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Multiple drug combinations with "low-dose" cyclosporin for renal transplantation

Multivariate analysis of risk factors determining short-term graft survival within one renal transplant center

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Abstract. The factors affecting graft survival in transplant recipients receiving cyclosporin (CsA) are still being debated. Our report is based on an analysis of 202 successive transplantations performed in our institution from May 1984 to December 1986, using low-dose CsA as the basic means of immunosuppression. A total of 142 patients received the triple combination CsA, azathioprine (AZA), and corticosteroids. Sixty patients received a prophylactic combination of CsA, corticosteroids, and antilymphocyte globulins (ALG). From January to December 1986, both regimens were compared in a prospective randomized trial. The factors that affect graft survival were analyzed using the Cox multivariate hazard analysis. The relative risks were calculated for pretransplant baseline risk factors and for outcome-dependent post-transplant risk factors for surviving grafts at 1 month. Transplants performed with a prolonged ischemia time and patients whose graft did not function immediately were statistically at higher risk of graft loss. Adding prophylactic ALG to CsA was associated with better graft survival. Patients who experienced more than 1 rejection crisis and patients whose 1-month CsA dose was lower than or equal to 5 mg/kg per day were also at significantly higher risk of further graft loss. Neither HLA matching, peak panel reactivity, age of the recipient, occurrence of post-transplant renal dysfunction nor 1-month renal function affected the short-term graft outcome.

Key words: Renal transplantation - Cyclosporin - Survival analysis.

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Since cyclosporin (CsA) has become the major immunosuppressant for patients receiving renal allografts from cadaveric donors [4], various immunosuppressive protocols have been designed, using this drug alone [5] or in combination with conventional immunosuppressants: steroids, azathioprine (AZA), and/or antilymphocyte globulins (ALG) [8-12, 24]. Although most studies have reported better graft and patient survival rates than were obtainable with conventional immunosuppression, many questions have been raised concerning the nephrotoxic effect of CsA [12, 18], its immunosuppressive properties [23, 25], and the appropriate dosage and time schedule to hold the effectiveness of the drug constant while still minimizing its side effects. Initial low doses of oral CsA, i.e., 8 mg/kg per day have been suggested to avoid the nephrotoxic effect of the higher doses given earlier in combination with either AZA and steroids [9, 10] or with ALG and steroids [11, 12].

To determine whether the classic factors influencing graft outcome such as HLA matching, panel reactivity, or age were still valuable in the CsA era, as well as whether new prognosis factors could be determined, we have retrospectively analyzed 202 cadaveric transplants performed in our unit from 1984 to 1986; all patients received multiple drugs regimens, using initial moderate doses of CsA, and were followed up for at least 1 year.

Patients and methods

The following data deal with 202 consecutive patients who had cadaveric transplants between May 1984 and December 1986 at our institution. During the pretransplant period, all patients automatically received transfusions consisting of six free-pack red cell

Table 1. Characteristics of the transplant recipients according to the immunosuppressive regimen. Age, panel reactivity, preimmunization, HLA-A, -B and -DR mismatch (MM), time in dialysis, and cold ischemia time are expressed as means ± SD. Number of patients, diabetics, and retransplants are expressed in numerals. CsA, Cyclosporin; S, steroids; ALG, antilymphocyte globulins. * $P < 0.02$

	Whole group	CsA + AZA + S	CsA + ALG + S
Patients (*n*)	202	142	60
Age (years)	38.4 ± 10.5	39.5 ± 10.8	35.9 ± 9.6*
Sex (M/F)	129/73	89/53	40/20
Diabetics	3	1	2
Retransplants	9	6	3
Time in dialysis (months)	41.6 ± 36.9	42.6 ± 37.3	39.1 ± 36
Panel reactivity (%)	13.4 ± 24.8	11.7 ± 22.6	17.3 ± 29.2
Preimmunized	67 (33.2%)	44 (31.9%)	23 (38.3%)
MM-A + B	1.98 ± 0.97	2.06 ± 0.99	1.8 ± 0.9
MM-DR (179 patients)	0.85 ± 0.75	0.83 ± 0.73	0.9 ± 0.79
Cold ischemia time (hours)	39.2 ± 8.9	39.3 ± 8.8	38.9 ± 9.1

units. All transplantations were performed with strict ABO matching and after a negative T and B cross-match, using positive and negative sera taken earlier from the recipients. The requirements for HLA matching in the France Transplant Association give priority to the best-matched recipients, especially for retransplantations where three B-DR identities between donor and recipient are required.

