Addition of Sirolimus to Cyclosporine Delays the Recovery from Delayed Graft Function but Does not Affect 1-Year Graft Function

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Abstract. Delayed graft function (DGF) has long been identified as one of the main correlates of poor graft survival in cadaveric renal transplantation, but the factors that affect its onset and duration are not fully elucidated. The impact of two immunosuppressive protocols on the incidence and length of DGF among kidney transplant recipients of a suboptimal organ was evaluated. Patients were randomly treated with corticosteroids (CS); low-dose cyclosporine (CsA) and sirolimus (SRL; group 1; $n = 42$); or CS, full-dose CsA, and mycophenolate mofetil (group 2; $n = 48$). All recipients received immunoprophylaxis with basiliximab. After 3 mo, group 1 discontinued CsA and continued with SRL, whereas group 2 continued the same treatment. The incidence of DGF was similar in the two groups (group 1 = 52.4%; group 2 = 58.3%), whereas its duration was significantly higher in the group 1 (19.0 ± 6.0 *versus* 10.3 ± 3.2 d; $P = 0.001$). Both groups showed 100% actuarial graft and patient survival at 1-yr. Among DGF patients, serum creatinine (sCr) at discharge was significantly worse in group 1 (sCr, 3.0 ± 1.0 *versus* 1.5 ± 0.2 mg/dl; calculated creatinine clearance, 31.2 ± 9.3 *versus* 61.1 ± 10 ml/min; $P = 0.001$). During the first year, the former group displayed a significant improvement of graft function, such that at 1-yr, no difference could be measured between groups (sCr, 1.8 ± 0.5 *versus* 1.7 ± 0.4 mg/dl; calculated creatinine clearance, 51.5 ± 10.2 *versus* 53.3 ± 9.4 ml/min). In conclusion, in *de novo* renal transplanted patients, the administration of SRL, in combination with low-dose CsA, is associated with a delayed recovery from DGF but does not worsen 1-yr graft function.

Delayed graft function (DGF) has long been identified as one of the main correlates of poor graft survival in cadaveric renal transplantation (1); however, its strength as an independent variable has been questioned. Previous studies had conflicting results on the importance of DGF in the absence of acute rejection (AR), with some groups finding no effect (2) and other groups finding a DGF effect independent from early AR (3,4). In addition, Giral-Classe *et al.* (5) reported that DGF strongly decreases long-term survival of first cadaveric transplanted kidneys but only when lasting more than 6 d. The incidence of this complication has recently increased, possibly because of a larger use of marginal donor organs, which display a low renal reserve and a greater susceptibility to ischemia-reperfusion injury (4), and the adoption of higher concentrations of calcineurin inhibitors (CNI) to avoid early allograft rejection (6).

The introduction of induction therapy with the chimeric (c-) anti–IL-2 receptor mAb basiliximab offers an adjunct to potentiate the immunosuppression provided by full therapeutic doses of cyclosporine (CsA) (7). However, there is no evidence that c-IL-2R mAb allows nephrotoxic calcineurin antagonists dose sparing, a limitation that may relate to its relatively restricted effect on IL-2–mediated events, without altering cell triggering via the redundant network of other lymphocyte-activating cytokines, such as IL-7 and IL-15 (8). In contrast, sirolimus (SRL) is a macrocyclin lactone with a novel mechanism of immunosuppressive action (9), which is complementary to both calcineurin antagonists and IL-2 receptor mAb (10). Its high degree of synergy with CsA would not only more efficiently prevent rejection but also allow minimization of CsA-induced toxicity. However, the well-established *in vitro* antiproliferative effect of SRL (11) and its ability to prolong acute renal failure in an experimental model of acute ischemic tubular injury (12) suggest a potential deleterious effect of this drug on the recovery from acute tubular necrosis (ATN) underlying DGF.

In the present study, we evaluated the impact of SRL in

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combination with low-dose CsA on the incidence and length of recovery of DGF on suboptimal kidneys, as compared with standard dose CsA plus mycophenolate mofetil (MMF). As a secondary aim, 1-yr graft function was evaluated to estimate indirectly the impact of the two immunosuppressive regimens on long-term graft outcome, taking graft function at 1 yr as a surrogate marker of late graft outcome.

Materials and Methods

Study Design

Starting from January 2000, transplant recipients of a "suboptimal" kidney (see below) were randomly assigned either to a SRL+low-dose CsA (early withdrawal)+corticosteroids (CS)-based immunosuppressive regimen (group 1; $n = 42$) or to CsA+MMF+CS (group 2; $n = 48$), with the aim to evaluate whether suboptimal organs would benefit from a CsA-sparing regimen in the early posttransplantation period and/or in the long term. The protocol provided that both kidneys of a given donor were assigned to the same immunosuppressive regimen, according to the sequence of randomization.

