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Early statin use is an independent predictor of long-term graft survival

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Abstract

Background. Statin use in renal transplantation has been associated with a lower risk of patient death but not with an improvement of graft functional survival. The aim of this study is to evaluate the effect of statin use in graft survival, death-censored graft survival and patient survival using the data recorded on the Spanish Late Allograft Dysfunction Study Group.

Patients and methods. Patients receiving a renal allograft in Spain in 1990, 1994, 1998 and 2002 were considered. Since the mean follow-up in the 2002 cohort was 3 years, statin use was analysed considering its introduction during the first year or during the initial 2 years after transplantation. Univariate and multivariate Cox regression analyses with a propensity score for statin use were employed to analyse graft survival, death-censored graft survival and patient survival.

Results. In the 4682 evaluated patients, the early statin use after transplantation significantly increased from 1990 to 2002 (12.7%, 27.9%, 47.7% and 53.0%, $P < 0.001$). Statin use during the first year was not associated with graft or patient survival. Statin use during the initial 2 years was associated with a lower risk of graft failure (relative risk [RR] = 0.741 and 95% confidence interval [CI] = 0.635–0.866, $P < 0.001$) and patient death (RR = 0.806 and 95% CI = 0.656–0.989, $P = 0.039$). Death-censored graft survival was not associated with statin use during the initial 2 years.

Conclusion. The early introduction of statin treatment after transplantation is associated with a significant decrease in late graft failure due to a risk reduction in patient death.

Keywords: graft failure; renal transplantation; statins

Introduction

Statins were introduced in clinical practice more than two decades ago to treat dyslipidaemia, especially hypercholesterolaemia with increased low-density lipoprotein (LDL)-cholesterol levels. Its efficacy in the general population with preserved renal function for primary and secondary prevention of cardiovascular events has been well established in different clinical trials and further confirmed in different meta-analyses [1,2]. For this reason, statins have been widely introduced in clinical practice to treat hypercholesterolaemia in patients with different co-morbidities, for example patients with chronic renal failure, despite its utility not having been evaluated in clinical trials in these specific groups of patients.

Patients with chronic kidney disease as well as patients with end-stage renal disease either treated with dialysis or receiving a kidney transplant have an increased cardiovascular risk that accounts for more than 50% of the overall mortality [3,4]. In patients with end-stage renal disease on haemodialysis, prospective randomized clinical trials testing the potential benefits of statin treatment have led to contradictory results [5–7]. In the setting of renal transplantation, only one large prospective, randomized, placebo-controlled study has been conducted to evaluate fluvastatin treatment: the ALERT trial [8]. In this study, the primary efficacy variable was defined as cardiac death, non-fatal myocardial infarction and/or a coronary intervention procedure. Despite a significant decrease in the number of cardiac deaths and non-fatal myocardial infarctions, the 13% reduction in the primary efficacy end point did not reach statistical significance. Nevertheless, the extension of the ALERT study for two additional years showed a significant reduction in major adverse cardiac events, supporting that the benefits of fluvastatin in renal transplant recipients are comparable to other patient groups [9].

On the other hand, the post hoc analysis of the ALERT study failed to reveal a beneficial effect of fluvastatin on renal outcome. However, in the general population, there is evidence linking dyslipidaemia and its treatment with reduced renal function decline [10–12]. It is important to remark that in the ALERT trial, patients were randomized at a mean follow-up time of 4 years, and it could be argued that at this time renal lesions may be too advanced. In renal transplantation, clinical trials with small sample size and short periods of follow-up have suggested that statins may

reduce acute rejection risk [13] or renal transplant vasculopathy [14] when they are introduced just after transplantation. However, information about the long-term evolution of renal function or death-censored graft survival is lacking. Thus, the potential benefit of statins on graft survival will not be evaluated until large, prospective, multicentre, placebo-controlled studies are conducted from the time of transplantation. Since such studies are difficult to perform, renal transplant registries may provide valuable information on the potential beneficial effect of statins on graft outcome.

