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ORIGINAL ARTICLE

Sirolimus monotherapy as maintenance immunosuppression: a multicenter experience

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Summary

The aim of this study was to retrospectively evaluate safety and feasibility of sirolimus (SRL) monotherapy in kidney transplant recipients. Patients older than 18 years, with monotherapy prescribed for more than 1 month and at least 6 months of follow-up were included. We analysed the data from 138 patients. Mean time period between transplantation and start of monotherapy was 6.5 ± 4.1 years.The most frequent reason was minimization of immunosuppression followed by malignancy. Acute rejection rate was 1.4% at 12 months (two episodes). Graft and patient survival were 94.2% and 97.1% respectively. Mean follow-up after initiation of monotherapy was 29.4 months. Two patients died as a result of cardiovascular diseases and two because of malignancy. Percentage of withdrawal from monotherapy was 14%. SRL trough levels were 10.2 ± 2.3 ng/ml at baseline and 9.6 6 ± 3.3 ng/ml at 12 months. Mean glomerular filtration rate was 48.4 ml/min/1.73 m^2 at baseline and 47.7 ml/min/1.73 m^2 at 12 months. Proteinuria was 499.7 mg/24 h at baseline and 543 ± 794 mg/24 h at 12 months. No significant changes in lipids, glucose, or hemoglobin occurred, although the percentage of patients treated with statins and Epo increased at the end of the follow-up. SRL monotherapy is suitable as long-term immunosuppression in selected patients with no significantly increased risk of late acute rejection.

Introduction

Most modern immunosuppressive regimens are based on calcineurin inhibitors (CNIs), which have made it possible to considerably reduce acute rejection rates. However, long-term use of CNIs is associated with several adverse effects, such as malignancy [1], dyslipidemia [2], diabetes mellitus [3], hypertension, and nephrotoxicity [4,5]. All CNIs can lead to severe cardiovascular disease and/or graft loss, or even to death with a functioning graft, thus explaining – at least in part – the failure to extend long-term graft survival [6].

Use of long-term immunosuppressive regimens also showed a direct relationship with the development of malignancy. Vajdic *et al.* found a significant increase in the standard incidence ratio of cancer after transplantation of 3.27 (95% confidence interval [CI], 3.09–3.46), compared with 1.35 (95% CI, 1.27–1.45) during dialysis

and 1.16 (95% CI, 1.08–1.25) before renal replacement therapy. After transplantation, the incidence of cancer increased significantly at 25 body sites. At 18 of these sites, the risk had increased more than threefold [1]. Kasiske *et al.* found a twofold increase in the incidence of cancer of the colon, lung, and prostate, and a 20-fold increase in the incidence of Kaposi's sarcoma compared with the general population. Interestingly, only 6% of patients in that study were treated with sirolimus (SRL) [7].

Therefore, several strategies have been developed to minimize these long-term risk factors without increasing the risk of graft loss or death. The non nephrotoxic and anti-angiogenic properties of SRL could make it the ideal long-term maintenance immunosuppressive agent in patients with a low immunologic risk.

This multicenter study aims to retrospectively analyse the safety and efficacy of SRL monotherapy as a long-term immunosuppressive regimen in a large series of kidney transplant recipients, with special emphasis on late acute rejection, renal function, and cardiovascular risk factors.

Patients and methods

We retrospectively reviewed medical records from five sites in Portugal and Spain to identify patients on SRL monotherapy. This study was approved by the Ethics Committee of Hospital Clínic, Barcelona, and patients gave their informed consent prior to their inclusion in the study. Inclusion criteria were patients aged above 18 years, beginning monotherapy earlier to March 2007, and with a long-term monotherapy treatment prescribed (at least 1 month). Patients with multiple organ transplants or with temporary monotherapy were excluded. SRL monotherapy was started by converting patients on CNI-based immunotherapy and withdrawing concomitant immunosuppressive agents before or after conversion to SRL, or by reducing the number of concomitant immunosuppressive drugs in SRL-based regimens. The primary objective was to evaluate the incidence and severity of late acute rejection after beginning SRL monotherapy. All patients aged above 18 years who had begun SRL monotherapy before March 2007 and had a follow-up of at least 6 months on monotherapy were eligible for participating in the study.

