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ORIGINAL ARTICLE

Early conversion to a sirolimus-based, calcineurin-inhibitor-free immunosuppression in the SMART trial: observational results at 24 and 36 months after transplantation

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Conflicts of interest
No conflict of interest to disclose for all authors.

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Summary

Early conversion to a calcineurin-inhibitor (CNI)-free maintenance immunosuppression with sirolimus (SRL), mycophenolate mofetil (MMF) and steroids was associated with an improved 1-year renal function as compared with a cyclosporine (CsA)-based regimen (SMART core-study). This observational follow-up describes 132 patients followed up within the SMART study framework for 36 months. At 36 months, renal function continued to be superior in SRL-treated patients [ITT-eGFR$_{@36m}$: 60.88 vs. 53.72 (CsA) ml/min/1.73 m^2, $P = 0.031$]. However, significantly more patients discontinued therapy in the SRL group 59.4% vs.42.3% (CsA). Patient [99% (SRL) vs.97% (CsA) and graft 96% (SRL) vs.94% (CsA)] survival at 36 months was excellent in both arms. There was no difference in late rejection episodes. Late infections and adverse events were similar in both arms except of a higher rate of hyperlipidemia in SRL and a higher incidence of malignancy in CsA-treated patients. In a multivariate analysis, donor age >60 years, S-creatinine at conversion >2 mg/dl, CMV naïve(-) recipients and immunosuppression with CsA were predictive of an impaired renal function at 36 months. Early conversion to a CNI-free SRL-based immunosuppression is associated with a sustained improvement of renal function up to 36 months after transplantation. Patient selection will be key to derive long-term benefit and avoid treatment failure using this mTOR-inhibitor-based immunosuppressive regimen.

Introduction

During the recent years, the improvement of long-term outcomes after transplantation has taken center stage as a main target in modern immunosuppressive concepts. As CNIs provide effective immunosuppression, they also contribute to chronic allograft nephropathy by acute and chronic nephrotoxicity. Attempts to completely avoid CNIs by using mammalian target of rapamycin(mTOR)-inhibitor-based regimens exposed their own challenges: (i) efficacy problems resulting in an increased rate of acute rejection, (ii) wound-healing issues probably due to the antiproliferative/antiangiogenic nature of mTOR-inhibitors, (iii) an unfamiliar side-effect profile causing a high rate of drug discontinuations [1].

In consideration of the above-mentioned problems, different conversion strategies were implemented to introduce an mTOR-inhibitor-based therapy through the back door. In these regimens, immunosuppression in the initial phase after transplantation relies on the efficacy of CNIs and their inert effects on wound-healing, whereas mTOR inhibitors, implemented sequentially, are thought to be a better choice in maintenance immunosuppression to avoid CNI-related nephrotoxicity [2–5]. However, the optimal time-point of conversion as well as the best immunosuppressive partner for an mTOR inhibitor after conversion has not yet been established on the grounds of clinical trials.

The SMART trial investigated the effect of an early CNI-free immunosuppression (2–3 weeks post transplant) with SRL + MMF + ST in comparison with a standard immunosuppression with CsA + MMF + ST on renal function 1 year after transplantation. Immediately after cessation of the CNI, patients on SRL + MMF + ST gained a significantly better renal function (~10 ml/min), which persisted up to 12 months – the primary study endpoint. Patients on SRL + MMF + ST had the additional benefit of a lower rate of CMV infections, but were affected by a plethora of side effects, which resulted in a substantial rate of drug discontinuations [3].

Currently, we do not really know how SRL-based regimes are tolerated long-term and whether the beneficial effects of renal function seen at 1 year after transplantation are sustained in an extended follow-up. This observational study describes the 3-year follow-up of our study population on the basis of the endpoints used in the original SMART core study [3]. In addition, we have made an effort to identify substrata of patients who may benefit more than others of a SRL-based, CNI-free immunosuppression.

