Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts

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Objective: Low-dose prednisone given on alternate days as a steroid adjunct to cyclosporine therapy was investigated primarily for its influence on kidney graft and patient survival and, secondarily, on renal function and complications.
Design: Multicentre randomized double-blind clinical trial.
Setting: Fourteen Canadian transplant centres.
Patients: A total of 523 patients with well-functioning renal transplants (cadaveric grafts or grafts from living related donors) and without active graft rejection reactions who were entered into the trial from 1982 to 1985.
Intervention: Patients were randomly assigned 90 days after transplantation to receive either placebo (260 patients) or low-dose prednisone (263 patients).
Main outcome measures: Graft and patient survival.
Main results: After at least 5 years of follow-up 50 patients assigned placebo had lost their graft and 17 had died; the corresponding figures for those assigned prednisone were 38 and 16. After an average interval of 1.4 years 143 patients in the placebo group and 123 patients in the prednisone group had stopped therapy with the test drug or had had their treatment group decoded or both. Patients were withdrawn from the study 2 years after stopping the test therapy. The actuarial 5-year graft survival rates were 73% and 85% in the placebo and prednisone groups respectively ($p = 0.03$), and the actuarial 5-year patient survival rates were 92% and 94% respectively ($p = 0.6$). This analysis included 43 and 29 graft losses and 14 and 12 deaths in the placebo and prednisone groups respectively. Weibull parametric modelling of graft survival identified the following variables as risk factors for graft loss: histocompatibility leukocyte antigen B (HLA-B) mismatching ($p = 0.007$), donor death from cerebrovascular accident ($p = 0.01$), increased donor age ($p = 0.02$) and being a male recipient ($p = 0.05$). When these factors were included in the Cox proportional hazards model, the influence of assigned treatment on graft survival was reduced to $p = 0.1$. Donor death from cerebrovascular

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accident ($p = 0.002$), diabetes mellitus in the recipient ($p = 0.02$) and increased recipient age ($p = 0.05$) were risk factors for patient death. Renal function and incidence of complications were similar in the treatment groups.
Conclusions: Continued administration of low-dose prednisone on alternate days is advisable, particularly in patients with cadaveric grafts and those with previously failed transplants.

Objectif : La prednisone à faible dose administrée à tous les 2 jours comme adjuvant stéroidien au traitement à la cyclosporine a fait l'objet d'une étude axée principalement sur son incidence sur la greffe du rein et la survie des patients et, secondairement, sur la fonction rénale et les complications.
Conception : Étude clinique multicentrique, randomisée et à double insu.
Contexte : Quatorze centres de transplantation canadiens.
Patients : Un total de 523 patients dont les transplantations rénales fonctionnent bien (greffons de cadavres ou de donneurs apparentés et vivants) et sans réaction active de rejet du greffon ont été inscrits à l'étude de 1982 à 1985.
Intervention : Quatre-vingt-dix jours après la transplantation, les patients ont été choisis au hasard pour recevoir un placebo (260 patients) ou de la prednisone à faible dose (263 patients).
Principales mesures des résultats : Survie du greffon et du patient.
Principaux résultats : Après au moins 5 ans de suivi, 50 des patients ayant reçu le placebo avaient perdu leur greffon et 17 étaient décédés; les chiffres correspondants pour ceux qui avaient reçu de la prednisone étaient de 38 et 16. Après un intervalle moyen de 1,4 année, 143 patients du groupe placebo et 123 patients du groupe prednisone avaient interrompu le traitement avec le médicament à l'étude, avaient fait décoder leur groupe de traitement ou les deux. Deux ans après l'interruption du traitement, on a retiré les patients de l'étude. Les taux actuariels de survie des greffons après 5 ans étaient de 73 % dans le groupe placebo et de 85 % dans le groupe prednisone ($p = 0,03$), et les taux actuariels de survie des patients après 5 ans étaient de 92 % et de 94 % respectivement ($p = 0,6$). Cette analyse comportait 43 et 29 pertes de greffons et 14 et 12 décès dans les groupes placebo et prednisone respectivement. La modélisation paramétrique de Weibull de la survie des greffons a identifié les variables suivantes comme facteurs de risque de perte de greffe : défaut des antigènes leucocytaires d'histocompatibilité B ($p = 0,007$), décès du donneur par accident cérébrovasculaire ($p = 0,01$), âge accru du donneur ($p = 0,02$) et receveur de sexe masculin ($p = 0,05$). Lorsque ces facteurs étaient versés au modèle des hasards proportionnels de Cox, l'incidence du traitement prescrit sur la survie des greffons était réduite à $p = 0,1$. La mort du donneur par accident cérébrovasculaire ($p = 0,002$), le diabète sucré chez le receveur ($p = 0,02$) et l'âge accru du receveur ($p = 0,05$) étaient des facteurs de risque de décès chez le patient. La fonction rénale et l'incidence des complications étaient semblables dans les groupes de traitement.
Conclusion : L'administration continue de prednisone à faible dose à tous les 2 jours est à conseiller, en particulier chez les patients qui reçoivent des greffons de cadavre et ceux qui ont subi des échecs antérieurs de transplantation.

Although much remains obscure, and will long remain obscure, I can entertain no doubt, after the most deliberate study and dispassionate judgement of which I am capable, that the view which most naturalists until recently entertained, and which I formerly entertained . . . is erroneous.

— Charles Darwin (1809-1882), Introduction,
On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life,
John Murray, London, 1859

The clinical course following renal transplantation is divided into two phases: an early, induction phase, when the incidence of graft failure is relatively high, and a later, long-term phase beginning 50 to 100 days after transplantation, when the graft failure rate declines. During the induction phase immune responses against graft antigens are frequent, and higher doses of maintenance immunosuppressive agents are needed to prevent rejection episodes. In the long-term phase rejection reactions subside, which allows the use of lower doses and circulating levels of immunosuppressive agents. An important therapeutic objective is to reduce the long-term maintenance level of immunosuppressive agents to as low a level as possible, without increasing the incidence of graft loss through rejection reactions, the latter being treated with

high, nonmaintenance doses of immunosuppressive agents.

Cyclosporine is the principal drug used to prevent rejection reactions and graft loss. Many centres have commented on the benefit, or otherwise, of therapy with low-dose steroids[1-27] coupled with cyclosporine (or, formerly, azathioprine). Although cyclosporine[28,29] controls rejection reactions,[30-33] the requirement for adjunct maintenance steroid therapy in the postinduction phase has not been investigated in an explicitly comparative, randomized, blinded study. Many of the centres that reported worse results in patients who received steroids merely linked the clinical use of steroids to graft outcome; such observations indicate that patients with poor graft function who are in active rejection tend to be given additional steroid immunosuppressive therapy. These studies did not address the question of the benefit of steroids in a defined group of transplant recipients with good graft function and no overt rejection reactions.

