

*Original Article*

## Conversion to sirolimus for chronic renal allograft dysfunction: risk factors for graft loss and severe side effects

Daniel Abramowicz<sup>1</sup>, Karine Hadaya<sup>1</sup>, Marc Hazzan<sup>2</sup>, Nilufer Broeders<sup>1</sup>, Anh-Dung Hoang<sup>1</sup>, Lidia Ghisdal<sup>1</sup>, Christian Noel<sup>2</sup> and Karl Martin Wissing<sup>1</sup>

<sup>1</sup>Service de Néphrologie, Hopital Erasme, Bruxelles, Belgique and <sup>2</sup>Service de Néphrologie, Hopital Calmette, Lille, France

### Abstract

We retrospectively reviewed our experience with 45 kidney transplant recipients (KTR) that were switched from CNI to SRL, mainly for chronic allograft dysfunction (CAD) (41/45). The mean serum creatinine at switch was  $2.5 \pm 0.8$  mg/dl. At 1 year, patient survival was 93%. Death-censored graft survival was 67% at 1 year and 54% at 2 years. SRL was stopped because of severe side effects in 15 patients. Among these, eight patients developed 'de novo' high-grade proteinuria. Univariate analysis revealed that (1) a higher SRL level at 1 month was a predictor of SRL withdrawal due to severe side effects ( $P = 0.006$ ), and (2) predictors of graft failure after SRL conversion were low SRL loading dose ( $P = 0.03$ ) and a higher creatinine level at conversion ( $P = 0.003$ ).

In conclusion, the therapeutic index of SRL in patients suffering from CAD is narrow, with high exposure triggering serious adverse events that may mandate SRL discontinuation, while too low exposure may expose patients to under-immunosuppression and graft loss.

**Keywords:** graft survival; proteinuria; renal transplantation; sirolimus; toxicity

### Introduction

In some renal transplant recipients, CsA or tacrolimus may lead to the development of CAD. SRL, a potent immunosuppressant with a distinct mechanism of action, may help to prevent CAD progression [1–9]. However, having observed a high rate of SRL discontinuation in patients switched from CNI- to SRL-based immunosuppression, we retrospectively analysed our data to further elucidate the safety, efficacy and side effects of this CAD-attenuating strategy.

*Correspondence and offprint requests to:* Daniel Abramowicz, Nephrology Department, Hopital Erasme, Université Libre de Bruxelles, 808 Route de Lennik, 1070 Brussels, Belgium. Tel: +32-2-555-33-34; Fax: +32-2-555-64-99; E-mail: dabram@ulb.ac.be

### Patients and methods

Our data include 45 renal transplant recipients from two centres who were switched from CNI- to SRL-based immunosuppressant therapy. The CNI was abruptly discontinued and patients were switched to SRL+steroids. Thirty-nine patients also received an anti-metabolite (34 received MMF; 5 received AZA).

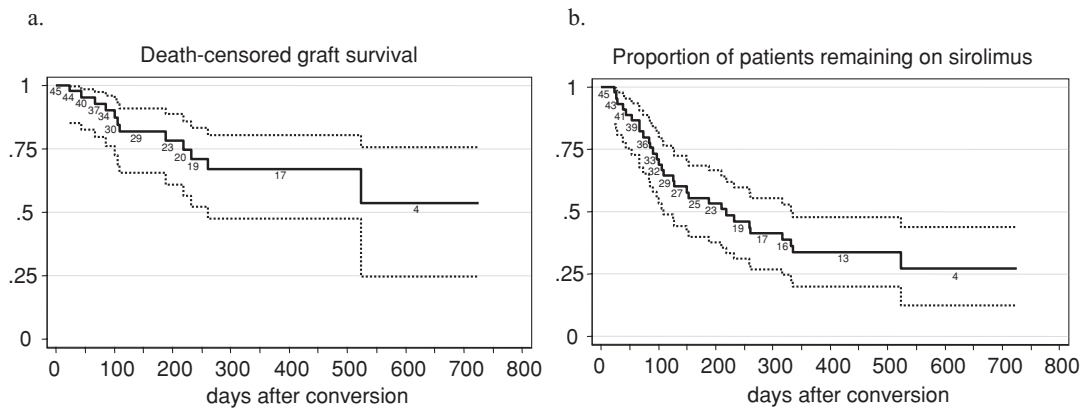
Mean age at switch was  $42.3 \pm 11$  (SD) years, and 22 patients (49%) were male. PRA was below 30% in 35/44 patients (79.5%), with a mean number of HLA mismatches of  $3.1 \pm 1.1$ . Twenty-four percent had experienced previous acute rejection before switching to SRL. The median time from transplantation to conversion was 28.1 months (range, 1.4–167 m), and the mean serum creatinine at the time of switch was  $2.5 \pm 0.8$  mg/dl. There was no deterioration of renal graft function during the 3-month preceding conversion (serum creatinine at –3 months:  $2.46 \pm 1.24$ ; at –1 month:  $2.46 \pm 0.85$ ,  $P = \text{NS}$ ).