Immunosuppressive regimens

Since the introduction of CsA in our transplant unit, two kinds of immunosuppressive combinations have been studied consecutively:

1. The triple drug regimen, combining low doses of CsA, AZA, and steroids (142 patients). CsA (4 mg/kg) was administered intravenously before the operation and then orally (8 mg/kg per day) day 1 after transplantation. Intravenous methylprednisolone (120 mg) was given intraoperatively and then oral prednisolone was begun on day 1 (2 mg/kg per day), with the dose tapered off by 10 mg every 2 days until there was a baseline of 10 mg per day. AZA was given each day after transplantation at a dose of 1.5-2 mg/kg per day, but not exceeding 125 mg/day. Rejections were treated by methylprednisolone given at a dose of 10 mg/kg, promptly tapered off to 1 mg/kg per day, and then progressively reduced.

A total of 142 patients received this low-dose combination, including one of the first groups of patients ($n = 79$) from May 1984 to December 1985, with a control group of 80 patients who received conventional drugs, and a second group of 63 patients transplanted between January and December 1986, and compared to a group of 60 patients who received ALG, CsA, and steroids.

2. The prophylactic combination ALG, CsA, and steroids. Sixty patients received this combination from January to December 1986. This group was compared to the second group of 60 randomly selected transplant recipients who received the triple drug regimen. This regimen consisted of methylprednisolone, administered intraoperatively (120 mg), and prednisolone, beginning the day following transplantation (2 mg/kg) and tapered off to 0.3 mg/kg per day by day 30, as well as CsA 4 mg/kg administered intravenously preoperatively, and then 8 mg/kg per day orally, beginning on day 1. Horse ALG (Lymphoglobulins, Merieux, France), 15 ml/day, was administered for 14 days post-transplantation.

AZA (1.5 mg/kg per day) was introduced later in the follow-up when (1) the CsA dose was reduced to below 4 mg/kg per day or (2) serious side effects such as diabetes or bone osteonecrosis occurred from the corticosteroids. Rejections were treated by a 7-day course of ALG and boluses of methylprednisolone.

Whatever the regimen used, the CsA doses were adjusted by twice-weekly doses in order to maintain trough levels between 50 and 250 ng/ml. When a renal dysfunction episode occurred, the diagnosis of CsA nephrotoxicity was considered when serum creatinine was stable or progressively rose to less than 20%, and the daily dose was reduced by 1-2 mg/kg. A renal biopsy was performed in order to distinguish between nephrotoxicity and potential rejection if renal function did not improve rapidly following dose reduction.

Additional treatments in both groups included intravenous perioperative antimicrobial prophylaxis with ampicillin, oxacillin and gentamicin, starting oral cimetidine (200 mg per day) on day 3 and cotrimoxazole (80/400 mg per day) within 6 weeks post-transplantation.

Patient population

The mean age, sex, transplantation history, mean anti-HLA antibodies, number of diabetics, retransplantations, HLA-AB and -DR matching data, and the duration of hemodialysis are shown in Table 1.

All patients with a functioning graft were followed up from 12 to 44 months after transplantation. The rejection frequency was defined as the number of rejection episodes registered during the first 3 months, divided by the number of transplantations done in the group. Grafts were recorded as lost when the patient died with a functioning graft. No patient was lost to follow-up.

Statistical methods

Statistical tests were carried out with the computer programs BMDP 1L and 2L. Graft survivals were studied with Cox's model of proportional hazards, which allows the influence of each of many variables to be assessed on patient survival [2]. Each variable can be tested while holding constant the influence of other variables. Cox's model specifies the hazard function as a function of covariates. Many different combinations of baseline and time-dependent covariates were considered. The baseline covariates included pretransplant and peritransplant risk factors: presensitization, HLA-AB and -DR matching, age of the recipient, cold ischemia time, early graft function, and the immunosuppressive regimen. We also studied the post-transplant-dependent outcome variables: the serum creatinine level at 1 month post-transplantation, the number of rejections during the initial postoperative period, the occurrence of renal dysfunction episodes, and the dose of CsA administered at 1 month, reflecting the total amount of CsA given in the early course of transplantation. Withdrawn from the latter analysis were transplants with early graft failure, namely, patients who did not leave the hospital with a functioning graft. Among the early failures were 24 grafts lost to permanent nonfunction, thrombosis, irreversible rejection, or abandoned due to infection. Variables found to be

significant in the multivariate analysis were analyzed using the actuarial life-table method, considering only one variable at a time, and survival curves were compared using the Mantel-Cox test and the Breslow test.