To study the null hypothesis that there is no difference in patient and graft survival when low-dose maintenance steroid therapy is stopped in patients with good graft function and a quiescent transplant course, we carried out a multicentre randomized double-blind clinical trial. Patients receiving maintenance cyclosporine and prednisone therapy who had good graft function and no active graft rejection reactions were assigned 90 days after transplantation to receive either low-dose, alternate-day steroid therapy or a placebo. The starting time of 90 days was chosen because this is roughly the time when graft and patient survival curves level off, and low maintenance doses and circulating levels of cyclosporine could be attained without the risk of frequent rejection episodes. In this setting physicians would have the option of starting known steroid treatment to control rejection, to maintain better graft function or to better interpret steroid side effects and could later return to the test drug only, if this seemed clinically appropriate. In this paper we report on our experience in attempting to stop long-term, adjunct immunosuppressive therapy with low doses of prednisone in a group of patients who were followed for 5 years after receiving transplants.

Methods

Organization

Fourteen transplant centres entered patients into the trial: Vancouver General Hospital (34 patients), Foothills General Hospital, Calgary (32), University of Alberta Hospitals, Edmonton (49), University Hospital, Saskatoon (4), Health Sciences Centre, Winnipeg (56), University Hospital, London, Ont. (53), Laurentian Hospital, Sudbury, Ont. (17), St. Michael's Hospital, Toronto (10), Ottawa Civic Hospital (28), Ottawa General Hospital (24), Hôpital Maisonneuve-Rosemont, Montreal (41), Hôpital Notre-Dame, Montreal (56), Montreal General Hospital (31) and Victoria General Hospital, Halifax (88). The Canadian Centre for Transplant Studies, University Hospital, London, Ont., was the organizing centre responsible for assigning patients to treatment groups, distributing drugs and collecting data through a Canada-wide computerized communications network.

Eligibility criteria

Patients were eligible for entry into the trial if the patient (or the guardian) gave informed consent, was available for regular follow-up, was not enrolled in other studies that conflicted with the protocol of the trial, had not previously been entered into the trial, and did not have a history of generalized malignant disease or had not had a localized malignant tumour removed within the previous year, the graft was functioning 90 days after transplantation, there had been no acute rejection episode within the previous 2 weeks and the serum creatinine level was below 220 μmol/L at the time of randomization.

Randomization and blinding

Randomized blocks of various sizes were generated and used to attain a balanced, restricted randomization according to treatment centre. The order of randomization did not have a repeating sequence. Physicians did not know the randomization number until the patient was enrolled, and the code was not broken until the analysis. Patients were randomly assigned at 90 days to receive either a placebo or prednisone by means of a process that prevented prior knowledge of their treatment group. Patients were not stratified according to risk factors present at either transplantation or randomization. The study was doubly blinded. The placebo and prednisone were prepared by Upjohn Ltd. (Kalamazoo, Mich.) in an indistinguishable form and dispensed as coded therapy. Patients were entered into the trial from 1982 to 1985. On the basis of an upper proportion of success of 0.80, an α value of 0.05 and a power of 80%, the planned treatment group size was set at 250 each.

Drug monitoring and other immunosuppressive drug therapy

Serum cyclosporine levels were monitored by means of radioimmunoassay[34] (kit provided by Sandoz Ltd., Basel, Switzerland) and high-performance

liquid chromatography.[35] A conversion factor, determined at times throughout the study, was used to express the values of the latter assay in terms of the former. Cyclosporine was administered twice daily by mouth, and the dosage was adjusted so that the 12-hour trough serum drug levels remained between 75 and 200 ng/mL. The average cyclosporine levels at 1, 2 and 3 years were 110, 107 and 102 ng/mL respectively, with no difference between the two treatment groups. Starting 1 day after transplantation patients were given 1 mg/kg body weight of prednisone orally on alternate days, the dosage being reduced by 5 mg on each occasion, clinical conditions allowing, until a dosage of 0.3 mg/kg body weight was reached. Rejection episodes were treated with methylprednisolone sodium succinate (maximum 4.5 g) and by increasing the dosage of cyclosporine to temporarily attain trough serum levels of 200 to 400 ng/mL, after which the levels returned to the range of 100 to 300 ng/mL.

Experimental treatment plan

A total of 260 patients were randomly assigned to receive the placebo and 263 to receive prednisone. Of the 679 patients who received transplants during the period of the trial but were not entered into the study, 239 lost their grafts before 90 days, 222 did not give informed consent, 144 had defined violations of the rules for entry, 58 were no longer being treated with cyclosporine, and 16 were not entered but no reason could be ascertained. Since all patients were receiving cyclosporine and prednisone at the time of randomization, known prednisone was reduced in dose gradually, by 5 mg with every third dose, and replaced with the test drug. The dosage of the test drug, either prednisone or placebo, was initially set at 0.25 mg/kg every other day and then decreased at 6 months to 0.2 mg/kg every other day. The total amount of prednisone administered, including prednisone in the test drug and additional steroid, is reported.

Ethics

Approval was obtained from the ethics committee at each centre. An external review committee oversaw the conduct of the trial. Patients were informed about the trial at the time of transplantation and at 90 days and were asked for consent on both occasions.

Exclusion after entry and loss to follow-up

No patients were excluded after entry (as distinct from withdrawals in the survival analysis) or lost to follow-up.

Data entry and verification of records

The data were collected by the Canadian Centre for Transplant Studies. Computer-based and visual checks of the data were done during the course of the trial. The information on background variables was checked for minimum and maximum values. Further verification was carried out in which fluctuations, discrepancies in dates and in categoric data, and large coefficients of variation were identified and the centres in question queried.

Withdrawals

To maximize the number of centres participating, we did not institute rules to limit cessation of the test drug or the use of known steroids. Patients who ceased to receive the test drug remained in the study until 2 years had elapsed or until graft loss or patient death occurred. This time was picked arbitrarily before the analysis and was based on the concept that what was being assessed was the attempt to stop steroid treatment; the effect of this attempt on graft and patient outcome may take years to evolve completely, and 2 years seemed a reasonable interval.

End points

Grafts were considered to have been completely rejected or to have failed if they had to be removed (by nephrectomy) or if the patient received another transplant or returned to dialysis for 6 weeks or more. There was no ambiguity as to whether an end point had occurred. All deaths of recipients were considered as transplant-related.

