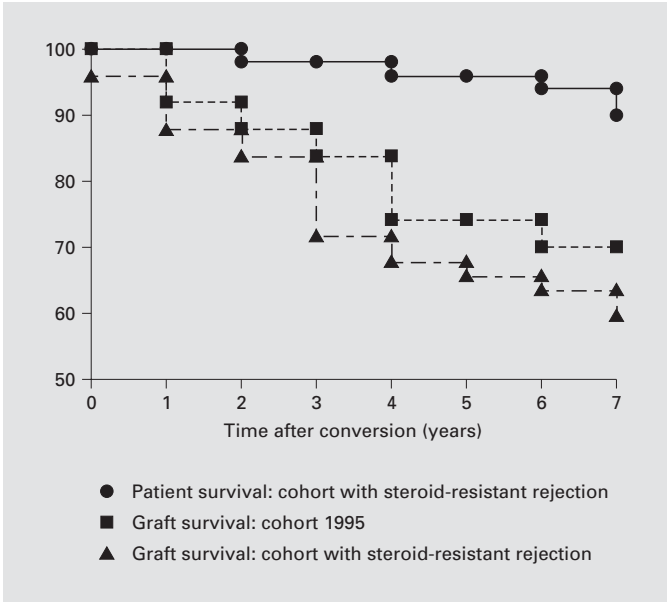

Fig. 1. Patient and allograft survival rates in patients with steroid resistant rejection ('cohort with resistant rejection') after switch to tacrolimus (n = 50) and allograft survival rate for all adult patients transplanted in 1995 ('cohort 1995'), excluding steroid-resistant rejection and early graft loss due to technical failure (n = 49).

Analysis of Prognostic Markers

Predictors of successful treatment of refractory rejection were evaluated in relation to graft function 5 and 7 years after switching the immunosuppressive medication to tacrolimus. In summary, there were no differences between successfully and unsuccessfully treated patients in the following categories: primary renal function, frequency of dialysis therapy after transplantation, grade of rejection, HLA compatibility, time until switch to tacrolimus, tacrolimus trough levels, age of the recipients and frequency of recipient CMV injection (table 1).

Strategy of Treating Recurrent Acute Rejection before Switching the Medication

Twenty patients (40%) with steroid-resistant acute rejection were treated with OKT3 in addition to being switched to tacrolimus as baseline immunosuppression. OKT3 therapy was associated with better 5- and 7-year allograft survival rates than tacrolimus treatment alone: 18/20 (90%) vs. 15/30 (50%), $p < 0.01$, and 16/20 (80%) vs. 15/30 (50%), $p = 0.04$, respectively (table 1). Analysis

Table 1. Analysis of factors predictive for 5- and 7-year allograft survival

	Graft survival		Risk ratio	
	5 years	7 years	5 years	7 years
Age of recipient, >40 vs. ≤40 years	18/25 vs. 15/25	16/25 vs. 15/25	0.83 (0.56–1.25)	0.94 (0.61–1.45)
Rejection, vascular vs. cellular	10/13 vs. 23/37	9/13 vs. 22/37	0.81 (0.55–1.19)	0.86 (0.55–1.37)
CMV infection, – vs. +	26/36 vs. 7/14	25/36 vs. 6/14	0.69 (0.39–1.21)	0.62 (0.32–1.17)
Dialysis, – vs. +	16/23 vs. 17/27	15/23 vs. 16/27	0.9 (0.63–1.35)	0.89 (0.53–1.49)
OKT3, + vs. –	18/20 vs. 15/30	16/20 vs. 15/30	**0.55 (0.38–0.82)**	**0.63 (0.41–0.95)**
Primary graft function, + vs. –	23/31 vs. 10/19	22/31 vs. 9/19	0.71 (0.44–1.14)	0.62 (0.37–1.05)
Tacrolimus trough levels, >6.4 vs. ≤6.4 ng/ml	18/26 vs. 15/24	18/26 vs. 13/24	0.86 (0.48–1.54)	0.72 (0.41–1.27)
Time until switch, ≤34 days vs. >34	20/27 vs. 13/23	19/27 vs. 12/23	0.76 (0.50–1.16)	0.74 (0.47–1.18)
Total HLA-mismatch, ≤2 vs. >2	20/29 vs. 13/21	19/29 vs. 12/21	0.84 (0.43–1.62)	0.82 (0.43–1.56)

– = No OKT3 treatment, + = with OTK3 treatment. OKT3 treatment in addition to tacrolimus therapy was the only factor predictive of long-term graft survival.

of patients with and without OKT3 treatment did not show any differences in terms of age (p = 0.5), gender (p = 0.16), primary renal function (p = 0.12), HLA mismatch (p = 0.24), histology (p = 0.37), dialysis (p = 0.3), starting point of tacrolimus therapy (p = 0.58), tacrolimus trough levels (p = 0.66) or number of CMV infections (p = 0.66). A multivariate analysis revealed OKT3 as an independent factor predicting 5- and 7-year graft survival.