In the present study, we evaluate the effect of statin use in patient survival, graft survival and death-censored graft survival using the data recorded by the Spanish Late Allograft Dysfunction Study Group.

Materials and methods

Study design

For the present study, patients receiving a renal allograft in Spain in 1990, 1994, 1998 and 2002 were considered. Only adult transplant centres were invited to participate, and only adult patients (≥18 years) receiving a single kidney transplant that was functioning at the end of the first year of follow-up were considered. Patients receiving multi-organic or double transplants were excluded. Last follow-up was on 31 December 2005.

Clinical variables

The following variables were evaluated in each patient at the time of surgery: source of the organ (living or deceased donor), donation before or after cardiac death, cause of donor death (trauma, stroke or others), age and gender of the donor and the recipient, height and weight of the recipient, presence of hepatitis B surface antigen and hepatitis C virus antibodies in the donor and the recipient, aetiology of end-stage renal disease, time on dialysis, last panel reactive antibodies (PRA), number of human leukocyte antigen (HLA) mismatches and cold ischaemia and re-anastomosis times.

After surgery, the presence of delayed graft function and acute rejection were recorded. Immunosuppressive treatment at 1 year was described on an intention-to-treat basis and classified in four major groups: (i) cyclosporine-based not associated with mycophenolate mofetil, (ii) cyclosporine-based associated with mycophenolate mofetil, (iii) tacrolimus-based treatment, and (iv) other treatments.

At 3 months and yearly thereafter, serum creatinine, 24 h proteinuria, serum fasting glucose and serum cholesterol and triglycerides were recorded. At the same time periods, treatment with statins was recorded as a dichotomous variable. Patients treated with statins either at 3 months or 1 year were classified as statin users during the first year. Similarly, patients receiving statins either at 3 months, 1 year or 2 years were classified as statin users during the first 2 years. Additionally, treatment with antihypertensive drugs including angiotensin-converting enzymes inhibitors (ACEi) or angiotensin II receptor blockers (ARB) were also recorded.

Definition of variables

Delayed graft function was defined as haemodialysis requirements during the first week after surgery, once accelerated or once hyperacute rejection, vascular complications and urinary tract obstruction were ruled out. The diagnosis of acute rejection was defined at each centre based on clinical and/or histological data.

The ethical committee of the Hospital Universitari de Bellvitge approved this study. Medical records review was performed according to Spanish law with reference to clinical data confidentiality protection. A blinded code was assigned to each participating hospital in order to take into consideration the centre effect.

Statistics

Descriptive results are expressed as frequencies and percentages for categorical variables and mean ± standard deviation for normally distributed continuous variables. These variables were compared in statin users and non-users by means of chi-square test for categorical data, Wilcoxon *T*-test for ordinal or not normally distributed continuous data and Students' *T*-test for continuous normally distributed data.

Kaplan–Meier analysis was used to estimate overall graft survival, death-censored graft survival and patient survival. Log rank test was employed to compare differences between groups.

Cox regression analysis adjusting for year of transplantation was employed to analyse the association between statin use and graft survival, death-censored graft survival and patient survival. Multivariate backward Cox regression analysis was performed to further evaluate the independent association of statin use and survival. In order to take into consideration confounding by indication, a propensity score of statin use was calculated and introduced in all multivariate analysis. The propensity score was calculated by a logistic regression considering all variables associated with statin use. This analysis provides a probability score of being treated with statins for each patient, and this score (ranging from 0 to 1) was divided in quartiles and considered in the multivariate Cox regression analysis.

Statin use was analysed considering two different settings in order to take into account the timing of the introduction of statin treatment: introduction of statins during the first year after transplantation and introduction of statins during the initial 2 years after transplantation. Since the mean follow-up in the 2002 cohort was 3 years, no attempts were made to evaluate introduction of statins after 3 years or later.

For all analysis, a two-sided P-value <0.05 was considered significant.

Results

Patients

A total of 4842 patients were included in the Spanish Late Allograft Dysfunction Study Group, but information about statin use was only available in 4682 patients (96.6%). The number of patients in the 1990, 1994, 1998 and 2002 cohorts were 809, 1083, 1507 and 1283, respectively.