Serum creatinine levels and calculated creatinine clearance

The serum creatinine levels measured closest to 60-day intervals were grouped at these intervals until 1260 days after transplantation and the means and confidence limits calculated from the available determinations. Creatinine clearance in male patients was calculated from the serum creatinine level, age and body weight in kilograms, according to the Cockcroft–Gault formula.[36,37] Clearance in female patients was considered to be 85% of that in a male patient with a comparable serum creatinine level, weight and age. The degree of error or bias associated with this formula is sufficiently small that the formula provides a reasonable approximation of overall renal function.[37] Measured creatinine clearance values were much more variable (unpublished observations), probably owing to technical difficulties.

Statistical analysis

The data for all 523 patients were evaluated with regard to assigned test therapy and risk factors, with follow-up to January 1990. Statistical analyses were done with SYSTAT[38] and the supplementary module SURVIVAL.[39] Graphic presentations were produced with SYGRAPH.[38] For statistical analysis of survival we used the Mantel–Cox test statistic, Weibull parametric modelling to identify risk factors and the semiparametric Cox regression to estimate the significance of the assigned treatment, the risk factors being taken into account as confounding variables.[40,41] Graft and patient survival were analysed on the basis of the original treatment group to which the patient was assigned. Two-tailed tests of significance were always used. Time series data were assessed by comparing means and 95% confidence limits,[42] again according to treatment group.

Results

Characteristics of the study population

Table 1 shows the background characteristics of the patients in the two treatment groups and according to graft outcome. Among the background variables identified in the Weibull survival analysis as risk factors for graft loss, the placebo group had a lower mean score for histocompatibility leukocyte antigen B (HLA-B) match (2.3 v. 2.5), proportionately more donor deaths due to cerebrovascular accident (25% v. 22%), a higher mean donor age (28.4 v. 27.2 years) and more males (65% v. 59%) than the prednisone group. Of the additional risk factors associated with patient death, diabetes mellitus in the recipient (12% v. 11%) and mean recipient age (38.8 v. 39.8 years) showed some variation between the placebo and prednisone groups respectively.

Graft and patient survival

In the main analysis there were 43 graft losses and 14 deaths in the placebo group, and 29 graft losses and 12 deaths in the prednisone group. The actuarial graft and patient survival curves for the first 2500 days (6.8 years) after transplantation are shown in Fig. 1. These survival curves include all 523 patients entered into the study on the principle of intention to treat, but in cases in which the test therapy was stopped we withdrew (censored) the patient from the graft survival curve (if the graft continued to function) or from the patient survival curve (if the patient was still alive) 2 years after cessation of therapy. There was no difference in patient survival between the two groups; however, graft survival was better in the prednisone group than in the placebo group (Mantel–Cox $p = 0.03$). Since this study deals with the requirement for steroids once the initial, high-loss phase has been traversed, the rapid loss of about 10% of the transplants and death of about 3% of the patients during the first 90 days after transplantation are not depicted. Although the graft survival curves are similar for the first 500 to 600 days after entry into the study, the survival curve for the placebo group falls off from this point onward. A total of 58 patients (33 in the placebo group and 25 in the prednisone group) were duly randomly assigned to receive one of the test drugs, including being assigned a randomization number, but were found at the time of analysis not to have received the test drug and continued to receive known prednisone. These patients were included in their assigned treatment group on the established "intention to treat" basis. When we excluded the results for these patients, the overall outcome was unchanged from the primary analysis (39 graft losses and 11 deaths in the placebo group, 28 graft losses and 11 deaths in the prednisone group) (Fig. 2). No estimate of significance was calculated for these curves because of the inadvisability of excluding patients at the analysis stage.

The rate of cessation of test therapy was significantly lower in the prednisone group than in the placebo group ($p = 0.03$) (Fig. 3). The mean intervals between entry into the study and withdrawal were 460 and 563 days in the placebo and prednisone groups respectively. The mean time between cessation of test therapy and graft loss was 329 days in the placebo group and 267 days in the prednisone group. The mean time between cessation of test therapy and death of the recipient was 341 days in the placebo group and 152 days in the prednisone group. Unlike the graft and patient survival rates, which varied over 20 and 10 percentage points respectively among the 14 participating centres, the rate of withdrawal varied from 27% to 91% among the 14 centres. A total of 60% of the graft losses in the placebo group occurred after therapy with the test drug was stopped, as compared with 30% of the graft losses in the prednisone group. Also, 50% of the deaths in the placebo group occurred after cessation of the test therapy, as compared with 25% of the deaths in the prednisone group. Therefore, twice the proportion of graft losses and patient deaths in the placebo group as compared with the prednisone group occurred after return to therapy with known steroids.

The causes of graft loss and withdrawal from the test drug are shown in Table 2. Although the absolute number of graft failures due to death of the recipient was the same in the two treatment groups, there were almost twice as many graft losses due to nephrectomy or return to dialysis in the placebo group (31) as in the prednisone group (17). All 12

Table 1: Background characteristics of renal transplant recipients randomly assigned 90 days after transplantation to receive either placebo or low-dose prednisone who were followed for at least 5 years, by treatment group and graft outcome