Methods

The SMART trial included adult immunological low-risk (PRA < 30%) patients. Patients were started on CsA, MMF, and steroids. After 2–3 weeks, patients were randomized to be converted to SRL, MMF (750 mg b.i.d.) and steroids or to be continued on CsA, MMF (1000 mg b.i.d.; 3). After conclusion of the core study at 12 months, patients were offered to enroll in this observational study of two additional years' duration.

During the second and third year, there was no mandatory treatment, and regimen modifications did not constitute protocol violations. However, centers were advised to follow a consistent strategy for all their patients. The participating centers agreed to keep patients on the assigned treatment whenever possible. The recommended trough levels for the follow-up phase were 5–7 ng/ml in the SRL arm and 50–80 ng/ml in the CsA arm. It was suggested to keep patients on a minimal dose of steroids.

The minimal data sets collected during follow-up at 24 and 36 months after transplantation included graft loss and patient death, incidence of biopsy-proven acute rejection beyond months 12, body weight, S-creatinine, S-urea, doses of SRL and CsA. Renal function was determined by serum-creatinine and the estimated glomerular filtration rate (GFR) using the Nankivell formula. Adverse events including the development of de-novo malignancy were recorded as reported or detected on follow-up visits at 24 and 36 months.

The primary analysis population was defined to include all patients who entered the follow-up and renal function was analyzed on available data. Patients were analyzed as per protocol, if they received their randomized treatment at least for 12 months.

Donor and recipient factors, which were associated with an unfavorable development of renal function (defined as eGFR <60 ml/min/1.73 m^2) were analyzed *post hoc* in a univariate fashion using Fisher's exact test. Multivariate analysis was performed by logistic regression modeling. Backward and stepwise procedures were used for parameter selection with a threshold of $P < 0.05$. Results are given as odds ratios together with 95% confidence intervals.

Results

Patients and treatments

During the study, many patients underwent changes in immunosuppressive maintenance (e.g. switch from SRL to CsA), but the vast majority remained on MMF. At 24 months, 46.4% of patients were on treatment in the SRL arm and 71.8% of patients in the CsA arm. At 36 months, only 40.6% patients were treated with SRL, whereas 57.7% still were on CsA. The course of the patients through the study phases is detailed in Fig. 1. While significantly more patients discontinued the SRL-based therapy in the first 12 months of the core study,

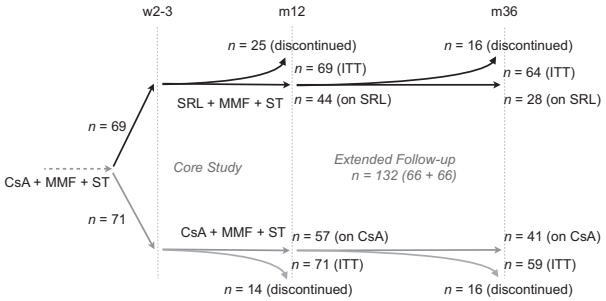

Figure 1 Patients flow through the study phases.

thereafter, the rate of discontinuations did not differ between patients on an SRL- or CsA-based immunosuppression. The reasons for discontinuations from the designated immunosuppressive regimen are summarized in Table 1. Interestingly, proteinuria did not trigger drug discontinuation in any of the study patients irrespective of the assigned treatment.

Renal function

Renal function during the extended follow-up continued to be superior for the SRL+MMF conversion group when compared to the CsA + MMF group (see Table 1). The intention-to-treat (ITT) analysis of the median eGFR revealed a benefit of 6.9 ml/min/1.73 m^2 at 24 and 7.2 ml/min/1.73 m^2 at 36 months (Fig. 2). The PP analysis at 36 months matches the ITT analysis, suggesting that differences in renal function are related to the immunosuppressive regimen used. We have further analyzed eGFR for patients who discontinued their treatment within the first 12 months (core study) and between months 12 and 36 (extended follow-up; Table 2). Renal function at 12 and 36 months was not significantly different between patients who dropped out of either of the study arms. Although there were no relevant differences in the slopes of renal function within the different treatment groups, the waterfall plots (Fig. 3) give the impression that there were more patients with more extreme changes in renal function in the SRL group as compared with the CsA group.

