

Effect of long-term steroid withdrawal in renal transplant recipients: a retrospective cohort study

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Abstract

Background. Steroids are largely effective for the immunosuppressive treatment in renal transplant patients, but cause severe side effects. Whether steroid withdrawal confers long-term beneficial effects remains unclear.

Methods. Data on 4481 cadaveric kidney transplant recipients were collected to estimate the impact of steroid withdrawal on kidney function and graft and patient survival using multivariate Cox regression models.

Results. A total of 923 patients (20.6%) had steroid treatment withdrawn. This was more common in recipients from younger donors and in older recipients, and in recipients with a first transplant, those who had pre-transplant or *de novo* diabetes mellitus and those with fewer episodes of acute rejection (AR) (22.4% vs. 29.2%, $P < 0.001$). Cox multivariate analysis stratifying by propensity scores showed that long-term steroid therapy was associated with a 70% increase in the risk of patient death. The repeated measures linear model showed that, although the abbreviated Modification of Diet in Renal Disease (aMDRD) values changed over time ($P = 0.002$), this was independent of steroid withdrawal ($P = 0.08$). In addition, of the 772 (17.2%) recipients who developed *de novo* diabetes mellitus, 204 (26.4%) ceased antidiabetic therapy, with more of these among those who ceased steroids (23% vs. 33.3%, $P = 0.003$). Blood pressure, cholesterol and triglyceride values were all significantly lower in the patients who ceased steroids.

Conclusions. Steroid withdrawal in selected patients had no negative effect over time on renal function and graft survival, and it was associated with reduced mortality.

Keywords: graft; patient survival; steroid withdrawal

Introduction

Steroids have proved to be very effective for immunosuppressive treatment in renal transplant patients, but long-

term therapy causes side effects leading to increased morbidity, mortality and economic costs [1]. Accordingly, it is of interest to reduce the dose of steroids, withdraw them early or even use a steroid-free immunosuppressant protocol in the modern transplant era in order to improve kidney transplant outcome [2].

In the era of cyclosporine (CsA), whether or not accompanied by azathioprine, steroids began to be withdrawn, with the results showing that early withdrawal, black race and renal function were all risk factors for acute rejection (AR) and long-term graft loss [3,4]. In light of these data, the European Best Practice Guidelines for Renal Transplantation recommended that steroid withdrawal is safe only in low-risk patients and that, after withdrawal, renal function should be monitored carefully because of the risk of progressive worsening [5].

The introduction of mycophenolate mofetil (MMF) reduced the number of episodes of AR, and steroid withdrawal in low-risk patients treated with CsA and MMF did not increase the incidence of AR, while renal function remained stable [6]. The association of MMF and tacrolimus (TAC) further lowered the incidence of AR and enabled earlier and safer withdrawal of steroids. As an example, a randomized study of steroid withdrawal 3 days after transplantation in patients treated with MMF, TAC and induction with daclizumab showed no significant differences in the incidence of AR and renal function at 1 year compared with the control group [7]. In selected patients [stable renal function, no AR and panel-reactive antibody (PRA) <50%] treated with TAC, MMF and steroids who were randomized to continue triple therapy or withdrawal of steroids beginning 3 months after transplantation, the incidence of AR was 6% in patients who ceased steroids and 3% in those who were maintained on steroids after 2 years of follow-up [8].

The aim of this retrospective cohort study was to analyse the effects of steroid withdrawal on renal function and graft and patient survival in deceased donor kidney transplantation performed in Spain since 1990.

Materials and methods

Study design and patient population

This retrospective cohort study was carried out in all recipients from 34 of the 38 adult kidney transplant centres in Spain. This population represents 96% of all adult recipients (≥ 18 years) who received a primary or repeat deceased donor transplant performed during the calendar years 1990, 1994, 1998 and 2002 and who survived at least 1 year, with a follow-up until 31 December 2005. The quality of the data set was verified by random examination of source documents at each of the participating transplant centres.

A total of 4842 recipients, mostly Caucasian, were analysed, of whom 361 were excluded as they had not received an initial steroid therapy ($n = 145$) or due to lack of follow-up data ($n = 131$). The primary study end point was to analyse the long-term effect of steroid withdrawal on kidney function and graft and patient survival.

Institutional review and patient protection

Medical record review was performed according to the Spanish law on clinical data confidentiality. This study was approved by the ethics committee of the hospital and was conducted according to the principles described in the Declaration of Helsinki.