Characteristic	Mean ± standard deviation*			
	Treatment group		Graft outcome	
	Placebo (n = 260)	Prednisone (n = 263)	Survived (n = 451)	Failed (n = 72)
Recipients				
Age, yr	38.8 ± 0.8 (260)	39.8 ± 0.8 (263)	39.4 ± 0.6 (451)	38.4 ± 1.6 (72)
No. (and %) male	168 (65)	156 (59)	273 (60)	51 (71)
No. (and %) with diabetes mellitus	31 (12)	30 (11)	47 (10)	14 (19)
Current panel reactive antibody,† %	8.0 ± 1.2 (224)	9.8 ± 1.4 (222)	9.2 ± 1.0 (380)	6.9 ± 1.9 (66)
Highest panel reactive antibody,† %	17 ± 1.7 (221)	17 ± 1.7 (223)	17 ± 1.4 (380)	15 ± 3.1 (64)
No. of pregnancies	1.5 ± 0.2 (90)	1.9 ± 0.2 (105)	1.8 ± 0.1 (176)	0.9 ± 0.2 (19)
No. of units received in prior transfusions	8.3 ± 0.7 (255)	10.2 ± 1.0 (257)	9.0 ± 0.7 (442)	10.8 ± 1.9 (70)
No. of prior transplants, no. (and %) of patients				
0	230 (88)	234 (89)	400 (89)	64 (89)
1	27 (10)	23 (9)	42 (9)	8 (11)
2	3 (1)	6 (2)	9 (2)	0 (0)
Donors				
Age, yr	28.4 ± 0.8 (258)	27.2 ± 0.7 (261)	27.4 ± 0.5 (447)	30.3 ± 1.5 (72)
No. (and %) male	184 (71)	170 (65)	300 (67)	54 (75)
No. (and %) of deaths due to cerebrovascular accident	65 (25)	57 (22)	95 (21)	27 (38)
No. (and %) who received				
Dopamine	156/241 (65)	138/242 (57)	250/414 (60)	44/69 (64)
Methylprednisolone	12/224 (5)	17/230 (7)	22/393 (6)	7/61 (11)
Mannitol	111/225 (49)	105/233 (45)	184/397 (46)	32/61 (52)
Heparin	76/224 (34)	86/233 (37)	139/395 (35)	23/62 (37)
Kidney function before removal from donor				
Serum creatinine level, μmol/L	96 ± 2.3 (233)	97 ± 2.5 (233)	96 ± 1.8 (404)	99 ± 4.8 (62)
Blood urea nitrogen level, mmol/L	5.2 ± 0.2 (228)	5.7 ± 0.5 (222)	5.5 ± 0.3 (387)	5.2 ± 0.5 (63)
Lowest systolic blood pressure, mm Hg	88 ± 1.8 (156)	90 ± 2.1 (144)	90 ± 1.5 (263)	84 ± 3.7 (37)
Lowest urine volume, mL/h	200 ± 23 (122)	154 ± 18 (120)	176 ± 16 (211)	185 ± 43 (31)
Nephrectomy urine volume, mL/h	373 ± 25 (136)	326 ± 25 (148)	354 ± 19 (248)	311 ± 41 (36)
Major histocompatibility complex match score‡				
HLA-A	2.9 ± 0.1 (259)	2.9 ± 0.1 (263)	2.9 ± 0.1 (450)	2.5 ± 0.2 (72)
HLA-B	2.3 ± 0.1 (259)	2.5 ± 0.1 (263)	2.5 ± 0.1 (450)	2.0 ± 0.1 (72)
HLA-DR	3.1 ± 0.1 (234)	2.9 ± 0.1 (237)	3.0 ± 0.1 (401)	2.9 ± 0.1 (70)
Graft preservation				
Warm ischemic time, min	3.3 ± 0.2 (260)	3.3 ± 0.2 (263)	3.1 ± 0.1 (451)	4.1 ± 0.8 (72)
Cold ischemic time, min	771 ± 37 (244)	717 ± 35 (255)	710 ± 27 (430)	959 ± 70 (69)
Graft status score§	1.7 ± 0.1 (213)	1.8 ± 0.1 (213)	1.8 ± 0.1 (370)	1.7 ± 0.1 (56)
Rewarm time, min	34.6 ± 0.7 (247)	35.0 ± 0.8 (251)	34.8 ± 0.7 (430)	34.6 ± 1.3 (68)
Transplantation operative and postoperative treatment				
Furosemide, mg	136 ± 10 (144)	118 ± 8.5 (143)	122 ± 6.9 (239)	154 ± 19 (48)
Mannitol, g	38 ± 2.8 (123)	33 ± 1.6 (129)	35 ± 1.8 (217)	37 ± 4.1 (35)
Methylprednisolone	332 ± 45 (76)	293 ± 43 (80)	332 ± 34 (140)	137 ± 58 (16)

*Except where proportions are indicated, numbers in parenthesis represent the number of subjects.
†Lymphocytes from a panel of 20 people served as targets for antibody-mediated complement-dependent cytotoxicity; numbers indicate the proportion of the lymphocyte panel scored as positive.
‡1 = none, 3 = one-antigen match and 5 = two-antigen match with all antigens identified; 2 = none and 4 = one-antigen match with missing antigen.
§1 = superb, 2 = good, 3 = fair.

patients in the prednisone group who died had functioning grafts at the time of death, as compared with 12 of the 14 patients in the placebo group who died.

Many physicians consider that the outcomes of first versus succeeding transplants and of cadaveric transplants from unrelated donors versus transplants from living related donors are so different that they should be presented separately. With this breakdown there was a noticeable difference in outcome (given as total number of patients/patient deaths/graft losses/5-year actuarial graft survival rate) between the two treatment groups among patients who received cadaveric transplants from unrelated donors and had previously received a transplant (26/0/1/95% for the prednisone group v. 25/1/7/63% for the placebo group) and a lesser difference among patients undergoing transplantation for the first time who received cadaveric transplants from unrelated donors (196/11/25/85% for the prednisone group v. 193/12/32/78% for the placebo group). Transplants from living related donors fared well as either first or succeeding transplants, and there was no noticeable effect of test treatment. We did not estimate the statistical significance of the outcomes in these subgroups, as this was not a previously established question in the study. No transplants from living unrelated donors were included.

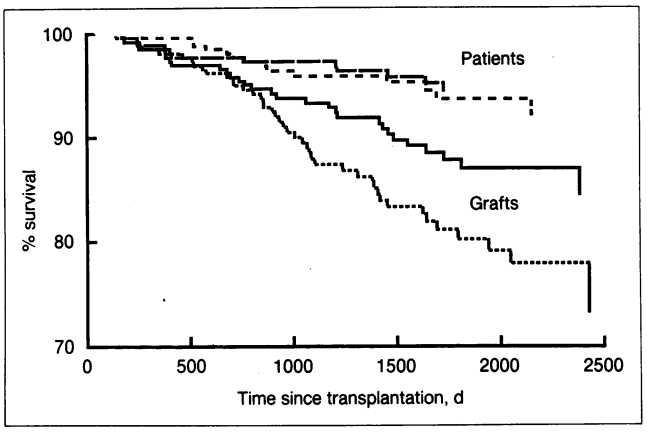

Fig. 1: Actuarial graft and patient survival curves for renal transplant recipients randomly assigned 90 days after transplantation to receive either placebo (dashed and dotted lines) (260 patients) or low-dose prednisone (solid lines and lines with slight breaks) (263 patients) who were followed for at least 5 years.

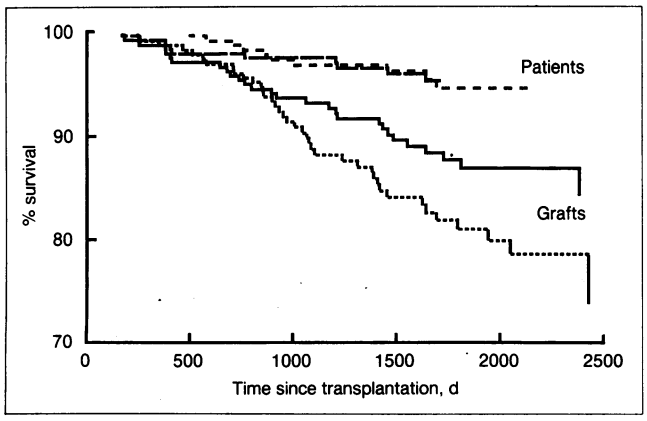

Fig. 2: Actuarial graft and patient survival curves for the placebo (dashed and dotted lines) and prednisone (solid lines and lines with slight breaks) treatment groups, excluding the 58 patients who were randomly assigned to one of the groups but not given the test drug.