Results

Graft and patient survivals

The actuarial graft and patient survival rates in the total population of transplant patients are shown in Fig. 1. At 1 year, the graft and patient survival rates were 84% and 96%, respectively. After 1 year, the graft loss rate began to decrease, and the survival curve was even less steep after 24 or 30 months. Among the 39 failures, 23 (59%) were due to rejection, 1 to a non-functioning kidney, and 4 to surgical complications, including 4 renal artery thromboses. Ten patients died with normal renal function, including 5 with sepsis. Five deaths of infectious origin were observed in the group of 142 patients treated with the triple drug regimen (3.5%), but no patient died in the group of 60 patients submitted to the prophylactic combination of ALG, CsA, and steroids (1.7%). Indeed, severe bacterial infections were more frequently observed in the group treated with the triple drug regimen (5 cases of septicemia and 5 of pneumonia) than in patients treated with the prophylactic combination (3 septicemias) in whom cytomegalovirus infections were more common: 11 patients (18.3%), versus 6 (4.2%) in the triple drug group.

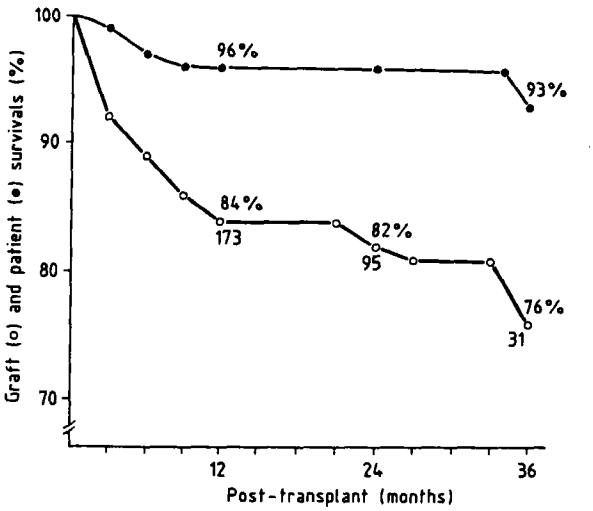

Fig. 1. Actuarial graft (O) and patient (●) survival curves of 202 cadaveric transplants given initial low-doses of cyclosporin

Table 2. Cox regression model. Analysis of baseline risk factors in the whole group of 202 patients. ALG, Anti-lymphocyte globulins; PRA, panel reactive activity; MM AB, class I mismatching; MM DR, class II mismatching

Covariates	R Risk[a]	*P* value
Regimen with ALG	0.32	<0.01
Age > 45 years	1.15	NS
Peak PRA	1.22	NS
Number of MM AB > 2	1.28	NS
Number of MM DR > 0	1.24	NS
Cold ischemia time > 40 h	2.1	<0.008
No immediate renal function	2.5	<0.002

[a] Values above 1.00 denote increased graft loss; those below denote better survival

Cox regression with baseline covariates

Table 2 gives the risk factors for graft loss as identified in Cox's proportional hazard model. This first-step analysis included only pretransplant and peri-transplant risk factors as covariates. Of the seven variables studied, the effect of the immunosuppressive regimen, namely, the adjunction of ALG to the combination CsA-steroids, appeared first to have a significant impact on graft survival. Patients treated with the prophylactic immunosuppressive combination showed a significant improvement in graft survival. Also, patients who did not have immediate graft function and grafts with a cold ischemia time greater than 40 h were statistically at higher risk of graft loss. Neither HLA-AB mismatching, DR mismatching, nor positive peak panel reactive activity was significant. Finally, the age of the recipient had no significant influence on the risk of graft loss.

Cox regression with post-transplant outcome-dependent variables

This analysis is shown in Table 3; 24 patients were excluded from this analysis, as their graft loss occurred within 1 month following transplantation. Among the four covariates entered in the model, the incidence of rejections had the greatest influence on further graft loss. Neither the incidence of nephrotoxicity nor the level of serum creatinine at 1 month post-transplantation had a significant influence on graft outcome. Finally, we found a significant correlation between risk of graft loss and the dose of CsA administered at 1 month post-transplantation: patients whose dose was lower than or equal to 5 mg/kg per day had a poorer outcome.