For 23 patients, the mean ( $\pm$ SD) SRL loading dose was  $12.00 \pm 4.41$  mg/day for 3 consecutive days, with target trough levels ranging from 10 to 30 ng/ml. In the remaining patients, the SRL loading dose was 0.1 mg/kg for 3 days (mean dose:  $5.05 \pm 1.68$  mg) and the target trough level was 10 ng/ml. Median follow-up (death, graft loss or last FU) after SRL conversion was 8.6 months (range, 0.8–37 months). Proteinuria was evaluated either by the morning protein/creatinine ratio or by dipstick analysis.

### Results

#### *Patient survival, graft survival and SRL discontinuation*

Three deaths occurred after SRL switch. One patient died from multiple organ failure on Day 58, one from sudden death on Day 96 and one from cerebral haemorrhage on Day 156. Actuarial patient survival was 93% at 1 year. Twelve patients experienced loss of graft function and resumed chronic haemodialysis at a median of 107 days after SRL conversion (range, 23–523). Death-censored graft survival was 67% at 1 year and 54% at 2 years (Figure 1a). In addition, SRL was discontinued in 15 patients (33.3%)



**Fig. 1.** Kaplan–Meier estimate of death-censored graft survival (A) and of patients remaining on sirolimus therapy (B) during 2 years after conversion. Survival estimates are shown with 95% confidence bands (dotted lines). The population at risk at different time points during follow-up is indicated on the plot.

because of the occurrence of severe side effects (some patients developed more than one side effect): resistant anaemia,  $N = 1$ ; multiple abdominal abscesses following acute pancreatitis,  $N = 1$ ; hepatitis,  $N = 1$ ; peritransplant abscess,  $N = 1$ ; delayed wound healing,  $N = 1$ ; stroke,  $N = 1$ ; infra-therapeutic SRL levels leading to AR,  $N = 1$ ; raised Screat  $>25\%$ ,  $N = 1$ ; severe acneiform cutaneous lesions,  $N = 2$ ; severe hyperlipaemia,  $N = 2$ ; and *de novo* high-grade proteinuria,  $N = 8$  (17.7%). In summary, SRL was stopped in 30/45 (66.6%) patients after conversion (3 deaths, 12 graft loss and 15 discontinuation for side effects). The actuarial proportion of patients remaining on SRL therapy over time was 33.6% at 1 year and 26.9% at 2 years after conversion (Figure 1b).

Univariate analysis revealed that SRL levels were higher at 1 month when the 15 AE-experiencing, SRL-discontinuing patients were compared with the 30 SRL-continuing patients ( $19.4 \pm 10$  ng/ml versus  $11.7 \pm 7.8$  ng/ml, respectively,  $P = 0.006$ ).

#### *De novo heavy proteinuria*

The mean proteinuria of the whole cohort was 1.0 g/day at conversion, 1.7 g/day at 1 month ( $P = 0.008$ ) and 1.9 g/day at 3 months ( $P < 0.0001$ ). Eight out of 45 patients (18%) developed heavy proteinuria (mean 4.4 g/day, range, 2.5–9.8), which was detected at a median of 9.5 days after conversion (range, 5–127). Their baseline proteinuria was  $1.24 \pm 1.16$  g/day. Proteinuria returned to pre-switch levels after SRL discontinuation in 7/8 patients.