Risk factors

To identify risk factors for graft loss and patient death, variables with limited missing values were analysed in a Weibull stepwise (upward) model selection, with the significance-to-include level set at $p = 0.05$ and the significance-to-exclude level at $p = 0.1$. This procedure identified HLA-B mismatching ($p = 0.007$), donor death from cerebrovascular accident ($p = 0.01$), increased donor age ($p = 0.02$) and being a male recipient ($p = 0.05$) as risk factors for graft loss. These risk factors were confirmed in the Cox proportional hazards estimation, and with the inclusion of these risk factors the influence of assigned treatment on graft survival was estimated to be $p = 0.1$.

Other background variables that showed some influence on graft survival included decreased recipient age ($p = 0.06$), diabetes in the recipient ($p = 0.08$), mismatching for HLA-A ($p = 0.09$), a longer warm ischemic time ($p = 0.1$) and receiving a transplant from a male donor ($p = 0.15$). Neither the source of the graft (cadaver or living relative; HLA matching took precedence in the multivariate analysis) nor prior transplantation was identified as a risk factor for graft loss or patient

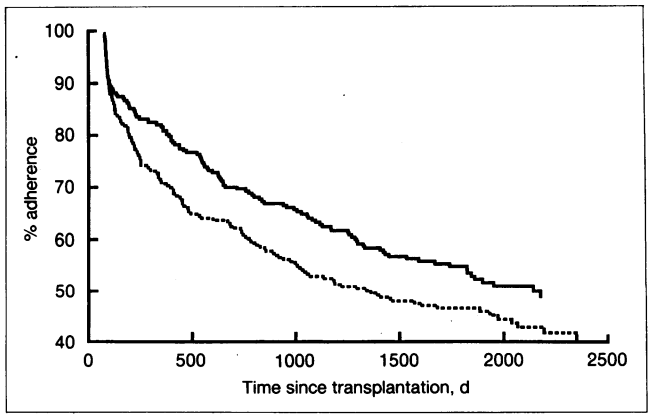

Fig. 3: Actuarial adherence to treatment with the test drug in the prednisone (solid line) and placebo (dotted line) treatment groups, plotted as survival curves. Graft losses are treated as withdrawals at the time of graft loss.

death. Because of unavailable data, other background variables could not be examined in these survival analyses (when entered, they have the effect of excluding cases); however, they are shown in Table 1.

Donor death from cerebrovascular accident ($p = 0.002$), diabetes in the recipient ($p = 0.02$) and increased recipient age ($p = 0.05$) were associated with patient death; factors with some, but not significant, influence included receiving a transplant from a male donor ($p = 0.2$) and HLA-B mismatching ($p = 0.2$).

The mean serum creatinine level 60 days after transplantation was lower in patients whose grafts continued to function than in those who had lost their graft (152 v. 161 μmol/L) but did not differ between the prednisone and the placebo group (152 v. 154 μmol/L).

Renal function

For entry into the study the recipient's graft function had to be good, with a serum creatinine level below 220 μmol/L. The mean serum creatinine level for the two groups at the time of entry was about 150 μmol/L. The renal function became worse, as shown by the rise in the mean serum creatinine level (Fig. 4) and the decrease in the mean calculated creatinine clearance (Fig. 5). These changes with time are due to the selection of patients with good renal function initially, in whom only changes for the worse can occur. Since the clinically important consideration is the function of surviving grafts, only the data for patients with surviving grafts at the end of the study are included in Figs. 4 and 5.

Renal function was slightly but not significantly (as judged from the overlapping confidence inter-

Table 2: Cause of graft loss and withdrawal from test therapy

Cause	Group; no. (and %) of patients		
	All	Placebo	Prednisone
Graft loss			
Return to dialysis	42 (58)	26 (60)	16 (55)
Death of patient	24 (33)	12 (28)	12 (41)
Nephrectomy	6 (8)	5 (12)	1 (3)
Total	72	43	29
Cessation of test therapy			
By physician	78 (29)	45 (31)	33 (27)
Decoded on request	66 (25)	34 (24)	32 (26)
No test drug given	58 (22)	33 (23)	25 (20)
Cyclosporine therapy stopped	33 (12)	15 (10)	18 (15)
Noncompliance	29 (11)	15 (10)	14 (11)
Technical withdrawal	2 (1)	1 (1)	1 (1)
Total	266	143	123

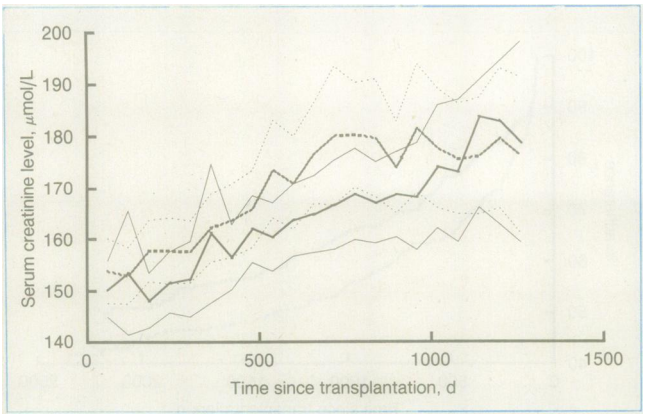

Fig. 4: Mean serum creatinine level in the prednisone (heavy solid line) and placebo (heavy dotted line) treatment groups, and 95% confidence limits (corresponding light lines). Only the data for patients with surviving grafts are included.

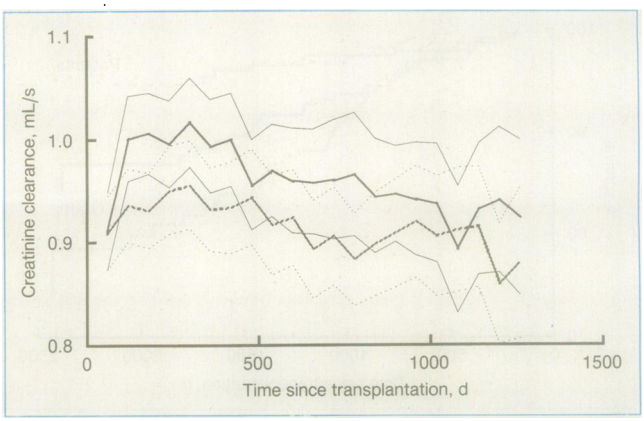

Fig. 5: Mean calculated creatinine clearance in the prednisone (heavy solid line) and placebo (heavy dotted line) treatment groups, and 95% confidence limits (corresponding light lines). Only the data for patients with surviving grafts are included.

vals) better in the prednisone group than in the placebo group for the first 1260 days after entry into the study. Since treatment with the test drug was stopped in 50% of the patients, analysis of renal function beyond 1260 days provides no further useful information.