Clinical variables

The variables analysed included the cause of donor death (trauma or stroke), age and gender of the donor and the recipient, body mass index (BMI), first or re-transplantation, time on dialysis, PRA at peak and at transplantation, human leucocyte antigen (HLA) mismatches, cold and re-warm ischaemia times, delayed graft function (DGF), AR (pre and post-steroid withdrawal), proteinuria, hepatitis C virus (HCV), diabetes mellitus pre- and post-transplantation, therapy with statins, immunosuppression (intention to treat), kidney function, and graft and patient survival.

Definition of variables

Delayed graft function was defined as the requirement for dialysis during the first week after transplantation, after ruling out accelerated or hyperacute rejection, vascular thrombosis and urinary tract obstruction. AR was defined by the need for treatment, with or without biopsy confirmation. Graft failure was defined as death or return to dialysis. The total number of HLA mismatches was calculated as the sum of the mismatches in the A, B and DR loci. New-onset diabetes after transplantation (NODAT) was defined as the need for treatment with insulin or oral antidiabetic agents after transplantation.

Immunosuppressive therapy

The patients in the 1990 and 1994 cohorts were treated with CsA and prednisone, with or without azathioprine. Most of the 1998 cohort was treated with CsA, MMF and prednisone, and the 2002 cohort was treated with TAC, MMF and prednisone. Induction therapy with polyclonal or monoclonal antibodies was received by 17.7% and 34% of the patients, respectively.

Renal function

Renal allograft function was calculated from the serum creatinine measurement, using the abbreviated Modification of Diet in Renal Disease (aMDRD) equation [9].

Statistical analysis

Descriptive results are expressed as the mean \pm standard deviation for continuous variables. Comparisons of continuous variables between study periods were made by the Mann–Whitney *U*-test. The chi-square test, or Pearson, and Fisher's exact test when appropriate, were used for intergroup comparisons of categorical variables. Kaplan–Meier survival curves were used to estimate graft and patient survival, and the log-rank test to compare survival curves. Univariate and multivariate Cox proportional hazards regression models were used to identify baseline risk fac-

tors for graft failure and patient death. The following variables were included in the model: recipient and donor age and gender, cause of donor death, DGF, AR, PRA ($\leq 15\%$ vs. $>15\%$), proteinuria (increase between 3 and 12 months), creatinine at 3 months and the creatinine delta (increase between 3 and 12 months), diabetes mellitus before transplantation, NODAT, re-transplant, therapy with statins, HCV-positive recipient, and mean times to transplantation and steroid withdrawal. Steroid withdrawal was introduced in the Cox regression model as a time-dependent variable. When steroid withdrawal was significant in the univariate Cox model, a multivariate Cox model was performed entering a propensity score as an independent variable. This score was defined as the conditional probability of steroids withdrawal during follow-up, based on the characteristic of the recipient [10]. The estimated propensity scores, categorized into quintiles, were used to stratify Cox regression analysis. A general linear model for repeated measures was used to assess the effect of renal function, estimated by aMDRD, on survival. *P*-values of <0.05 were considered to indicate statistical significance.

The SPSS program (version 15; Inc, Chicago, IL) was used as a database and for the descriptive statistical analysis.

Results

Table 1 shows the significant demographic and background characteristics of patients with or without steroid withdrawal. Steroids were withdrawn in 923 (20.6%) patients after a mean time of 3.7 ± 2.8 years (23.2% during the first year). Table 2 shows the immunosuppressive treatment and differences between the different cohorts. With effect from the introduction of MMF, and later TAC (1998 and 2002 cohorts), steroid suppression was earlier and more usual. No significant differences were found in cold ischaemia time, BMI, gender, PRA at the time of transplant or the historical peak value or in HLA mismatches. The incidence of AR after steroid withdrawal was 3%.

Graft survival

The Kaplan–Meier uncensored and death-censored graft survival curves were significantly greater in the patients who had steroids withdrawn. Mean graft survival was 13.6 vs. 12.6 years ($P < 0.001$) and 14.3 vs. 13.8 years ($P < 0.001$), respectively. The multivariate Cox proportional regression analysis showed that those patients who did not cease steroids had a greater risk for death-censored

Table 1. Significant demographic and background characteristics of the patients with and without steroid withdrawal

	Steroid withdrawal		<i>P</i>
	No	Yes	
Transplants (<i>n</i>)	3,558	923	
Donor age (years)	42.7 \pm 16.8	39.5 \pm 16.8	<0.001
Recipient age (years)	46.1 \pm 13.2	48.0 \pm 13.1	<0.001
WIT (min)	46.7 \pm 19.3	39.4 \pm 19.3	<0.001
AR (%)	29.2	22.4	<0.001
Donor death (% stroke)	51.4	44.2	<0.001
Re-transplant (%)	13.5	8.1	<0.001
Diabetes mellitus (%)	4.7	9.9	<0.001
New-onset diabetes mellitus (%)	15.5	23.1	<0.001
MWT (years)	3.4 \pm 3.8	2.9 \pm 3.8	<0.001

WIT, warm ischaemia time; AR, acute rejection; MWT, mean wait for transplantation.