In the 1990 and 1994 cohorts, statins were used marginally during the initial years after transplantation, while in the 1998 and 2002 cohorts, a significant proportion of patients were treated with statins during the initial years after transplantation. However, since the follow-up period was longer in the 1990 and 1994 cohorts, at the end of follow-up the proportion of patients receiving statins was similar in the different cohorts (Figure 1). Demographic characteristics of patients and clinical data after transplan-

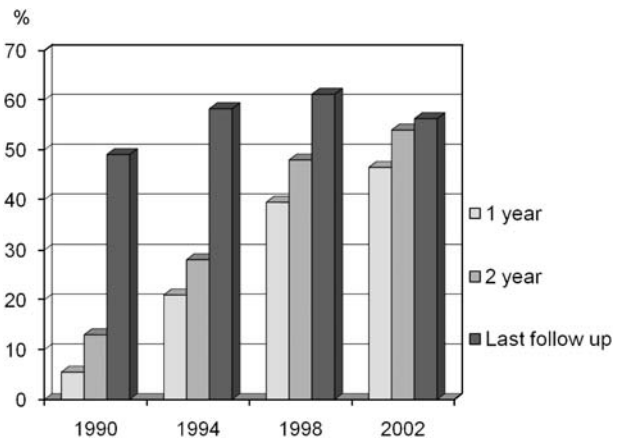

Fig. 1. Percentage of patients treated with statins during the first and second years and at the end of follow-up.

Table 1. Patient characteristics according to statin use at 2 years

Variable	No statin use	Statin use	*P*-value
N	2879	1803	
Donor age (years)	40.1 ± 16.9	44.8 ± 16.5	< 0.001
Donor gender (% male)	65.5	63.4	ns
Patient age (years)	44.8 ± 13.5	49.2 ± 12.2	< 0.001
Patient gender (% male)	64.6	60.7	< 0.001
Pre-transplant diabetes (%)	4.6	7.3	< 0.001
Hepatitis C virus (% positive)	17.9	8.1	< 0.001
Weight at transplant (kg)	65.5 ± 12.2	67.8 ± 12.3	< 0.001
HLA DR mm (0/1/2)	36.8 / 54.5 / 8.7	30.5 / 60.0 / 9.4	
Baseline immunosupression (%)			
CsA without MMF	55.7	32.6	
CsA with MMF	17.2	32.7	
Tacrolimus	18.9	24.0	
Other	8.2	10.7	< 0.001
Delayed graft function (%)	30.0	31.7	ns
Acute rejection (%)	31.3	23.2	< 0.001
Diabetes at 1 year (%)	4.1%	7.8%	< 0.001
Creatinine 1 year (mg%)	1.6 ± 0.7	1.6 ± 0.6	ns
Proteinuria (g/day)	0.3 ± 0.8	0.4 ± 0.9	ns
Cholesterol 1 year (mg%)	212 ± 43	230 ± 49	< 0.001
Triglycerides 1 year (mg%)	140 ± 64	164 ± 81	< 0.001

HLA DR mm, number of mismatches in DR loci; CsA, cylosporine A; MMF, mycophenolate mofetil.

tation according to statin use at 2 years are summarized in Table 1.

Survival and statin use during the first year after transplant

During the first year of follow-up, a total of 1440 patients (30.7%) were treated with statins. Graft survival was 50.2% for patients not receiving statins and 55.6% for statin users (P<0.001). However, Cox regression analysis adjusting for the year of transplant did not confirm this association (relative risk [RR] for statin users 0.901, 95% confidence interval [CI] 0.757–1.064; P = 0.210).

Death-censored graft survival was 62.6% for patients not receiving statins and 64.3% for statin users (P = 0.005). Once again, Cox regression analysis adjusting for the year of transplant showed that there was no association between statin use and death-censored graft survival (RR 1.909, 95% CI 0.741–1.112; P = 0.349).

