Determinants of Successful Use of Sirolimus in Renal Transplant Patients

Marcel G. Naik, Jan Steffen Jürgensen, Wolfgang Arns, Edin Basic, Klemens Budde, Frank Eitner,Michael Fischereder, Jan Goßmann, Katharina M. Heller, Nils Heyne, Christian Morath, Udo Riester,Fritz Diekmann, and Wilfried Gwinner

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Introduction:

Regimens with a conversion from a calcineurin inhibitor-based therapy to SRL as early as 3 months after transplantation have demonstrated a superior long-term graft function compared with continuation with a standard immunosuppression with calcineurin inhibitors (CNI) [1-3]. Other reasonable indications for SRL are declining renal graft function resulting from calcineurin inhibitor toxicity, progressive interstitial fibrosis and tubular atrophy [4-6], extrarenal CNI-related side effects, and de novo malignancies [7-9]. Moreover, benefits of mTORI therapy have been reported in patients with viral infection, including CMV and BK virus [1, 10, and 11].

Drug-associated side effects are an important issue in terms of a patient's health, quality of life, and compliance. Some side effects can be managed by dose reduction of SRL or by adjustments of the concomitant medical therapy [12, 13].

To avoid treatment failures with SRL, criteria would be valuable, which can identify those patients who will benefit most from the mTOR-inhibitor therapy.

Aim of the present analysis is to identify predictors, which can help to assign those patients for SRL who benefit from this therapy most likely.

Methods:

This multicenter, retrospective study includes 726 patients with a kidney or combined kidney transplantation with another solid organ who were put on an SRL-based maintenance immunosuppression at 3 months post-transplantation or later, between January 1, 2000, and December 31, 2008. Observation times after switching to SRL-based immunosuppression ranged from 4 days to 9 years, with a median time of 24.3 months. SRL initiation occurred on average 6.1 years after transplantation.

Outcomes were defined as Terminal graft failure, cessation of SRL therapy in patient with a functioning renal graft (allograft related or other reasons) and continued maintenance therapy with SRL.

Results:

Study Population

The study population was predominantly of Caucasian origin (99%). A proportion of 16.4% were living-donor transplantations, 10.5% combined organ transplantations, and one-quarter re-transplantations. One third of patients received an induction with depleting antibodies or with IL-2 receptor antibodies, depending on local center policies.

Reasons for initiation of sirolimus therapy were documented in 722 of the 726 patients. Graft-related reasons were implicated in half of patients, mostly CNI toxicity and chronic GFR decline. A second common cause was the presence of malignancies (24.9%)

Clinical course after SRL initiation

Successful SRL use was reported in 304 (41.9%) patients (Table 1).

Table1. Outcome of Patients after Sirolimus Initiation

Outcome	N	%
Successful treatment	304	41.9
Death with functioning graft on SRL treatment	40	5.5
Graft failure on SRL treatment	106	14.6
thereof death afterwards	8	1.1
SRL discontinuation with functioning graft	276	38.0
thereof death afterwards	5	0.7

Factors Associated With Successful Use of SRL

At the time of SRL initiation, patients with successful SRL use had better graft function (eGFR 45±18 vs 35± 19 mL/min; P<.0001), compared with patients with treatment failure. One year after SRL initiation, eGFR remained stable in patients with successful SRL use (47±18 mL/min).

- **ROC curve analyses showed an eGFR cut-off of 33.6 mL/min for successful SRL use vs treatment failure from all reasons.**

In patients with successful SRL treatment, proteinuria at the time of SRL initiation was 112 ±130 mg/L (224±260 mg/d), compared with 510±937 mg/L (1020±1874 mg/d) in patients with treatment failure.

In patients with successful SRL therapy, protein excretion increased to 327±582 mg/L (654±1164 mg/d) one year after SRL initiation (Table 2).

Table2. Comparison of proteinuria in the Subgroups of Patients at the time of SRL initiation

Subgroups	Successful SRL use patients	Treatment failure	Graft failure patients	Discontinued SRL patients
Proteinuria mg/L	112±130	510±937 P<. 001	750±1066 P<. 001	406±799 P<.001

- **ROC curve analysis indicated a cut-off of 272 mg/L (544 mg/d) vs graft failure (P<.001).**

Variables with significant differences between patients with successful SRL use and with treatment failure were entered into a regression analysis. eGFR was entered as a continuous variable because this led to the highest possible correct prediction. With the obtained model, successful SRL use was predicted in 82.5%, graft failure in 65.4%, SRL termination for graft-related reasons in 25%, and in 21.5% for other reasons. Regarding time factors, most favorable results for SRL use were observed in the most recent era.

Predictive factors for graft failure were lower eGFR, higher proteinuria, and with borderline significance, acute rejection before SRL initiation.

Lower eGFR and higher proteinuria were also predictive for SRL termination for graft-related reasons, besides several other factors including renal CNI toxicity and acute rejection.

In patients with termination of SRL for other reasons, lower eGFR, higher proteinuria, and initiation of SRL because of nonrenal CNI side effects were predictive. In this group time from transplantation to initiation of SRL therapy was associated with an increased risk of 7.5% per year. This may be because of the higher proportion of patients with tumors.

Discussion:

Lower eGFR and higher proteinuria were consistently associated with SRL therapy failure. This was most evident in patients with graft loss, with no other identifiable specific factors, apart from the time era of SRL initiation. The results of the regression analysis show that successful therapy with SRL can be predicted in the majority of patients (82%). Failure of SRL therapy can be anticipated in patients who have a priori high likelihood of graft loss indicated by poor graft function, previous rejections, and in these, SRL therapy should be not attempted.

Thresholds of proteinuria for successful mTORI-based therapy have been suggested in the range of 500 to 800 mg/day [13, 14, 15], or even higher with 1g/L [16]. Similarly, our results indicate that protein excretion above a relatively low threshold of 151 mg/L (302 mg/d) before SRL initiation carries a significant risk of graft failure. Previous study [17] and this analysis showed that daily protein excretion cutoff values of 300-500 mg/d (151-268mg/L) at conversion were clearly associated with inferior graft survival.[17] These results can provide clear recommendations that predicts successful use of SRL.

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