Efficacy

In both treatment groups, an excellent 2- and 3-year patient and graft survival was achieved. At 3 years, 99% of patients were alive and 96% still had a functioning graft in the SRL arm. At the same time, patient survival in the CsA arm was 97% and graft survival was 94%. Five patients reported late (>12 months) biopsy-proven rejections, two in the SRL arm and three in the CsA arm.

Adverse events

Between 12 and 36 months (extended follow-up), new adverse events were reported in 26 (39.4%) patients in the SRL group and 33 (50%) in the CsA group. There were no notable differences in most categories except of metabolic disorders –primarily hyperlipidemia –reported more frequently in SRL-treated patients. Proteinuria was found to be not significantly different in both study arms. (Table 3) In contrast, de-novo malignancies, which developed in 5 patients, were only seen in the CsA arm ($P = 0.026$, Fig. 4).

Multivariate analysis

Uni- and multivariate analyses of potential donor and recipient factors were performed to specify risk factors

Table 1. Reasons for discontinuation from the designated immunosuppressive regimen.

	SMART core (≤12 months)			Follow up (12–36 months)			Total		
	SRL, *n* (%)	CsA, *n* (%)	*P*-value	SRL, *n* (%)	CsA, *n* (%)	*P*-value	SRL, *n* (%)	CsA, *n* (%)	*P*-value
Total	69 (100)	71 (100)		69 (100)	71 (100)		69 (100)	71 (100)	
Total discontinued	25 (36.2)	14 (19.7)	**0.0380**	16 (23.2)	16 (22.5)	1.0000	41 (59.4)	30 (42.3)	**0.0450**
Death	1 (1.4)	1 (1.4)	1.0000	0 (0.0)	0 (0.0)	–	1 (1.4)	1 (1.4)	1.0000
Graft loss	0 (0.0)	1 (1.4)	1.0000	0 (0.0)	0 (0.0)	–	0 (0.0)	1 (1.4)	1.0000
Treatment changed	23 (33.3)	8 (11.3)	**0.0021**	15 (21.7)	9 (12.7)	0.1823	38 (55.1)	17 (23.9)	**0.0002**
Rejection	3 (4.3)	2 (2.8)	0.6784	1 (1.4)	3 (4.2)	0.6197	4 (5.8)	5 (7.0)	1.0000
Impaired renal function	1 (1.4)	1 (1.4)	1.0000	5 (7.2)	1 (1.4)	0.1131	6 (8.7)	2 (2.8)	0.1625
Wound healing	2 (2.9)	0 (0.0)	0.2411	2 (2.9)	0 (0.0)	0.2411	4 (5.8)	0 (0.0)	0.0564
Pneumonia/Pneumonitis	4 (5.8)	0 (0.0)	0.0564	0 (0.0)	0 (0.0)	–	4 (5.8)	0 (0.0)	0.0564
CNI-Tox.	0 (0.0)	1 (1.4)	1.0000	0 (0.0)	2 (2.8)	0.4965	0 (0.0)	3 (4.2)	0.2448
Other AE*	11 (15.9)	4 (5.6)	0.0587	6 (8.7)	2 (2.8)	0.1625	17 (24.6)	6 (8.5)	**0.0120**
Other reasons	2 (2.9)	0 (0.0)	0.2411	1 (1.4)	1 (1.4)	1.0000	3 (4.3)	1 (1.4)	0.3624
Missing or lost to follow-up	1 (1.4)	4 (5.6)	0.3662	1 (1.4)	7 (9.9)	0.0628	2 (2.9)	11 (15.5)	**0.0169**

*Proteinuria was not reported as a reason for changing the randomized regimen; Bold face indicates significant values.

and to identify individuals who may benefit most of a CNI-free immunosuppression. The univariate analysis suggests that the factors donor age >60 years, S-creatinine ≥2 mg/dl at the time of conversion and an immunosuppression with CsA are predictive of an impaired renal function at 12 months. At 36 months, also a CMV (-) naive serostatus became predictive of an inferior renal function at 36 months. (Table 4).