Follow-Up Biopsy

Follow-up biopsies after switch to tacrolimus were performed within 3 months in 23 patients (46%). Chronic transplant glomerulopathy was diagnosed in 7 patients, signs of ongoing rejection in 13 patients and a combination of transplantation glomerulopathy and ongoing rejection in 2 patients. Only 1 patient with chronic transplant glomerulopathy had been treated with OKT3, him being the only of these 9 patients achieving 7-year graft survival. Eight patients with ongoing acute allograft rejection after switch to tacrolimus achieved 7-year graft survival and 7 patients developed graft failure. Six of the 8 patients with 7-year graft survival had been treated with OKT3, while 1 of the patients without 7-year graft survival had received OKT3.

Discussion

The data of this prospective observational study implicate a reasonable long-term patient and graft survival in patients with steroid refractory renal allograft rejection after changing baseline immunosuppression from cyclosporine to tacrolimus. Graft survival was only slightly inferior compared with a patient cohort without steroid-resistant rejection, indicating that these patients receive a long-term benefit from their transplant despite the intense immunosuppression necessary to overcome rejection. An independent predictive parameter for successful long-term graft survival was treatment with OKT3 in addition to tacrolimus therapy. This finding seems to be important, even though our patients were not randomized for OKT3/tacrolimus treatment versus immediate switch of the baseline therapy to tacrolimus. The patient groups with and without OKT3 therapy were not different in other parameters known to predict long-term graft survival, and the effect of OKT3 was independent in a multivariate analysis. The beneficial effects of OKT3 administration in addition to tacrolimus as baseline immunosuppression observed in this study were not seen in a study by Kliem et al. [17]. The follow-up period of their study was inhomogeneous (71 patients with a median of 24 months). This could explain the differences to our long-term observations. Regarding the application of our results to current clinical practice, it has to be noticed that nowadays most patients receive mycophenolate mofetil as immunosuppression, which results in a decrease in the number of steroid-resistant rejections. However, newer, more detailed data about the long-term outcome of steroid-resistant rejection in the mycophenolate mofetile era are not available.

Two detailed studies on long-term outcome (>3 years) of patients with steroid refractory renal allograft rejection have been published so far. Jordan et al. [13] prospec-

tively attempted allograft salvage with switch to tacrolimus in 169 patients suffering from ongoing rejection on cyclosporine baseline immunosuppression despite treatment with pulse steroids. The mean follow-up was 30 months and the overall allograft survival rate was 74% (125/169) after this period. Only 18 out of 169 patients were followed for 5 years. A detailed analysis of predicting factors of successful rescue therapy was not performed. Interestingly, the authors found a slight but statistically significant advantage for a switch to tacrolimus before 6 months after transplantation. In the present study, all but 1 patient received tacrolimus earlier than 6 months after transplantation and therefore an analysis of this issue was not possible.

Rostaing et al. [2] analyzed long-term outcome of 73 patients with steroid-resistant acute rejection after treatment with OKT3. The baseline immunosuppressive therapy was not changed and patients were generally treated with a combination of cyclosporine, azathioprine and steroids. The overall cumulative graft survival was 52.5% at 5 years. Parameters predictive for graft function 2 years after OKT3 therapy were panel reactive antibodies of less than 25%, a grade I acute rejection according to the Banff classification and lower serum creatinine levels 1 month after administration of OKT3. The study did not show differences in terms of recipient age, gender, HLA mismatch, or chronic lesions or grade II and III rejection in histology. Therefore, the study of Rostaing et al. [2] indicates a predictive value for the histological findings of preconversion biopsies in steroid-resistant rejection. Furthermore, the presence of chronic rejection has been reported to worsen prognosis in steroid-resistant rejection [12]. In accordance with this, all patients with signs of chronic transplant glomerulopathy in the follow-up biopsy lost their graft in the present study. Interestingly, none of these patients was pre-treated with OKT3. Thirteen patients showed signs of ongoing acute rejection after conversion to tacrolimus. This finding did not seem to have a major impact on the final outcome as 7/13 of these patients achieved 7-year graft survival. The grade of rejection according to the Banff classification has been shown to be predictive for the overall renal allograft survival [22]. This predictive value does not seem to apply for graft survival in patients with steroid refractory renal allograft rejection [23]. The biopsy specimens in our study were not classified according to Banff. There was no difference in long-term outcome between cellular and vascular rejection episodes, suggesting that the type of rejection may not be predictive in cases of steroid-resistant rejection.

In conclusion, our data indicate a reasonable long-term patient and graft survival in patients with steroid refractory renal allograft rejection after switching baseline immunosuppression from cyclosporine to tacrolimus. OKT3 treatment in addition to tacrolimus therapy is associated with improved long-term outcome.

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