As a part of the above clinical trial, the primary objective of the present study was to explore the relationship of immunosuppressive regimens to the incidence and length of DGF. In addition, the impact of the two immunosuppressive regimens on long-term graft function of patients who experience DGF was assessed. For the latter analysis, serum creatinine (sCr) and calculated creatinine clearance at 12 mo were determined. The study was approved by the local Ethical Committee, and all patients gave their informed consent.

Donors

All donors were white; in all but eight, brain stroke was the cause of death. They were >55 yr old and/or had a long-standing history of hypertension; therefore, they were defined, according to the policy of our center, as potential "suboptimal" donors. The final diagnosis, however, was based on the histologic examination of pretransplantation biopsy of each donor kidney. At the time of donation request, information on the donor's medical condition and particularly on donor hypertension and duration of disease was obtained from medical records and next of kin. Arterial hypertension was diagnosed when the patient had been taking antihypertensive therapy for >5 yr and when concentric left ventricular hypertrophy was revealed by bidimensional echocardiography during donor screening examination (13).

Pretransplantation Biopsy

Renal specimens were obtained by wedge biopsy performed after the perfusion (time 0 biopsy), fixed by 4% formaldehyde or Bouin, and then used for histologic staining (hematoxylin-eosin, periodic acid-Schiff, silver methenamine, and Masson's trichrome). The histologic lesions of the four compartments of renal tissue (glomeruli, tubules, interstitium, and vessels) were scored by light microscopy by a pathologist who was blinded to the clinical history of the donor. The severity of chronic lesions was evaluated semiquantitatively using in part the criteria suggested by the '97 Banff classification on chronic/sclerotic allograft (14), as illustrated in Table 1. Kidneys with a total score ≥4 were classified as suboptimal.

Recipients

Cadaveric kidneys were allocated according to four parameters (blood group, HLA histocompatibility, time on dialysis, and presence of high-titer panel reactive antibodies). Moreover, organs from suboptimal donors were assigned to recipients >45 yr old.

For excluding patients who were dialyzed for reasons other than impaired graft function, DGF was diagnosed when sCr level increased or remained unchanged immediately after surgery during three consecutive days. All patients with DGF underwent routine graft biopsy after the first posttransplantation week (and at weekly intervals thereafter); when AR was diagnosed, the graft was categorized as primary function. In fact, no such case could be observed in the population studied.

Immunosuppressive Regimens

All patients were given CS (500 mg of methylprednisolone intraoperatively, then 250 mg of prednisone daily, tapered to 25 mg by day 8 and to 5 mg by month 2) and basiliximab in two divided doses of 20 mg each on day 0 and day 4 after transplantation. Patients of group 1 were treated with SRL (15 mg as loading dose, then 5 mg/d, with dosage adjusted to maintain whole-blood trough levels of 6 to 10 ng/ml), and CsA (4 to 7 mg/kg per d, resulting in whole-blood C2 levels between 600 and 800 ng/ml). In patients who experienced DGF, CsA dose was reduced to 3 to 5 mg/kg per d, with target C2 levels between 400 and 600 ng/ml). Group 2 patients were treated with CsA (10 mg/kg per d, target C2 levels between 1200 and 1400 ng/ml, reduced to 800 to 1000 in case of DGF) and MMF (2 g/d), without SRL. In both groups, immunosuppressive drugs were administered orally starting from 36 to 48 h after engraftment.

Table 1. Histologic grading of the renal biopsy score[a]

Grade	Score	Glomerular Sclerosis (%)	Tubular Atrophy (%)	Interstitial Fibrosis (%)	Vascular Damage	
					Vascular Fibrous Intimal Thickening (% Diameter Lumen Reduction)	Arteriolar Hyaline Thickening (% Diameter Lumen Reduction)
Absence	0	0	0	0	0	0
Mild	1	1–10	1–10	1–10	<25	<25
Moderate	2	11–20	11–20	11–20	26–50	26–50
Severe	3	21–30	21–30	21–30	>50	>50

[a] The degree of chronic lesions in each compartment of renal tissue (glomeruli, tubules, interstitium, and vessels) was scored semiquantitatively (0 to 3). Vascular damage was evaluated separately for arteries and arterioles, and the final score of vascular compartment was represented by the highest score of either arteries or arterioles. The global histologic score of each biopsy specimen resulted from the sum of individual scores achieved in each of the four compartments considered (maximal global histological score, 12).