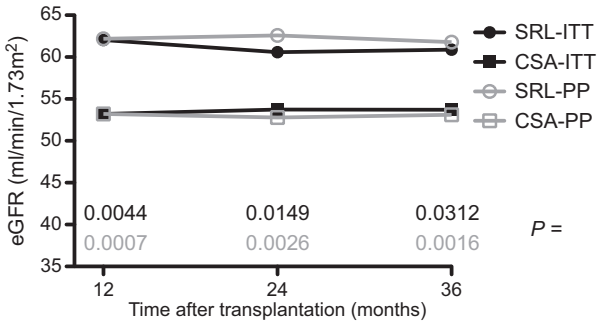

Figure 2 eGFR determined by the Nankivell equation. Median values and respective *P*-values (Wilcoxon rank sum test) are shown for the intention-to treat and per-protocol population.

Multivariate logistic regression showed that main factors associated with impaired renal function (defined as eGFR <60 ml/min/1.73 m^2) 12 months after transplantation were donor age (OR: 3.4 [1.1–10.2]) and CsA (OR: 3.1 [1.5–6.5]). When S-creatinine levels at conversion were included in the model search procedure, S-creatinine at conversion >2.0 mg/dl (OR: 16.7 [6.0–46.7]) and CsA (OR: 4.7 [1.9–11.4]) were selected.

After 36 months, the selected models included CMV-naive recipients (OR: 3.6 [1.6–8.0]), donor age (OR: 5.0 [1.3–19.6]) and CsA (OR: 3.1 [1.4–7.0]). When S-creatinine levels at conversion were included in the model search procedure, it replaced donor age. The resulting model identified as predictive factors, CMV naive recipients [OR: 4.1 [1.7–10.3]), S-creatinine at conversion >2 mg/dl (OR: 10.6 [3.9–28.6]) and CsA (OR: 3.5 [1.4–8.7]).

Discussion

The SMART study was one of the first to show the feasibility of an early conversion approach to a CNI-free mTOR-inhibitor-based therapy to preserve renal function.

Table 2. eGFR (Nankivell) at 36 months.

Mean (median) ± SD	SRL group	CsA group	*P*-value
ITT analysis	61.05 (60.88) ± 22.22 *n* = 64	54.10 (53.72) ± 18.19 *n* = 59	**0.0312**
Discontinued <12 months	53.78 (52.83) ± 20.69 *n* = 23	54.59 (54.53) ± 22.10 *n* = 11	0.9706
PP analysis (at least 12 months on randomized treatment)	65.14 (61.79) ± 22.23 *n* = 41	53.98 (53.11) ± 17.45 *n* = 48	**0.0016**
Total discontinued	55.64 (55.13) ± 19.48 *n* = 36	57.32 (57.25) ± 20.02 *n* = 18	0.8186
36 months on randomized treatment	68.02 (63.15) ± 23.88 *n* = 28	52.68 (51.68) ± 17.40 *n* = 41	**0.0006**

Bold face indicates significant values.

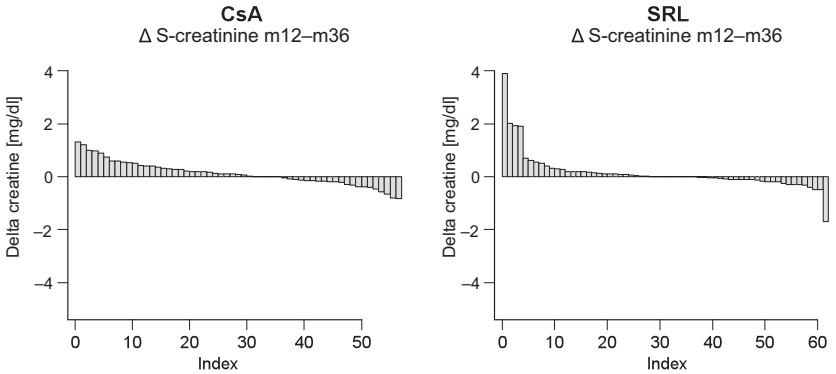

Figure 3 The waterfall-plots show the change in S-creatinine of individual patients between 12 and 36 months in relation to the assigned study treatment at the time of transplantation.