Table 2. Immunosuppressive treatment in the different cohorts and data related with steroid withdrawal

	Year of transplantation			
	1990	1994	1998	2002
Transplants (<i>n</i>)	740	1040	1465	1236
CsA (%)	97.27	78.87	74.53	17.39
Az (%)	58.11	68.02	20.13	0.56
TAC (%)	0.13	0.77	12.08	66.66
Prednisone (%)	100	100	100	100
MMF (%)	0.13	0.58	62.59	79.77
ALA (%)	26.87	17.73	25.80	34.38
SRL (%)			2.38	3.31
Follow-up (years)	15	11	8	3
TPSW (%)	15	11	25.4	16.3
First year (%)	15.4	9.7	22	44.8
MTW (years)	6.1 ± 3.8	5.0 ± 2.6	3.2 ± 2.0	1.6 ± 0.8
ARSW (%)	5.4	3.9	0	3

CsA, cyclosporine; Az, azathioprine; TAC, tacrolimus; MMF, mycophenolate mofetil; ALA, anti-lymphocyte antibodies; SRL, sirolimus; TPSW, total percent of steroid withdrawal; MTW, mean time of steroid withdrawal; ARSW, acute rejection post-steroid withdrawal.

graft loss [relative risk (RR) 1.50, 95% confidence interval, 1.21–1.85; *P* < 0.001].

The multivariate Cox model of factors predicting the relative risk of uncensored graft loss by propensity scores showed that non-withdrawal of steroids represented an increased risk of graft loss of 36% (Table 3) after adjusting

Table 3. Multivariate Cox model (uncensored): factors predictive of the risk of graft loss stratified by propensity scores

	Beta	Standard error	RR (e ^{Beta})	95% CI	<i>P</i>
Recipient age ^a	0.45	0.09	1.58	1.32–1.89	<0.0001
HCV ^b	0.33	0.07	1.39	1.19–1.63	<0.0001
Re-transplant ^c	0.30	0.10	1.35	1.10–1.64	0.002
Donor age ^d	0.19	0.08	1.21	1.02–1.45	0.02
Acute rejection ^e	0.33	0.06	1.39	1.21–1.58	<0.0001
Statins at 1 year ^f	0.21	0.08	1.23	1.04–1.47	0.01
Serum creatinine at 3 months	0.53	0.06	1.69	1.49–1.93	<0.0001
Delta of serum creatinine	0.67	0.04	1.96	1.80–2.13	<0.0001
Proteinuria at 3 months	0.15	0.02	1.16	1.10–1.23	<0.0001
Increase in proteinuria from 3 to 12 months	0.22	0.02	1.24	1.17–1.31	<0.0001
Diabetes mellitus ^g					
No post-transplant diabetes	0.00		1		
Pre-transplant diabetes	0.62	0.15	1.86	1.37–2.51	<0.0001
Post-transplant diabetes	0.48	0.12	1.62	1.26–2.08	0.0001
No steroid withdrawal ^h	0.31	0.09	1.36	1.44–1.63	0.0006

Included in the model but not in the table was transplant year (*P* > 0.05). HCV, hepatitis C virus; DGF, delayed graft function; Delta of serum creatinine, difference between 12 and 3 months; CI, confidence interval.

^aRecipients <60 years.

^bFirst transplant.

^cHepatitis C virus negative.

^dDonor <60 years.

^eNo acute rejection.

^fStatin treatment.

^gNo pre-transplant diabetes mellitus.

^hSteroid withdrawal.