At the end of month 3, group 1 patients withdrew CsA and continued SRL (trough levels 10 to 15 ng/ml). Group 2 patients progressively tapered CsA dosage, which was adjusted to maintain whole-blood C2 levels of 700 to 900 ng/ml by the end of month 6.

Kidney Function

Kidney graft function was evaluated by sCr and creatinine clearance (Nankivell formula) at discharge, 3 mo, and at 1 yr posttransplantation (15).

Statistical Analyses

The results of the quantitative variables were expressed as mean ± SD, and those of the qualitative variables were expressed as proportions. The Mann-Whitney and χ^2 tests were used for testing the differences between the quantitative and qualitative variables, respectively. The relationship between nonparametric variables was tested by Spearman rank correlation.

Actuarial graft survival was calculated from the date of renal transplantation to graft failure or patient death. Survival curves were generated using the Kaplan-Meier method and compared using the long-rank (Mantel-Cox) test.

All tests were two-tailed. $P < 0.05$ was considered statistically significant. The Statview software package (5.0 version; SAS Inc., Cary, NC) was used for all analyses.

Results

Table 2 shows the demographic data of the whole group of donors and recipients. The patients in the two groups did not significantly differ for either clinical and histologic features of donors or cold ischemia time or number of HLA mismatches (Table 2). At 1 yr posttransplantation, we were unable to find any difference between the two immunosuppressive regimens, both in terms of actuarial graft and patient survival (100%) and in terms of kidney graft function (sCr, 1.6 ± 0.5 *versus* 1.7 ± 0.7 mg/dl; creatinine clearance, 61.5 ± 11.2 *versus* 60.3 ± 9.2 ml/min; group 1 *versus* group 2).

Also in the early posttransplantation period, the two groups of patients showed a similar behavior. Specifically, DGF occurred at a similar rate in the two groups of patients: 52.4% in patients who were treated with low-dose CsA+SRL+CS and 58.3% among those who were treated with CsA+MMF+CS (Table 2). In contrast, the duration of DGF was significantly different between the two groups of patients (Figure 1). Of note, the duration of DGF failed to correlate either with the mean daily dose or with the cumulative dose or the mean trough levels of the immunosuppressive drugs used (not shown).

Baseline biopsy examination of patients who experienced DGF showed a mild to moderate degree of renal damage in all of the compartments examined (Table 3). In particular, all organs displayed the signs of acute tubular injury, compatible with the diagnosis of ATN, with a low degree of tubular atrophy, defining chronic tubular damage.

Graft biopsies performed at weekly intervals during DGF revealed the presence of acute tubulopathy, without any evidence of AR. It is interesting that an initial proliferative activity of tubular cells could be observed already at 1 wk from engraftment but only in graft biopsies from group 2 patients.

Finally, both immunosuppressive regimens were associated with a low AR risk (Table 2). Of note, the rate of AR did not significantly increase in the patients who displayed DGF.

Graft Outcome of DGF Patients

Kidney graft function at discharge (28 ± 4 d posttransplantation for group 1 patients and 17 ± 3 d posttransplantation for group 2) and at the time of CsA discontinuation, 3 mo after engraftment, was significantly worse in group 1 patients (Figure 2). One year after transplantation, however, graft function failed to show any significant difference between the two groups of patients (Figure 2). Thus, whereas DGF patients of group 2 showed a stable graft function throughout the study period, without any significant modification from discharge to the end of follow-up, DGF patients of group 1 displayed a

Table 2. Clinical features of cadaveric donors and renal transplant recipients divided according to the immunosuppressive regimen adopted

	Group 1[a]	Group 2[b]
Donors (*n*)	21	24
age (yr)	64 ± 8.1	60.9 ± 7.8
cause of death, brain stroke (%)	85.7	79.2
Cockcroft creatinine clearance (ml/min)	55 ± 16.3	69.4 ± 20
mean of total histologic score	4.50 ± 0.6	4.28 ± 0.9
Recipients (*n*)	42	48
patients with DGF (*n* [%])	22 (52.4)	28 (58.3)
age (yr)	50.4 ± 7.8	51.8 ± 6.3
cold ischemia time (h)	14 ± 5.1	15.7 ± 5.9
HLA-MM	3.25 ± 0.7	3.14 ± 0.6
acute rejection overall (%)	9.5	10.4
acute rejection in DGF patients (%)	9	7.1

[a] Group 1: CS+CNI+SRL.
[b] Group 2: CS+CNI+MMF.