Finally, patient survival was 65.4% for patients not receiving statins and 78.4% for statin users (P = 0.014), but once more, Cox regression analysis adjusting for the year of transplant showed that there was no association between statin use during the first year and patient survival (RR 0.869, 95% CI 0.689–1.087; P = 0.226).

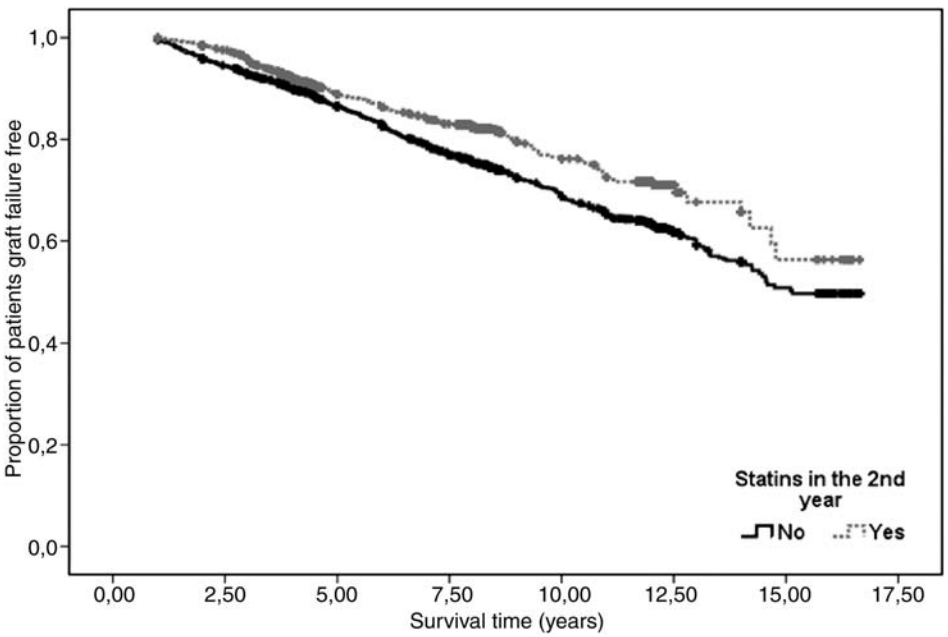

Fig. 2. Graft survival according to statin treatment during the initial 2 years after transplantation (P < 0.001, log rank test).

Table 2. Multivariate Cox regression analysis of graft survival with a propensity score for statin use at 2 years adjusted for the year of transplant

Variable	Relative risk	95% confidence interval	*P*-value
Donor age > 60 years	1.396	1.159–1.681	< 0.001
Patient age > 60 years	1.686	1.400–2.031	< 0.001
Re-transplant	1.441	1.203–1.726	< 0.001
Pre-transplant diabetes	1.912	1.424–2.571	< 0.001
Acute rejection	1.226	1.059–1.418	0.006
3 months creatinine (mg%)	1.857	1.706–2.022	< 0.001
Delta creatinine 3 m-1 y	2.084	1.932–2.247	< 0.001
3 months proteinuria (g/day)	1.218	1.148–1.292	< 0.001
Delta proteinuria 3 m-1 y	1.256	1.191–1.333	< 0.001
3 months triglycerides (mg%)	1.002	1.001–1.003	< 0.001
Statin use at 2 years	0.741	0.635–0.866	< 0.001

Survival and statin use during the initial 2 years after transplant

During the initial 2 years after transplantation, 1803 patients (38.5%) received treatment with statins, and graft survival was 55.6% for patients treated with statins and 50.2% for patients not receiving statins, $P < 0.001$ (Figure 2). Cox regression analysis adjusting for the year of transplantation confirmed a lower graft survival for patients not receiving statins (RR 0.837, 95% CI 0.720–0.974; $P = 0.022$). Multivariate Cox regression analysis with a propensity score for statin use confirmed that statin use during the initial 2 years after transplantation is an independent predictor of graft survival (Table 2).