#### *Graft function and risk factors for graft loss after SRL switch*

Serum creatinine levels of the cohort are shown in Figure 2. For the overall cohort, serum creatinine levels were stable during the 3 months before conversion, but increased significantly thereafter. When the subgroup of patients who did not return to dialysis was analysed separately, conversion to sirolimus had no detectable effect on graft function (mean Pcreat:  $2.3 \pm 0.7$  at conversion versus  $2.2 \pm 0.8$

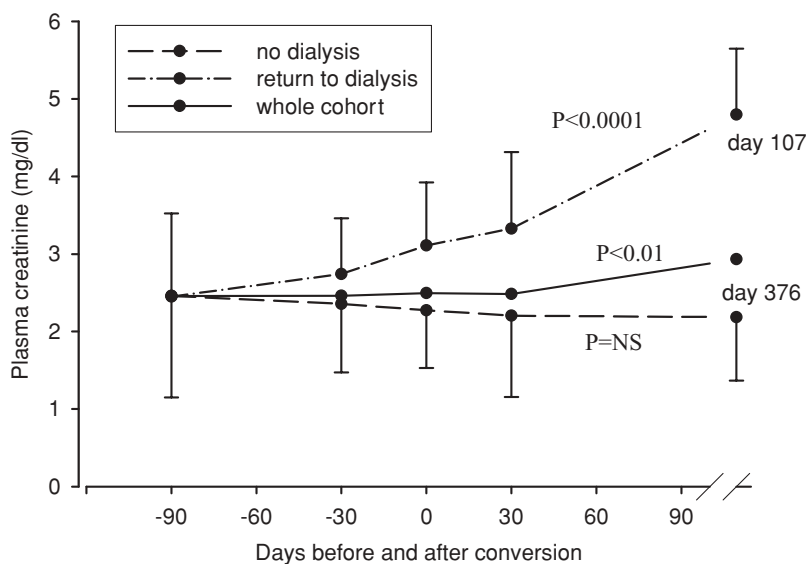
at final analysis;  $P = \text{NS}$ ; Figure 2). Univariate analysis comparing the 12 patients who lost their graft with the 33 patients who retained a functioning graft revealed that a lower SRL loading dose (5.2 mg/day versus 9.8 mg/day,  $P = 0.03$ ) and higher serum creatinine at the time of switch (3.10 mg/dl versus 2.27 mg/dl,  $P = 0.003$ ) were significant risk factors for subsequent graft loss. Proteinuria at switch was higher in patients who went on to lose their graft but this did not reach statistical significance (1.46 g/day versus 0.84 g/day,  $P = 0.29$ ).

## Discussion

We must first acknowledge that the three obvious shortcomings to our study are that it is retrospective, it has no control group and it involves difficult-to-manage CAD patients. Notwithstanding, a high incidence of severe side effects mandating SRL discontinuation was observed in one-third of the patients and was typical of those seen with mTOR inhibitors.

In our cohort, we could identify that high SRL trough levels at 1 month after the switch was a significant risk factor for severe side effects. In our early experience, we targeted SRL trough levels between 20 and 30 ng/ml, as recommended in the two Phase II trials where *de novo* KTR received CNI-free, SRL-based therapy [10,11]. Nowadays, lower trough levels, such as 8–15 ng/ml, are targeted, with less toxicity [12].

We found no improvement of renal function after the switch to sirolimus. This contrasts with a recent meta-analysis, where patients with CAD switched from CNI to SRL experienced a significant 6 ml/min improvement in creatinine clearance [13]. This difference is probably due to the patients in the meta-analysis having better preserved renal function at the time of switch (CrCl was 47 ml/min, versus 35 ml/min in our study). Indeed, results from the recent ‘Convert’ study, where patients with creatinine clearance  $<40$  ml/min experienced a high incidence of adverse events with no corresponding renal function benefits [14], have suggested that conversion to SRL following



**Fig. 2.** Serum creatinine over time. Data were available for 41, 44, 45, 44 and 42 patients at  $-3$  months,  $-1$  month, at switch,  $+1$  month and last follow-up, respectively. Hypothesis testing by repeated measures ANOVA, between day of switch and day of last follow-up. The median days of follow-up for patients who lost graft function and those who retained a functioning graft were 107 and 376, respectively.

CAD should only be undertaken in patients with creatinine  $<2.5$  mg/dl [15]. Similarly, Wali *et al.* concluded that conversion from tacrolimus to SRL is ineffective when the mean creatinine level reaches 3.8 mg/dl [16]. Our findings substantiate these observations.

*Conflict of interest statement.* None declared.

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