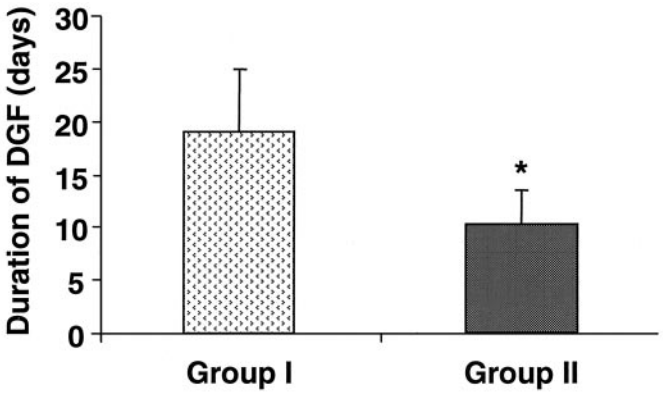

Figure 1. Duration of delayed graft function in the two groups of patients. Group 1, corticosteroids (CS) + low-dose cyclosporine + sirolimus; group 2: CS + calcineurin inhibitors + mycophenolate mofetil; *$P = 0.001$.

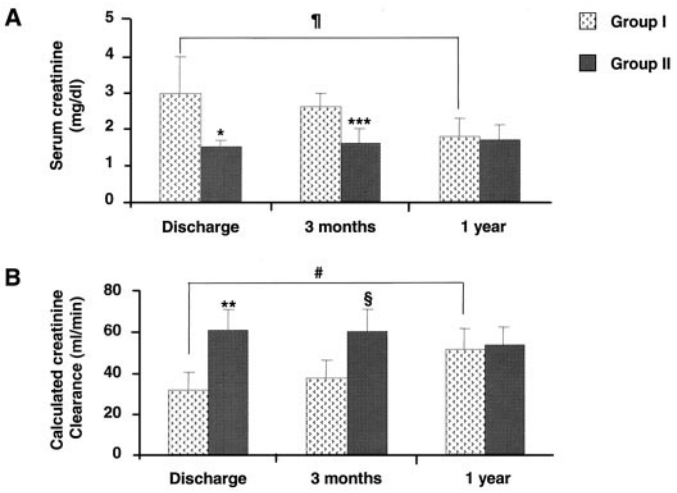

Figure 2. Kidney graft function in the two groups of patients examined. (A) Serum creatinine levels at discharge and at 3 and 12 mo posttransplantation. (B) Creatinine clearance (Nankivell formula) at the same time periods. *$P = 0.002$ *versus* group 2; **$P = 0.001$ *versus* group 2; ***$P = 0.02$ *versus* group 2; §$P = 0.002$ *versus* group 2; ¶$P = 0.002$; #$P = 0.001$.

significant and progressive improvement of graft function in the same time period (Figure 2).

Discussion

Here we report that the administration of SRL, in combination with low-dose CsA, to kidney transplant recipients from a suboptimal donor is associated with a longer duration of DGF, when compared with patients who received full-dose CsA+MMF. One-year graft function, however, is not significantly different in the two groups of patients, *i.e.*, in those taking CsA throughout the study period *versus* patients with early discontinuation of the calcineurin inhibitor. Although several studies examined the possible variables that determine the onset of DGF, the factors that affect its duration need to be clarified. In this setting, the impact of different immunosuppressive regimens may potentially be critical.

Very recently, Smith *et al.* (16) reported that SRL treatment combined with CNI leads to extensive tubular cell injury and death and increased incidence of DGF. We could not confirm this finding but observed a higher risk of longer duration of DGF in patients taking SRL, as described by McTaggart *et al.* (17).

The first logical explanation for our finding is that the contemporary administration of CsA and SRL may amplify the nephrotoxic effects of the former drug, as suggested by both human (18) and experimental studies (19). Indeed, recent experiments demonstrated that the pharmacokinetic interaction of CsA and SRL leads to a disproportionate elevation of renal tissue CsA concentration that is not mirrored by whole-blood drug levels (20). Such possibility might especially hold true in patients who receive an organ from a suboptimal donor, as all our patients.