Death-censored graft survival was 65.1% for patients treated with statins and 62.5% for patients not receiving statins, $P = 0.001$. Cox regression analysis adjusting for the year of transplantation showed that there was no association between death-censored graft survival and statin use (RR 0.869, 95% CI 0.724–1.042; $P = 0.125$).

Patient survival was 74.6% for patients treated with statins and 64.7% for patients not receiving statins during the initial 2 years, $P = 0.003$ (Figure 3). Cox regression analysis adjusting for the year of transplantation showed a trend for higher graft survival for patients receiving statins (RR 0.820, 95% confidence interval 0.671–1.010; $P = 0.059$). Multivariate Cox regression analysis with a propensity score for statin use showed that statin treatment during the initial 2 years after transplantation was an independent predictor of patient death (Table 3).

Discussion

In this retrospective observational study evaluating the potential benefits of early introduction of statins after transplantation, we observed that statin treatment during the initial 2 years is associated with a longer renal allograft survival, but we failed to detect a significant modification on death-censored graft survival. Moreover, despite the

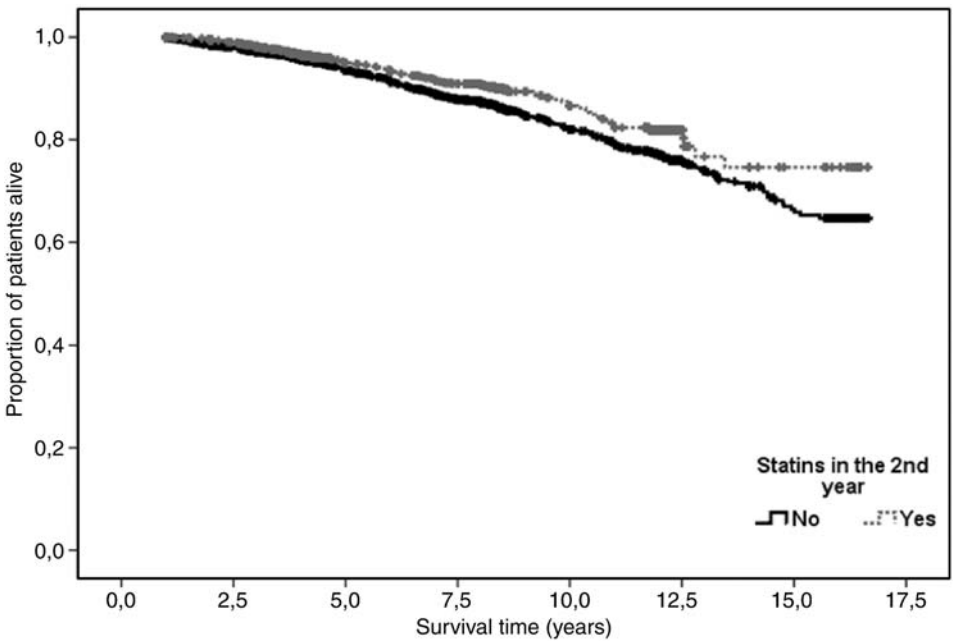

Fig. 3. Patient survival according to statin treatment during the initial 2 years after transplantation ($P = 0.003$, log rank test).

Table 3. Multivariate Cox regression analysis of patient survival with a propensity score for statin use at 2 years adjusted for the year of transplant

Variable	Relative risk	95% confidence interval	*P*-value
Patient age >60 years	2.514	2.040–3.097	< 0.001
Hepatitis C virus positive	1.921	1.415–2.609	< 0.001
3 months creatinine (mg%)	1.545	1.365–1.749	< 0.001
Delta creatinine 3 m-1 y	1.391	1.207–1.604	< 0.001
Delta proteinuria 3 m-1 y	1.154	1.052–1.266	0.002
Statin use at 2 years	0.806	0.656–0.989	0.039

Delta creatinine between 3 months and 1 year (3 m-1y) was calculated as the difference between 1 year and 2 months serum creatinine.