Table 3. Adverse events and onset of new concomittant diseases.

	SMART Core (≤12 months)			Follow up (12–36 months)		
Event, % (n)	SRL (*n* = 69)	CsA (*n* = 71)	*P*-value	SRL (*n* = 66)	CsA (*n* = 66)	*P*-value
Infections and infestations	52.2 (36)	60.6 (43)	0.3942	12.1 (8)	13.6 (9)	1.0000
CMV	7.3 (5)	28.2 (20)	**0.0016**	0.0 (0)	1.5 (1)	1.0000
Pneumonia	11.6 (8)	9.9 (7)	0.7901	3.0 (2)	0.0 (0)	0.4962
Urinary tract infections	18.8 (13)	29.6 (21)	0.1691	7.6 (5)	7.6 (5)	1.0000
Injury, poisoning and procedural complications	40.6 (28)	33.8 (24)	0.4847	1.5 (1)	6.1 (4)	0.36553
Lymphocele	27.5 (19)	23.9 (17)	0.7005	0.0 (0)	1.5 (1)	1.0000
Technical, surgical complications	10.1 (7)	9.9 (7)	1.0000	0.0 (0)	1.5 (1)	1.0000
Wound healing disorders	10.1 (7)	11.3 (8)	1.0000	0.0 (0)	0.0 (0)	–
Gastrointestinal disorders	29.0 (20)	33.8 (24)	0.5877	7.6 (5)	9.1 (6)	1.0000
Diarrhea	13.0 (9)	9.9 (7)	0.6037	0.0 (0)	0.0 (0)	–
Abdominal pain	2.9 (2)	7.0 (5)	0.4414	0.0 (0)	0.0 (0)	–
Metabolism and nutrition disorders	30.4 (21)	29.6 (21)	1.0000	15.2 (10)	3.0 (2)	**0.0303**
Hyperlipidemia	20.3 (14)	7.0 (5)	**0.0269**	7.6 (5)	0.0 (0)	0.0578
Diabetes mellitus	7.3 (5)	5.6 (4)	0.7430	3.0 (2)	1.5 (1)	1.0000
Blood and lymphatic disorders	26.1 (18)	23.9 (17)	0.8462	1.5 (1)	1.5 (1)	1.0000
Anemia	13.0 (9)	5.6 (4)	0.1545	1.5 (1)	0.0 (0)	1.0000
Thrombopenia	2.9 (2)	4.2 (3)	1.0000	1.5 (1)	0.0 (0)	1.0000
Leucopenia	10.1 (7)	11.3 (8)	1.0000	0.0 (0)	1.5 (1)	1.0000
General and application site disorders	17.4 (12)	21.1 (15)	0.6700	4.6 (3)	1.5 (1)	0.6192
Edema	7.3 (5)	12.7 (9)	0.3997	3.0 (2)	1.5 (1)	1.0000
Pyrexia	7.3 (5)	5.6 (4)	0.7430	0.0 (0)	0.0 (0)	–
Vascular disorders	10.1 (7)	18.3 (13)	0.2277	9.1 (6)	3.0 (2)	0.2737
Hypertonia	0.00 (0)	4.2 (3)	0.2448	1.5 (1)	0.0 (0)	1.0000
Muscoskeleton and connective tissue disorders	15.9 (11)	11.3 (8)	0.4668	13.6 (9)	6.1 (4)	0.2420
Skin and subcutaneous tissue disorders	20.3 (14)	7.0 (5)	**0.0269**	3.0 (2)	0.0 (0)	0.4962
Hepatobiliary disorders	11.6 (8)	9.9 (7)	0.7901	3.0 (2)	1.5 (1)	1.0000
Nervous system disorders	10.1 (7)	9.9 (7)	1.0000	4.6 (3)	1.5 (1)	0.6192
Cardiac disorders	13.0 (9)	5.6 (4)	0.1545	1.5 (1)	4.6 (3)	0.6192
Respiratory disorders	13.0 (9)	7.0 (5)	0.2711	4.6 (3)	1.5 (1)	0.6192
Renal and urinary disorders	63.8 (44)	56.3 (40)	0.3929	13.6 (9)	19.7 (13)	0.4842
Proteinuria	10.1 (7)	2.8 (2)	0.0945	0.0 (0)	3.0 (2)	0.4962
Rejection	49.3 (34)	40.9 (29)	0.3958	3.0 (2)	4.6 (3)	1.0000
Surgical and medical procedures	2.9 (2)	1.4 (1)	0.6169	6.1 (4)	1.5 (1)	0.3653