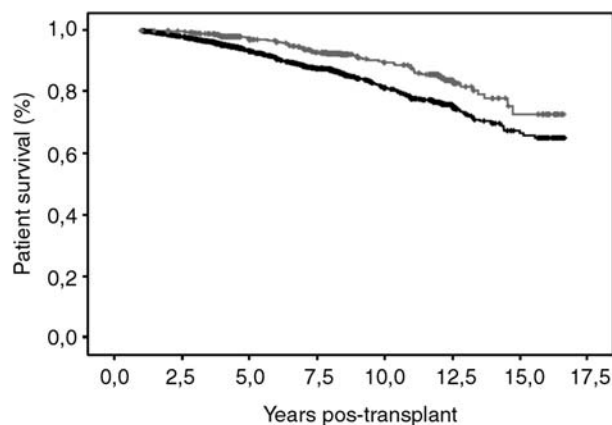


Fig. 1. Kaplan–Meier patient survival with and without steroid withdrawal (log-rank test, *P* < 0.001).

for other confounder variables, including transplant year. However, when the model was censored for patient death, the differences were not significant.

Patient survival

Kaplan–Meier patient survival (Figure 1) was significantly greater in the patients who ceased steroids (*P* < 0.001). Deaths occurred in 8.5% vs. 12.5% (*P* < 0.001), respectively. Non-withdrawal of steroids was associated with a higher risk for death (70%) in multivariate regression analysis (Table 4).

Special mention should be made of the analysis of the 1990 cohort after 15 years of follow-up. Of the 740 patients, 143 (19.3%) ceased steroids, with no differences between the two groups according to donor age, PRA, cold ischaemia time, gender, AR during the first year, HLA or

Table 4. Cox multivariate model: factors predictive of the risk of death stratified by propensity scores

	Beta	Standard error	RR (e ^{Beta})	95% CI	<i>P</i>
Recipient age ^a	1.17	0.09	3.23	2.68–3.90	<0.0001
HCV ^b	0.32	0.10	1.38	1.13–1.70	0.0017
DGF ^c	0.18	0.09	1.20	1.00–1.44	0.04
Serum creatinine at 3 months	0.21	0.09	1.23	1.02–1.48	0.026
Delta of serum creatinine	0.25	0.08	1.29	1.10–1.51	0.0014
Proteinuria at 3 months	0.12	0.60	1.13	1.01–1.27	0.034
Increase in proteinuria from 3 to 12 months	0.14	0.04	1.15	1.05–1.26	0.0001
Diabetes mellitus ^d					
No post-transplant diabetes	0.00		1		
Pre-transplant diabetes	0.68	0.19	1.97	1.35–2.87	0.0004
Post-transplant diabetes	0.45	0.16	1.58	1.15–2.16	0.0044
No steroid withdrawal ^e	0.53	0.12	1.70	1.33–2.18	<0.0001

Included in the model but not in the table was transplant year (*P* > 0.05). HCV, hepatitis C virus; DGF, delayed graft function; Delta of serum creatinine, difference between 12 and 3 months; CI, confidence interval.

^aRecipients <60 years.

^bHepatitis C virus negative.

^cNo DGF.

^dNo pre-transplant diabetes mellitus.

^eSteroid withdrawal.

cause of donor death. Differences were found, however, between those who did not and those who did cease steroid therapy in recipient age (42.1 ± 12.2 vs. 45.8 ± 11.7 year, $P = 0.001$), time on dialysis (3.7 ± 3.8 vs. 3.0 ± 3.0 years, $P = 0.04$), re-transplant (11.7% vs. 4.2%, $P = 0.008$), pre-transplant diabetes mellitus (1.2% vs. 9.5%, $P < 0.001$) and NODAT (11.2% vs. 23.8%, $P < 0.001$). Again, non-withdrawal of steroids was associated with a higher risk for uncensored (RR 1.65, 95% confidence interval, 1.21–2.25; $P = 0.001$) and death-censored graft survival (RR 1.48, 95% confidence interval, 1.03–2.13; $P = 0.03$) as well as patient death (RR 1.66, 95% confidence interval, 1.11–2.49; $P = 0.01$). The mean aMDRD at 1 year in the non-withdrawal and the withdrawal groups was similar (52.4 ± 18.7 and 49.2 ± 19.3 mL/min/1.73 m²; $P = 0.69$, respectively), remaining non-significant over time.

Renal function

The aMDRD was significantly greater at the time of withdrawal in the patients who ceased steroids (except in the 1990 cohort) and remained so during the follow-up ($P < 0.05$). By applying a general linear model for repeated means showed that aMDRD values changed over time ($P = 0.002$), but independently of steroid withdrawal ($P = 0.08$).

Cardiovascular risk factors

Pre-transplant diabetes mellitus was more prevalent in patients with steroid withdrawal (Table 1). A total of 772 (17.2%) patients developed NODAT. Of these, 204 (26.4%) stopped treatment with insulin or oral antidiabetic agents during the post-transplant period, and the highest percentage belonged to patients who discontinued steroids (23% vs. 33.3%, $P = 0.003$).