However, it cannot be ignored that patients of group 1 were administered one half the dose of CsA prescribed to group 2 patients, in combination with low to moderate doses of SRL (on average, 3 mg daily). This would point, at least in part, to a direct, independent effect of SRL, as suggested by some experimental studies (12). In the event of acute tubular damage, the rate of recovery of tubular function depends on a balance between proximal tubular cell death (21) and the ability of sublethally injured tubular cells to enter the cell cycle and proliferate (22). SRL was shown to inhibit growth factor–induced proliferation of cultured mouse proximal tubular cells and to promote apoptosis by impairing the survival effects of the same growth factors (12). *In vivo*, SRL markedly delays the recovery of renal function after experimental ischemic acute renal failure but has no adverse effect on renal function in sham-operated rats, *i.e.*, on uninjured quiescent tubular cells (12).

Accordingly, serial graft biopsies performed at weekly intervals during DGF in our patients revealed an initial prolifer-

Table 3. Number of pretransplantation biopsies divided according to histologic score for each examined renal compartment

	Glomerular Sclerosis			Tubular Atrophy			Interstitial Fibrosis			Vascular Damage		
Score	0	1	2	0	1	2	0	1	2	0	1	2
Group 1[a] (*n*)	0	15	6	3	17	1	0	17	4	2	16	3
Group 2[b] (*n*)	0	22	2	1	22	1	0	20	4	0	21	3

[a] Group 1: CS+CNI+SRL.
[b] CS+CNI+MMF.

ative activity of tubular cells only in group 2, whereas it was remarkably delayed or absent in patients who were taking SRL. Such pattern might reflect differences existing between the two drugs. In fact, CsA seems to induce acute tubular damage mainly through a potent vasoconstrictive effect, with only minor effects on tubular cell proliferation, whereas SRL exerts a direct antiproliferative action on tubular cells by inhibiting normal cell growth (23). Therefore, the delay of recovery from DGF, *i.e.*, from ATN, may result from a direct effect of SRL largely independent from its synergistic interaction with CsA.

The impact of DGF on long-term outcome of kidney allografts is still controversial. Evidence exists that DGF increases the susceptibility of engrafted kidney to further insults, including AR and CNI toxicity (2). Several centers reported an adverse effect of DGF on long-term graft survival (1,4). Analysis of >50,000 cadaveric renal transplants reported in the UNOS Scientific Renal transplant registry between 1991 and 1997 showed that DGF reduced the half-life of the transplant from 10.5 yr for grafts with immediate function to 6.9 yr (24). Troppmann *et al.* (2) and Lehtonnen *et al.* (25), however, reported that DGF had an adverse effect on long-term outcome only in patients who also experienced AR. Furthermore, a recent report suggests that DGF has an adverse impact on graft survival only in the first year after transplantation (26). Conversely, Boom *et al.* (27) reported that DGF is one of the several risk factors of AR and suboptimal function at 1 yr, but it is not independently associated with an increased rate of graft loss.

Despite a longer duration of DGF and a worse graft function at discharge but a similar rate of AR, patients who took SRL had a progressive amelioration of kidney graft function during the first year after engraftment, after the discontinuation of CsA, and reached sCr values similar to those of group 2 patients at the end of follow-up. This might suggest that the length of recovery from DGF has only a negligible effect on long-term graft function, the two immunosuppressive regimens leading to substantially similar results at 1 yr. Alternatively, it may be hypothesized that SRL-based therapy, by avoiding the nephrotoxic effect induced by CNI, counterbalances, in the long term, its negative impact on early graft function. The latter hypothesis would be supported by recent studies demonstrating that patients with SRL-based immunosuppression and early withdrawal of CsA (3 mo after engraftment) display a better graft function (28) and a marked reduction in the progression of chronic histologic damage, mainly in the vascular compartment (29).

We must recognize, however, that the limited length of follow-up may mask, at least in part, the long-term impact of DGF length on kidney graft outcome. Indeed, data available from 32 of 50 patients (15 of group 1 and 17 in group 2) who reached 21 mo of follow-up did not differ from those reported at 1 yr (sCr, 1.76 ± 0.4 *versus* 1.80 ± 0.5 mg/dl; creatinine clearance, 54.5 ± 9.0 *versus* 54.1 ± 9.8 ml/min; group 1 *versus* group 2). Moreover, we must admit that several different variables may interfere with the end result, flanking or even overlapping the only two variables examined in the present study: the length of DGF and the type of immunosuppressive regimen adopted. Finally, the limited number of patients included in the study obviously limits the strength of any categorical conclusion.

In view of the above findings, it is proposed that patients who undergo DGF may benefit from avoiding SRL until the complete recovery from ATN. The possible advantage of the adoption of SRL after DGF recovery and the discontinuation of CNI on long-term graft outcome of renal recipients from suboptimal donors deserves further investigations.

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