Bold face indicates significant values.

Meanwhile, 1-year data of other early conversion studies (CONCEPT/with SRL [4] and ZEUS/with everolimus [2]) became available showing similar results with an advantage in eGFR of roughly 10 ml/min. [2,4,5] Long-term data, however, are scarce to completely appraise the value of these approaches. We have followed up our SMART study population for additional 2 years, providing now a 3-year follow-up. Renal function in the SRL group was significantly better in both the ITT and the PP populations over the entire follow-up period. The benefit in renal function was gained immediately after conversion; slopes of renal function were identical in both study arms over 36 months.

There were only few late rejection episodes reported after the first year of transplantation, equally distributed between both study arms, suggesting that efficacy problems observed in the first 3 months after transplantation in the SRL arm are no longer relevant in patients with successful long-term maintenance immunosuppression.

At 36 months, differences in the development of *de novo* malignancy reached a significant level. This is well in line with our previous clinical observation and results of other randomized trials showing a lower malignancy rate with an mTOR-inhibitor-based therapy [4]. Does anyone benefit from an SRL-based immunosuppression long-term?

This question is essentially influenced by the number of patients, who tolerate therapy with an mTOR-inhibitor and are long enough on the drug to reveal the potential merits of the CNI-free therapy with SRL. Our study shows that only 40.6% were still on SRL at the end of the third year of therapy. The majority of dropouts in the SRL arm occurred during the first year, most of them shortly after conversion. One of the reasons for the high rate of drop

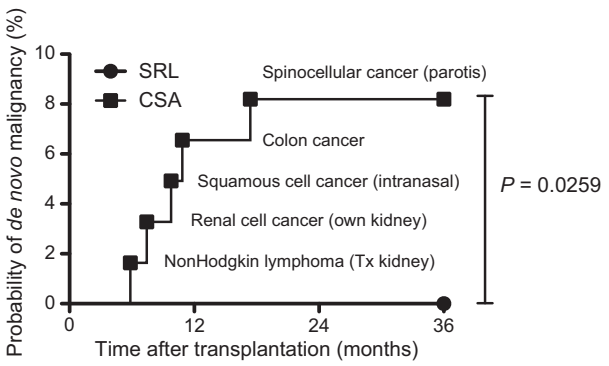

Figure 4 *De novo* malignancy after transplantation. Percentage of patients is shown. Tumor location at presentation is indicated.

outs early on may be the fact that conversion in the SMART trial was still early (2–3 weeks after transplantation) compared with other conversion trials [CONCEPT [4], HERACLES (publication pending) = 3 months, ZEUS (2) = 4.5 months, CONVERT (5) = 6–120 months]; still in the most vulnerable phase for acute rejection, opportunistic infections and delayed surgical problems. However, in retrospect, a significant number of conversions would not have been necessary with today's knowledge of management of SRL-related side effects. But at the time of the study, unfamiliar side effects usually triggered drug discontinuations. After the first year, there were no differences in the rate of drug discontinuations between the CsA and the SRL groups, and reasons for discontinuation were randomly distributed. The development of new onset proteinuria was not significantly different between the study arms. None of the patients on SRL developed proteinuria to an extent which mandated reconversion. However, a small number of patients in the SRL arm had an unfavorable development of renal function, independent of proteinuria, which triggered the reconversion to a CNI-based therapy.