Total cholesterol values were significantly lower in the patients who ceased steroids from the first post-transplant year (220.7 ± 46.4 vs. 214.4 ± 44.5 mg/dL, $P = 0.001$) to the 10th year (211.7 ± 41.1 vs. 199.9 ± 34.1 mg/dL, $P < 0.001$). A similar situation was seen with the triglycerides from the first year (152.2 ± 74.0 vs. 138.7 ± 65.6 mg/dL, $P < 0.001$) to the 12th year (148.2 ± 81.8 vs. 118.8 ± 49.8 mg/dL, $P = 0.008$).

Finally, although the number of antihypertensive drugs was significantly higher in patients who did not cease steroids, both systolic and diastolic blood pressures were similar during long-term follow-up.

Discussion

This retrospective cohort study carried out in adult renal transplant units in Spain analysed the very long-term impact of steroid withdrawal on renal function and graft and patient survival. This is a hotly debated topic in the field of renal transplantation that has been analysed by many investigators [11,12], although mostly focused on the short- or medium-term risk–benefit ratio [8,13,14].

During the era of CsA, an early and rapid discontinuation of steroids was associated with a high incidence of AR

and worsening renal function [15]. However, in favour of early steroid withdrawal was the fact that certain side effects of steroids, once begun, progressed despite withdrawal. With this in mind, many studies of steroid withdrawal in this period focused mainly on analysing which group of patients could benefit from steroid suppression and with effect from when [2,3], limiting the implementation of this therapeutic strategy in routine clinical practice.

With the introduction of TAC and MMF, steroid withdrawal in selected patients did not significantly increase the risk of AR or influence graft or patient survival and kidney function. Consequently, withdrawal began to take place earlier and in more patients, as seen in this study [16,17].

In support of these arguments, a prospective, multi-centre study of 1110 renal transplant patients with no immunological risk and with good renal function who discontinued steroids after 6 months showed increases of graft ($81.9\% \pm 1.8\%$ vs. $75.3\% \pm 1.2\%$, $P = 0.0001$) and patient survival ($88.8\% \pm 1.5\%$ vs. $84.3\% \pm 1.0\%$; $P = 0.0016$), as well as a reduction in cardiovascular risk factors [18].

Although in our study steroid withdrawal was later, unscheduled and under variable criteria, the results are similar to previous reports. Of note was the higher mortality in the patients who did not cease steroids in all the multivariate models tested and in all the cohorts studied. We conducted an analysis of propensity for steroid withdrawal in order to avoid selection bias with the elimination of steroids based on clinical characteristics during follow-up. In addition, steroid withdrawal was entered in the Cox model as a time-dependent covariate. Thus, patients with no steroid withdrawal showed a higher relative risk for uncensored graft loss in the Cox regression analysis after adjusting for other confounding covariates, including propensity score. Nevertheless, this was not observed when death-censored graft analysis was assessed. A higher mortality in the patients who continued steroids may explain these differences.

The analysis of the 1990 cohort deserves special mention. This cohort of 740 patients with a follow-up of 15 years experienced significantly higher mortality in those who continued steroids, despite the fact that the other group (who did cease steroids) had a higher recipient age and greater proportion of diabetes mellitus. No differences were found in the selection variables most commonly used to withdraw steroids (good renal function and absence or lower incidence of AR).

Steroid withdrawal is a usual clinical practice in Spain, where selected patients only received 5 mg per day of prednisone. Although this dosage may confer a low risk for cardiovascular disease, it is possible that steroid suppression could optimize the cardiovascular profile by reducing risk factors for mortality such as blood pressure or insulin resistance, especially in predisposed individuals. In our study, elimination of steroids was associated with a better control of glucose metabolism, lipid profile and blood pressure compared with the recipients who continued steroids. Previous studies have demonstrated similar findings [18–20].

Regarding renal function, steroid withdrawal did not modify long-term graft function. Although renal function,

evaluated by aMDRD, showed changes over time, this effect was independent of steroid withdrawal. This was observed in all the cohorts analysed and confirms that this therapeutic strategy may preserve renal function in the long term, even in the presence of other risk factors.

In conclusion, this large retrospective study demonstrates that, with effect from the era of CsA, steroid withdrawal in renal transplant recipients does not have a negative impact on graft function or survival, and is associated, in the long term, with a significant reduction in mortality.

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