univariate analysis showing that the improvement of patient survival was on the verge of significance, multivariate analysis confirmed a 20% risk reduction in death in patients receiving statins. Thus, our results showed that the benefit of statins on graft outcome is mainly due to an improvement of patient survival, but we failed to detect a beneficial effect on kidney functional survival. This result is in agreement with the ALERT study, a prospective randomized trial of statin use in renal transplantation [7,8]. In the same way, the analysis of the Austrian registry showed that statin use was associated with a 36% reduction in all-cause mortality, while risk reduction in death-censored graft survival was in the limit of significance (76% for statin users and 70% for non-users; $P = 0.055$), once more pointing out that the benefit of statins in renal transplant population is mainly due to an improvement in patient survival [15]. Our cohort of patients was rather different from the Austrian cohort since in the Austrian study all patients transplanted between 1990 and 2003 were considered, while we only evaluated patients transplanted in 1990, 1994, 1998 and 2002. It is important to take into consideration this difference since it has determined a different statistical approach. The Austrian cohort was analysed considering statin use as a time-dependent variable which may be the most appropriate approach to evaluate the retrospective use of a treatment that is introduced at different time points of follow-up. We were not able to deal with statins as a time-dependent variable since follow-up in the 2002 cohort was too short.

Despite the above-mentioned limitation, we explored whether statin introduction during the first year or the two initial years implied a different outcome since it has been claimed that the maximal benefit may be obtained when statins are introduced as early as possible. In our study, we failed to observe a significant reduction in patient or graft survival when the impact of statin introduction during the first year after transplantation was analysed. In this evaluation, the number of patients using statins was rather low in the cohorts of patients transplanted in 1990 and 1994, while time of follow-up was only 2 years in patients transplanted in 2002. Thus, it may be argued that these epidemiological characteristics of our cohort of patients limited the possibility to detect a risk reduction in this very early intervention. However, the analysis of introduction of statins during the initial 2 years after transplantation yielded positive results. In this second analysis, the number of patients using statins in the 1990 and 1994 cohorts was twice that in the previous analysis, and it has allowed us to increase our statistical power to detect the risk reduction associated with statin use.

On the other hand, between 1990 and 2002, demographic characteristics of donor and recipients as well as immunosuppression have significantly changed. In the 1998 and 2002 cohorts, older kidney donors were transplanted into older transplant recipients, and the introduction of mycophenolate mofetil and tacrolimus yielded a lower acute rejection rate. Multivariate analysis showed that the association between statins and survival was independent of these major determinants of graft and patient survival.

One important limitation of retrospective studies about the impact of an intervention on outcome is confounding by indication. In order to overcome this potential bias, it has been proposed to use propensity scores to balance baseline covariates between exposure groups [16]. Of course, this approach does not take into consideration unmeasured characteristics or confounders. We have done Cox multivariate regression analysis with and without the propensity scores, and results were very similar with minimal modifications in the risks estimates (data not shown). Despite it being proposed that propensity scores are especially useful to analyse populations with a low number of events or a large number of confounders [16], we prefer to show our results using propensity scores since there were important differences in the population receiving and not receiving statins.

We have failed to show a reduction in death-censored graft failure in statin-treated patients. This benefit has been demonstrated in the general population [10–12], but it has not been confirmed in renal transplant patients [8]. In our study, intervention with statins was done during the first or second year after transplantation, and the number of patients, as well as the number of events, were sufficiently large to detect a significant benefit. However, there was a minimal difference in death-censored graft survival (65.1% for statin users at 2 years and 62.5% for non-users). Moreover, since we did not find any interaction between statin use and year of transplant, it would not be expected a significant benefit in any cohort. Thus, our results agree with previous studies failing to demonstrate that statin use is associated with a risk reduction in graft functional deterioration. However, our results do not deny the possibility that statin use may be beneficial in high-risk patients, for example, patients with significant proteinuria.

In summary, we showed in a large cohort of patients transplanted in Spain between 1990 and 2002 that the early introduction of statin treatment is associated with a significant decrease in late graft failure due to patient death.

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