In a clinical scenario, physicians have to follow a ''trial and error'' strategy if they wish to convert a patient to an SRL-based therapy. Our data, however, suggest that failure of an mTOR-inhibitor therapy and consecutive reconversion to a CNI-based regimen do not endanger the patient. Similar experiences were made in several other studies using mTOR-inhibitors early after transplantation. So far, no clear predictors of tolerability of an mTOR-inhibitor treatment are established. Some of the toxicity may also be related to the combination of two antiproliferative agents (SRL and MMF), which may also act synergistically in their unwanted effects, i.e. wound-healing problems, leucopenia, and anemia.

As a CNI-free, SRL-based therapy is not for everyone, it may be interesting to know which patients may benefit most from the therapy. Although there are multiple confounders, the multivariate analysis may give some hints.

Table 4. Factors for impaired renal function as defined by eGFR (Nankivell) <60 ml/min/1.73 m^2 at 12 and 36 months after transplantation.

	After 12 months			After 36 months		
	eGFR < 60 ml/min/1.73 m^2	eGFR ≥ 60 ml/min/1.73 m^2		eGFR < 60 ml/min/1.73 m^2	eGFR ≥ 60 ml/min/1.73 m^2	
Factor	*N* = 73% (*n*)	*N* = 59% (*n*)	*P*-value	*N* = 71% (*n*)	*N* = 52% (*n*)	*P*-value
Male gender	65.7 (48)	69.4 (41)	0.7107	73.2 (52)	59.6 (31)	0.1231
PRA > 0	2.7 (2)	1.6 (1)	1.0000	2.8 (2)	1.9 (1)	1.0000
CIT > 12h	53.4 (39)	49.1 (29)	0.7265	56.3 (40)	48.0 (25)	0.4648
HLA mismatch ≥5	6.8 (5)	10.1 (6)	0.5395	8.4 (6)	7.6 (4)	1.0000
Second NTX	8.2 (6)	6.7 (4)	1.0000	7.0 (5)	7.6 (4)	1.0000
CMV naive (neg.) recipient	47.9 (35)	40.6 (24)	0.4819	59.1 (42)	28.8 (15)	**0.0010**
BMI ≥ 25	49.3 (36)	42.3 (25)	0.4842	49.3 (35)	42.3 (22)	0.4692
Low ATG induction	13.7 (10)	11.8 (7)	0.7997	14.0 (10)	9.6 (5)	0.5808
Living donor	10.9 (8)	11.8 (7)	1.0000	12.6 (9)	9.6 (5)	0.7755
Donor age > 60	23.2 (17)	8.4 (5)	**0.0332**	21.1 (15)	5.7 (3)	**0.0201**
DGF	45.2 (33)	33.9 (20)	0.2140	39.4 (28)	36.5 (19)	1.8514
Lymphocele	21.9 (16)	13.5 (8)	0.2604	22.5 (16)	15.3 (8)	0.3647
Glomerulonephritis	45.2 (33)	35.5 (21)	0.2896	43.6 (31)	34.6 (18)	0.3543
Polycystic RD	10.9 (8)	13.5 (8)	0.7897	12.6 (9)	13.4 (7)	1.0000
Diabetes	8.2 (6)	3.3 (2)	0.2967	7.0 (5)	5.7 (3)	1.0000
Hypertension	6.8 (5)	8.4 (5)	0.7517	7.0 (5)	9.6 (5)	0.7415
Banff four in the first 3 months	20.5 (15)	18.6 (11)	0.8289	18.3 (13)	25.0 (13)	0.3814
S-creatinine at conversion ≥2.0 mg/dl	61.6 (45)	13.5 (8)	**<0.0001**	60.5 (43)	15.3 (8)	**<0.0001**
CsA	63.0 (46)	35.5 (21)	**0.0028**	59.1 (42)	32.6 (17)	**0.0059**

Bold face indicates significant values.