Univariate analysis

In order better to display the influence of risk factors that were found to be significant in the Cox's

Table 3. Cox regression model. Analysis of post-transplant outcome-dependent risk factors in the group of 178 patients with functioning kidney at 1 month post-transplantation. CsA, Cyclosporin

Covariates	R Risk[a]	*P* value
One-month serum creatinine above 150 μmol per liter	1.17	NS
One month CsA daily dose > 5 mg per kg	0.29	< 0.008
Number of rejections within 3 months > or = 2	1.96	< 0.004
Occurrence of renal dysfunction episodes	1.22	NS

[a] Values above 1.00 denote increased graft loss; those below denote better survival

Table 4. One-year graft survival according to risk factors found to be significant in the Cox analysis. CsA, cyclosporin; AZA, azathioprine; ALG, anti-lymphocyte globulins; S, steroids

Risk factors	*n*	Survival	*P*
Regimen			
CsA + AZA + S	142	80.3%	
CsA + ALG + P	60	93.1%	< 0.05
Cold ischemia time			
40 h	101	79%	
< = 40	101	89%	< 0.01
Immediate function			
Yes	135	88%	
No	67	76%	< 0.01
Number of rejections			
0-1	117	93%	
> 1	61	78%	< 0.01
One-month CsA dose			
< = 5 mg/kg/day	99	85%	
> 5 mg/kg/day	79	95%	< 0.05

regression analysis, 1-year graft survival rates and graft survival curves were compared between groups of patients for each baseline mentioned above and for the outcome-dependent variables (Table 4). Overall, there was a 13% improvement in 1-year survival due to the use of the regimen combining CsA and prophylactic ALG (60 patients), as compared with the group of 142 patients treated with the triple combination CsA-ALG steroids. Initial kidney nonfunction (67 patients) is associated with a poor 1-year graft survival rate: 76% as compared with 88% when the kidney functioned immediately ($n = 135$; $P < 0.01$). Transplants wherein the cold ischemia time was shorter or equal to 40 h (1-year graft survival rate: 89%) did significantly better ($P < 0.01$) than did grafts transplanted after a greater cold ischemia time (79%). Patients with 0 or 1 rejection episode had a better ($P < 0.01$) 1-year graft survival rate (93%) than patients who experienced 2 or more rejections (78%). Patients whose 1-month CsA dose was lower than or equal to 5 mg/kg per day had a poorer 1-year graft survival (75%) than patients whose dose was 5-8 mg/kg per day (93%; $P < 0.05$).

The results of univariate and multivariate analyses were generally in agreement. Other variables, such as the age of the recipient, panel reactivity, HLA-AB and DR mismatching, the level of serum creatinine at 1 month, and the occurrence of nephrotoxic episodes, did not significantly influence graft survival and were not found to represent significant risk factors in the multivariate analysis.

Discussion

This study analyzes the influence of various risk factors on short-term kidney graft survival in a defined group of 202 patients, who were consecutively transplanted in a single institution using low initial CsA doses as the basic method of immunosuppression. There is considerable literature on this topic, but there are also conflicting results in the data, which are usually accumulated from collaborative registries [7] or collaborative studies [20, 21], including homogeneous data from numerous transplant centers. Indeed, the center effect has been specified as a risk factor by itself by some authors [26] and may alter the concentrated data since the policy concerning HLA matching, transfusions, cold ischemia, and management of immunosuppression may vary considerably between centers. For instance, in one of the first studies [6] the impact of initial graft function was demonstrated to be an important factor in transplants performed with CsA. However, in a second paper containing data from 303 transplants performed in a single center [13], there was no evidence of an adverse impact on graft survival. Also, the respective influence of pretransplantation transfusions and HLA matching has long been disputed [7, 14, 17, 19]. Our data are from a large, homogeneous cohort of transplantations performed in a single unit. All recipients had transfusions, and the policy regarding HLA matching did not vary. The immunosuppressive regimen was identical for the whole group with regard to the doses and management of CsA, but a group of 60 patients received a prophylactic course of 14 days ALG instead of oral AZA.