Steroid dose

The mean total prednisone dose (test drug plus any additional prednisone) for the two treatment groups is shown in Fig. 6. Both groups are subdivided at each time point into patients who remained in their treatment group and those who came out of their treatment group to be treated with known prednisone. The mean prednisone dose 90 days after transplantation (before therapy with the test drug was started) was 22.1 (standard deviation [SD] 2.0) mg every other day for the placebo group and 20.5 (SD 0.6) mg every other day for the prednisone group, a nonsignificant difference. While the patients in the placebo group remained in their treatment group they received a mean prednisone dose of 2 to 3 mg every other day, about 10% to 15% of the steroid dose in the prednisone group and among patients in the placebo group who came out of their treatment group to be treated with known prednisone. Therefore, the placebo group was not prednisone "free," but the prednisone dose was "ultra-low" compared with that in the prednisone group (however, some patients in the placebo group received only placebo and were prednisone free).

Metabolic differences

Because about half the patients in the study were returned permanently to therapy with known steroids, we investigated some established effects of steroid treatment to determine whether a difference in steroid effects, as opposed to dose administered, could be observed. The prednisone group had a lower serum potassium level (4.4 v. 4.5 mmol/L), a higher absolute neutrophil count (7 v. 6 × 10^9/L) and more rapid return to normal of hemoglobin and hematocrit levels (135 v. 125 g/L and 0.40 v. 0.38 respectively 500 days after transplantation) than the placebo group. These differences were statistically significant, as judged from the nonoverlapping confidence intervals. There was no difference between the two treatment groups in the mean levels of blood glucose or of serum sodium, cholesterol or triglycerides. Therefore, some differences between the two treatment groups attributable to steroid effects are evident in the first year or so after entry into the study, before most of the patients stopped therapy with the test drug.

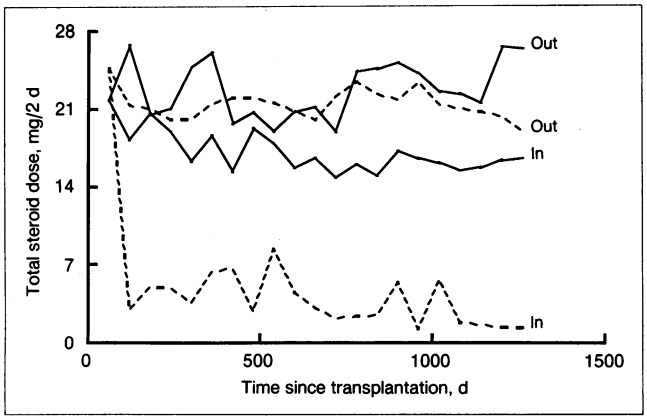

Fig. 6: Mean steroid dose (actual steroid in test drug plus any additional prednisone) for the prednisone (solid lines) and placebo (dashed lines) treatment groups. Each group is subdivided into patients who remained in their treatment group (In) and those who came out of their treatment group to be treated with known prednisone (Out).

Complications

Complications (collated by the Clinical Trials Resources Group, Robarts Research Institute, London, Ont.) did not differ between the two treatment

Table 3: Complications reported in the treatment groups up to 2 years after withdrawal

	Group; no. of patients	
Complication	Placebo	Prednisone
Avascular necrosis	3	3
Cancer	12	13
Cardiovascular problem	6	4
Gastrointestinal problem		
Hemorrhage	3	3
Pancreatitis	0	1
Other	9	13
Genitourinary problem	3	2
Hyperparathyroidism	10	13
Hypertensive episodes		
Mild	70	64
Moderate	88	109
Severe	44	48
Infection		
Bacterial	72	72
Fungal	8	6
Viral		
Cytomegalovirus infection		
Mild	10	12
Severe	0	1
Other	16	19
Neurologic problem		
Psychosis	1	3
Other	33	27
Orthopedic problem		
Mild trauma	1	7
Major trauma	2	4
Pulmonary problem	2	6
Steroid-induced diabetes	9	15

groups (Table 3). Although there was no difference in systolic or diastolic blood pressure between the two groups during the course of the study, there was some indication that more antihypertensive drugs were given in the prednisone group. Patients were categorized according to their worst hypertensive episode, which was defined on the basis of the drugs used to treat the hypertension. Therefore, a hypertensive trend may have been more common in the prednisone group but was adequately treated. Although clinically discernible cataracts were few and were not obviously related to the assigned therapy, an ophthalmologic study investigating more subtle lens changes is under way to study possible differences between the assigned treatment and actual steroids given. Because of the high rate of reinstitution of therapy with known prednisone we cannot compare complications between the prednisone-treated and prednisone-free states.

Discussion

This study deals specifically with the attempt to remove maintenance steroid therapy after the initial, induction phase. Steroids were given to all patients during the early course after transplantation for induction of immunosuppression. Without changing the null hypothesis we could rephrase the research question as In patients with no rejection activity and good graft function, is it advisable to attempt to stop steroid therapy altogether?

Patients received prednisone until randomization, and over half the patients returned to treatment with known prednisone after randomization. Since temporary recourse to steroid therapy was allowed, a portion of the patients for whom the test therapy was not stopped or the treatment group decoded received additional known prednisone. Therefore, the placebo group actually received an ultra-low average dose of prednisone during the trial, in the range of 2 to 3 mg every other day. Despite this treatment contamination of one study group by the other, a significant between-group difference emerged in the simple actuarial survival analyses ($p = 0.03$); this difference was reduced ($p = 0.1$) in the Cox model, which takes into account confounding variables identified as having a significant effect on graft survival (risk factors[40-45]). Since data on confounding variables were not complete (many times with good reason) and since inclusion of some of these variables in the Cox model would have favoured the placebo group, the best estimate of significance is in the range of 0.03 to 0.1.

A preliminary report of this study in which the present form of analysis was not used indicated no statistically significant difference between the two treatment groups, although a trend to greater graft loss in the placebo group was noted, particularly among those who returned to treatment with known prednisone.[46] In the present study the treatment contamination and the analysis used would have reduced the chance of finding a significant difference between the treatment groups. Yet withholding steroids from patients can be seen in this study to be associated with poorer graft survival. The observed difference cannot be ascribed to the rigidity of the treatment protocol, since clinicians were free to optimize the treatment of their patients as they saw fit. The chances of there being a type III error (concluding that placebo treatment is worse when, in reality, it is better[43]) are remote. On the other hand, the opposite conclusion — that it is advisable to stop alternate-day, low-dose steroid therapy in patients with well-functioning grafts — could be a type III error with its associated γ function[43] and was not the experience of this trial, in which the rate of adherence 6 years after entry was only 40%.