CMV recipient status, old donor age, and S-creatinine were identified to be significant predictors of long-term renal function, and thus may be important in the treatment decision pro or against an mTOR-inhibitor-based therapy in clinical practice.

A CMV risk constellation with CMV negative recipient was identified as one factor where an SRL-based therapy may have advantages over a cyclosporine-based therapy. This is not quite surprising as already the 1-year data clearly showed a significant lower rate of CMV infection in the SRL group, as compared with the cyclosporine group. The anti-CMV effect has been confirmed now in other studies using mTOR in a head-to-head comparison with a CNI [6,7]. The correlation between CMV infection and graft (long-term) outcome is well established and may also play a role in the beneficial effects of SRL in our study. Of note, we have to assume that the anti-CMV effect of an mTOR-inhibitor-based therapy is more likely to elicit its full potential in a *de novo* or early conversion setting and a scenario of preemptive therapy (as practiced in the majority of our study patients). Prophylactic therapy with 100–200 days valgancyclovir may render this effect negligible. However, on the basis of this anti-CMV effect of an SRL-based therapy, the question whether patients on mTOR-inhibitors require CMV prophylaxis at all has to be investigated [8–11].

Also, overall transplant/graft quality reflected by donor age (Fig. 5) and renal function at time of conversion seems to influence the results of an mTOR-inhibitor-based therapy. It is reasonable to believe that the avoidance of CNIs can only prevent graft deterioration, slow down graft fibrosis and chronic allograft nephropathy, but will not lead to significant regeneration of parenchymal losses [12]. From a theoretical standpoint, immunosuppression at its best can only preserve kidney function. Consequently, only kidneys where there is enough to preserve will eventually benefit from such a treatment. Our results underscore this notion. In other words, marginal kidneys with poor initial graft function are not likely to benefit from the mTOR-inhibitor-based therapy long-term. The correlation between renal function before conversion and success of an mTOR inhibitor-based therapy was also shown for late ''on demand'' conversion approaches [13,14].

In summary, our data show that the initial advantage in renal function established shortly after conversion persists over a follow-up of 36 months. However, not even half of the patients could be maintained on SRL for the entire study period. Therefore, in a clinical setting, patient selection will be crucial to avoid futile conversions. In this aspect, patients receiving good quality organs, starting off with good initial renal function and/or who are at risk for CMV infections seem to be good candidates for an early conversion to a CNI-free, SRL-based therapy.

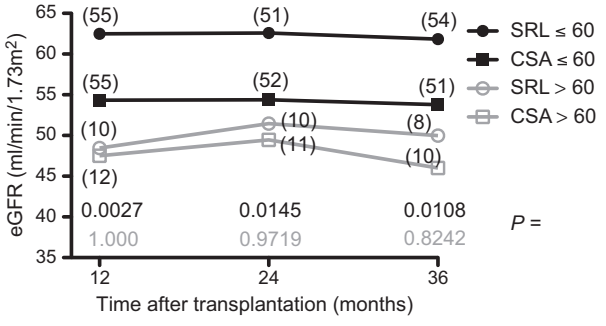

Figure 5 eGFR determined by the Nankivell equation. Median values and respective *P*-values (Wilcoxon rank sum test) are separately shown for donors ≤60 versus >60 years of age. Numbers at risk are depicted in brackets.

Authorship

MG: designed study, performed study, collected data, analyzed data, wrote the paper. JP, CH, BKK, AP, KP, OH, MF, JB, JA and BB: performed study, collected data. KWJ: designed study, performed study, analyzed data.

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