It is obvious that the addition of ALG to the immunosuppressive regimens with low-dose CsA pro-

duced a striking effect on graft outcome: both univariate and multivariate analysis showed a significant disadvantage for the group of 142 patients to whom ALG was not given. Our data confirm the excellent results published elsewhere [12]. There is a 1-year graft survival time in 90%, and only four patients (6.7%) have lost their kidney because of graft rejection. These results support other reports on the powerful combination of CsA and ALG [11], as this combination provides optimal efficiency in the prevention of kidney rejection, while minimizing the incidence of serious bacterial infections.

The negative effect of nonimmediate kidney function on short-term graft survival has been underlined by several authors in groups of patients - whether initially treated by CsA or not [3, 6]. This effect on graft survival showed a 14% difference in the 3-month graft survival rate, but remained stable or even declined at 1 year (10%). In other words, this factor seems to be linked to *early* graft failures such as renal thrombosis or nonfunctional kidneys but does not represent a criterion for the longer prognosis per se. Our data, like those reported in other studies [22], confirm the negative influence of a long period of cold ischemia (> 40 h), even when CsA was prescribed at the relatively low dose of 8 mg/kg per day after the day of transplantation. Both prolonged ischemia and physical damage to the kidney may enhance the nephrotoxicity of CsA. Therefore, avoiding very long periods of ischemia may significantly improve graft survival.

The HLA-AB and DR mismatching detected in our data showed no significant effect. The matching effect, still obvious in some studies [7, 21], was denied by several groups [14, 17]. Considering that in our study high-risk transplants such as strongly immunized recipients or retransplants were the "best" matched, no definitive conclusions can be made. On the other hand, a longer period of follow-up and a larger number of patients may be necessary to evaluate the influence of HLA matching on selected events such as the occurrence of chronic rejection.

Among the post-transplantation variables studied, the number of rejections during the first 3 months had the most significant impact on graft survival. Patients who experienced more than one rejection episode had a 15% lower graft survival rate than did patients in whom rejection was not detected. Despite the short follow-up time, it is clear that the occurrence of rejection in CsA-treated kidney graft recipients has a negative effect on the ultimate graft outcome. This emphasizes the crucial importance of multiple drug combinations with conventional immunosuppressants such as AZA, ALG, and steroids when low-dose CsA is employed in order to minimize the clinically obvious and also nonclinically demonstrated rejections. The negative effect of the low 1-month CsA dose is more difficult to explain [15]. In effect, patients whose CsA dose was reduced below 5 mg/kg per day experienced renal dysfunction that may have been induced by nephrotoxicity or by subclinical rejection as well. This effect, also reported by others [1], on renal function may be explained by the selection of a group of patients who "tolerated CsA well."

Since transplant biopsies are not routinely performed when a mild rise in serum creatinine occurs, this question remains unanswered. Finally, our data indicated that neither short-term renal function nor the occurrence of renal dysfunction episodes, mainly acute nephrotoxic episodes, were prognostic factors for short-term graft survival in CsA-treated patients. Long-term follow-up studies are necessary to determine whether CsA-induced renal dysfunction would impair long-term graft survival. Data from heart transplant recipients given CsA [18], but in higher initial dosages, suggest that both the evaluation of the glomerular filtration rate and transplant biopsies are poor indicators of long-term, progressive CsA injury. Serum CsA trough levels were not considered a risk factor for short-term graft survival in our study. Our policy in multiple drug regimens was to maintain CsA levels precisely between 50 and 250 ng/ml during the 1st month after transplantation, the daily dose being systematically reduced when the level exceeded this range. Experiments in rats receiving CsA have shown that there is a definite correlation between the severity of histological features and the CsA levels in respective tissues rather than with the blood levels [16]. Long-term functional and morphological studies performed in such patients given multiple drug regimens will determine whether blood levels, CsA dosages, or nephrotoxic episodes correlate with functional disorders and the magnitude of histological changes such as interstitial fibrosis.

In conclusion, this study shows that the prognostic factors for early success in renal transplantation, using low-dose CsA as the basic immunosuppressive drug, are approximately identical to the classic prognostic factors with conventional immunosuppression, including the effect of prophylactic ALG. Nevertheless, there is a marked difference in factors which may have an additive CsA effect on graft function and thus greater impact, namely, the cold ischemia time and the occurrence of initial tubulonephritis. The effect of other factors such as HLA matching must still be determined with long-term data in large homogeneous studies.

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