Many of the graft losses in the placebo group occurred in patients who had been returned to therapy with known steroid. This suggests that the lack of this immunosuppressive and anti-inflammatory agent, even as a temporary measure (average duration 1.3 years in the placebo group), sets in motion pathological events in the graft that eventually result in an increased risk of graft loss. A study in which steroid therapy was stopped shortly after transplantation in cyclosporine-treated patients showed that various forms of immune response and inflammation (i.e., accumulation of T and B lymphoblasts and monocyte-macrophages, thrombocytosis, plasmacytosis and eosinophilia) were more frequent in the renal grafts of cyclosporine-treated patients not receiving steroids than those so treated.[47,48]

Glucocorticoids have a documented action in increasing the level of lymphocytic programmed cell death.[49] Steroids may be needed for the censoring of antigraft lymphocytes, a process with which cyclosporine interferes in syngeneic graft-v.-host disease,[50,51] T-cell anergy[52,53] and programmed cell death in T[54] or B[55] cells. Hence, it is not the complementation of immunosuppressive or anti-inflammatory activity but, rather, the addition of a censoring process that may make steroids useful in renal transplantation.

That cyclosporine therapy in renal transplant recipients necessitates additional, low-dose, alternate-day steroid treatment should not be considered a black mark against cyclosporine.[56-59] Two antirejection drugs can be varied independently of each other to attain optimal results. Given the findings of this study, in future trials on the comparative efficacy of cyclosporine versus other immunosuppressive agents cyclosporine groups should re-

ceive steroids for optimum maintenance therapy. In a prospective study Schulak and colleagues[60] found that the attempt to remove steroid therapy resulted in more frequent rejection episodes; however, in the present study the number of rejection episodes was similar in the two treatment groups (data not presented) even though graft loss was greater in the placebo group.

In conclusion, we attempted to stop steroid treatment in patients with well-functioning renal grafts and quiescent transplant courses. We found that it was difficult to maintain patients on the test drug (half the patients being withdrawn, with a mean time to cessation of test therapy of 1.4 years) and that graft survival was poorer in the placebo group than among the patients assigned to receive low-dose, alternate-day prednisone along with cyclosporine ($0.1 > p > 0.03$). There appears to be an advantage in maintaining cyclosporine-treated recipients of renal cadaveric transplants on prednisone, especially those with previously failed transplants (5-year actuarial graft survival rate 63% v. 95% for the placebo v. prednisone group). Since many of the graft losses in the placebo group occurred many months after a return to treatment with known steroids, one cannot hope that reinstitution of steroid therapy will reverse the negative effects of the steroid-free (steroid-low) phase.

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References

1. McGeown MG, Douglas JF, Brown WA et al: Advantages of low dose steroid from the day after renal transplantation. *Transplantation* 1980; 29: 287-289
2. Starzl TE, Weil R, Iwatsuki S et al: The use of cyclosporin A and prednisone in cadaver kidney transplantation. *Surg Gynecol Obstet* 1980; 151: 17-26
3. Morris PJ, Chan L, French MR et al: Low dose oral prednisolone in renal transplantation. *Lancet* 1982; 1: 525-527
4. Theil G, Harder F, Loertscher R et al: Cyclosporine alone or in combination with prednisone in cadaveric renal transplantation. *Transplant Proc* 1984; 16: 1187-1190
5. Dupont E, Wybran J, Toussaint C: Glucocorticosteroids and organ transplantation. *Transplantation* 1984; 37: 331-335
6. D'Apice AJF, Becker GJ, Kincaid-Smith P et al: A prospective randomized trial of low-dose versus high-dose steroids in cadaveric renal transplantation. Ibid: 373-377
7. Brown MW, Forwell MA: Rejection reaction after stopping prednisolone in kidney-transplant recipients taking cyclosporine [C]. *N Engl J Med* 1986; 314: 183
8. MacDonald AS, Daloze P, Dandavino R et al: A randomized study of cyclosporine with and without prednisone in renal allograft recipients. *Transplant Proc* 1987; 19: 1865-1866
9. Lloveras J, Masramon J, Orfila A et al: Stopping prednisone in kidney transplant recipients taking cyclosporine: safety conditions. Ibid: 2027-2028
10. Griffin PJA, Da Costa CA, Salaman JR: A controlled trial of steroids in cyclosporine-treated renal transplant recipients. *Transplantation* 1987; 43: 505-508
11. Cristinelli L, Brunori G, Setti G et al: Withdrawal of methylprednisolone at the sixth month in renal transplant recipients treated with cyclosporine. *Transplant Proc* 1987; 19: 2021-2023
12. Kupin W, Venkat KK, Florence-Green D et al: Corticosteroid withdrawal with substitution of azathioprine in cyclosporine-treated primary cadaveric renal transplant recipients. Ibid: 2024-2026
13. Kahan BD, Flechner SM, Lorber MI et al: Complications of cyclosporine-prednisone immunosuppression in 402 renal allograft recipients exclusively followed at a single center for from one to five years. *Transplantation* 1987; 43: 197-204
14. Grino JM, Alsina J, Castelao AM et al: Low-dose cyclosporine, anti-lymphocyte globulin, and steroids in first cadaveric renal transplantation. *Transplant Proc* 1988; 20 (suppl 6): 18-20
15. Prieto C, Morales JM, Andres A et al: Three-year experience with cyclosporine and steroid double therapy in renal transplantation. Ibid: 21-22
16. Fries D, Hiesse C, Charpentier B et al: Optimal results in cadaveric renal transplantation with low-dose cyclosporine and steroids combined with prophylactic anti-lymphocyte globulin. Ibid: 23-25
17. Pallardo LM, Sanchez J, Garcia J et al: Low doses of cyclosporine, azathioprine, and prednisone in renal transplantation: immunosuppressive efficacy and reduced nephrotoxicity. Ibid: 26-27
18. Oppenheimer F, Andreu J, Ricart MJ et al: Benefit of selective treatment with steroids in renal transplantation in various immunosuppressive regimens. Ibid: 32-35
19. Opelz G, for the Collaborative Transplant Study: Collaborative Transplant Study data on efficacy of cyclosporine A in renal transplantation. Ibid: 41-44
20. Alsina J, Grino JM, Carrera M et al: Acute rejection in the cyclosporine era. Ibid: 56-62
21. Kahan BD: Renal transplantation. *Transplant Proc* 1988; 20 (suppl 3): 297-310
22. Dunn J, Vathsala A, Golden D et al: Impact of race on the outcome of renal transplantation under cyclosporine-prednisone. *Transplant Proc* 1989; 21: 3946-3948
23. Kahan BD: Cyclosporine. *N Engl J Med* 1989; 321: 1725-1738
24. Vathsala A, Weinberg RB, Schoenberg L et al: Lipid abnormalities in cyclosporine-prednisone-treated renal transplant recipients. *Transplantation* 1989; 48: 37-43
25. Johnson RWG, Mallick NP, Bakran RC et al: Cadaver renal transplantation without maintenance steroids. *Transplant Proc* 1989; 21: 1581-1582
26. Reisman L, Lieberman KV, Burrows L et al: Follow-up of cyclosporine-treated pediatric renal allograft recipients after cessation of prednisone. *Transplantation* 1990; 49: 76-80
27. Vathsala A, Chou TC, Kahan BD: Analysis of the interactions of immunosuppressive drugs with cyclosporine in inhibiting DNA proliferation. Ibid: 463-472
28. Borel JF: Comparative study of in vitro and in vivo drug effects on cell-mediated cytotoxicity. *Immunology* 1976; 31: 631-641

29. Calne RY, Rolles K, White DJG et al: Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* 1979; 2: 1033-1036

30. Stiller CR, for the Canadian Multicentre Transplant Study Group: A randomized clinical trial of cyclosporine in cadaveric renal transplantation. *N Engl J Med* 1983; 309: 809-815

31. European Multicentre Trial Group: Cyclosporin in cadaveric renal transplantation: one-year follow-up of a multicentre trial. *Lancet* 1983; 2: 986-989

32. Sinclair NR, for the Canadian Multicentre Transplant Study Group: A randomized clinical trial of cyclosporine in cadaveric renal transplantation. Analysis at three years. *N Engl J Med* 1986; 314: 1219-1225 (see correction, ibid: 1652)

33. Kahan BD: Individualization of cyclosporine therapy using pharmacokinetic and pharmacodynamic parameters. *Transplantation* 1985; 40: 457-476

34. Donatsch P, Abisch E, Homberger M et al: A radioimmunoassay to measure cyclosporin A in plasma and serum samples. *J Immunoassay* 1981; 2: 19-32

35. Keown PA, Stiller CR, Stawecki M et al: Pharmacokinetics of cyclosporine in solid organ transplantation. *Transplant Proc* 1986; 18 (suppl 5): 160-164

36. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31-41

37. Rolin HA, Hall PM, Wei R: Inaccuracy of estimated creatinine clearance for prediction of iothalamate glomerular filtration rate. *Am J Kidney Dis* 1984; 4: 48-54

38. Wilkinson L: *SYSTAT: the System for Statistics*, SYSTAT Inc, Evanston, Ill, 1988

39. Steinberg D, Colla P: *SURVIVAL: Survival Analysis — a Supplementary Module for SYSTAT*, SYSTAT Inc, Evanston, Ill, 1988

40. Lee ET: *Statistical Methods for Survival Data Analysis*, Lifetime Learn, Belmont, Calif, 1980: 122-364

41. Anderson S, Auquier A, Hauch WW et al: *Statistical Methods for Comparative Studies: Techniques for Bias Reduction*, Wiley, New York, 1980: 199-234

42. Zar JH: *Biostatistical Analysis*, 2nd ed, P-H, Englewood Cliffs, NJ, 1984: 97-149

43. Schwartz D, Flamant R, Lellouch J: *Clinical Trials*, Acad Pr, London, 1980: 77-86

44. Dunn J, Golden D, Van Buren CT et al: Causes of graft loss beyond two years in the cyclosporine era. *Transplantation* 1990; 49: 349-353

45. Rao KV, Kasiske BL, Odlund MD et al: Influence of cadaver donor age on posttransplant renal function and graft outcome. Ibid: 91-95

46. Stiller CR, Opelz G: Should cyclosporine be continued indefinitely? *Transplant Proc* 1991; 23: 36-40

47. Hayry P, von Willebrand E: The influence of the pattern of inflammation and administration of steroids on class II MHC antigen expression in renal transplants. *Transplantation* 1986; 42: 358-363

48. Hayry P, von Willebrand E, Ahonen J et al: Effects of cyclosporine, azathioprine, and steroids on the renal transplant, on the cytologic patterns of intragraft inflammation, and on concomitant rejection-associated changes in recipient blood. *Transplant Proc* 1988; 20 (suppl 2): 153-162

49. Iseki R, Mukai M, Iwata M: Regulation of T lymphocyte apoptosis. Signals for the antagonism between activation- and glucocorticoid-induced death. *J Immunol* 1991; 147: 4286-4292

50. Jones RJ, Vogelsang GB, Hess AD et al: Induction of graft-versus-host disease after autologous bone marrow transplantation. *Lancet* 1989; 1: 754-757

51. Beschorner WE, Ren H, Phillips J et al: Prevention of syngeneic graft-versus-host disease by recovery of thymic microenvironment after cyclosporine. *Transplantation* 1991; 52: 668-674

52. Jenkins MK, Schwartz RH, Pardoll DM: Effects of cyclosporine A on T cell development and clonal deletion. *Science* 1988; 241: 1655-1658

53. Jenkins MK, Chen C, Jung G et al: Inhibition of antigen-specific proliferation of type 1 murine T cell clones after stimulation with immobilized anti-CD3 monoclonal antibody. *J Immunol* 1990; 144: 16-22

54. Liu Y, Janeway CA: Interferon-γ plays a critical role in induced cell death of effector T cell: a possible third mechanism of self-tolerance. *J Exp Med* 1990; 172: 1735-1739

55. Ishigami T, Kim KM, Horiguchi Y et al: Anti-IgM antibody-induced cell death in a human B lymphoma cell line, B104, represents a novel programmed cell death. *J Immunol* 1992; 148: 360-368

56. Salaman J: Cyclosporine mono-drug therapy. *Transplant Proc* 1988; 20 (suppl 3): 117-120

57. Maiorca R, Cristinelli L, Brunori G et al: Prospective controlled trial of steroid withdrawal after six months in renal transplant patients treated with cyclosporine. Ibid: 121-125

58. Hillebrand G, Krumme D, Schleibner S et al: Is withdrawal of steroids hazardous to cadaveric renal transplants under treatment with cyclosporine? Ibid: 126-129

59. Lewis RM, Janney RP, Van Buren CT et al: A retrospective analysis of long-term renal allograft function associated with cyclosporine-prednisone immunosuppressive therapy. Ibid: 534-539

60. Schulak JA, Mayes JT, Moritz CE et al: A prospective randomized trial of prednisone versus no prednisone maintenance therapy in cyclosporine-treated and azathioprine-treated renal transplant patients. *Transplantation* 1990; 49: 327-332

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