Follow-up included a physical examination, laboratory screening, and determination of SRL trough levels. Data on new cardiovascular events (acute coronary syndrome, peripheral vascular disease, and stroke), cancer, and nephrotoxicity episodes were collected. SRL trough levels were measured according to the usual practice of the study site. Laboratory parameters from one year before initiation of SRL monotherapy until the last available follow-up visit were recorded.

All data were expressed as the mean and standard deviation. Statistical differences between values before and after the start of SRL monotherapy were tested using the Wilcoxon and McNemar's test where applicable. A two-tailed P value <0.05 was considered to be significant.

Results

A total of 138 patients were eligible for analysis (80 male and 58 female subjects), mean age was 52 years (range, 26–78), and 117 patients (86%) were receiving SRL before starting monotherapy. All patients with intended monotherapy from the participating centers were included. The percentage of acute rejection before monotherapy was 12.3%. Most patients had a low immunologic risk. It means that 90% had a panel reactive antibodies (PRA)≤10% at the point of transplantation, 90% had received a first transplant, and only 12.3% had had a previous acute rejection (grade I in 81% of cases, grade II A in 19%). Other demographic and clinical characteristics are shown in Table 1.

The mean time period between transplantation and the beginning of (baseline) was 6.5 ± 4.1 years. Interestingly, 45.5% of patients started monotherapy within the first 5 years after their transplant. Mean follow-up time on SRL monotherapy was 29.4 months (CI 95% = 27–31.85), whereas median follow-up was 28.75 (range 4.5–72.2 months).

The most frequent cause to initiate monotherapy was minimization of immunosuppression (50.7%) resulting from local practice. Cancer was the reason in 29%. More data are detailed in Table 2. The most frequent treatment before monotherapy was based on SRL (86%) mainly associated to steroids (ST), whereas the other most frequent treatments were with mycophenolate mofetil (MMF) and tacrolimus (Tac). Previous treatments are described in Table 3.

Mean doses of other immunosuppressants previous to initiation of monotherapy were the following: CsA = 128 mg/day (CI 95% = 98.46–157.54), Tac = 1.48 mg/day (CI 95% = 0.74–2.23), MMF = 428.5 mg/day (CI 95% = 319.76–537.38), AZA = 47.50 mg/day (CI 95% = 31.84–63.61), steroids = 3.36 mg/day (CI 95% = 2.88–3.84).

The mean dose of SRL used at baseline was 3.7 ± 1.8 mg/day reaching trough levels of 10.2 ± 2.3 ng/ml. Doses and trough levels at 12 months were 3.1 ± 1.6 mg/day and 9.6 ± 3.3 ng/ml respectively. The mean glomerular filtration rate (measured using the abbreviated modified diet in renal disease formula) was 47 ml/min/1.73 m^2 at baseline and 48 ml/min/1.73 m^2 at 12 months. Baseline proteinuria was 499.7 ± 1257 mg/24 h,

Table 1. Clinical and demographic characteristics.

	N = 138
Male	80 (58)
Caucasian race	130 (94.2)
Afro-American race	2 (1.4)
Other races	6 (4.3)
Age (years)	52; 26–78
Cadaveric donor	136 (98.6)
Living donor	2 (1.4)
First transplant	124 (89.9)
Second transplant	13 (9.4)
Third transplant	1 (0.7)
Time on dialysis (years)	3.6; 0.3–20
HLA mismatches	2.7; 0–5
PRA%	5.6; 0–50
HCV	10 (7.2)
Leading cause of renal failure	
Glomerular disease	39 (28)
Diabetes	8 (6)
ADPKD	19 (14)
Hypertension	28 (20)
Unknown	44 (32)
Post-transplant complications	
Acute rejection	17 (12.3)
Diabetes mellitus	9 (6.6)
Concomitant treatment	
ARB	35%
ACE inhibitors	21.3%
Statins	50%
Erythropoetin	12.5%

Qualitative variables are expressed as n (%). Quantitative variables are expressed as mean; range. Concomitant treatment is expressed as percentage of a smaller n attributable to missing data. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; HCV, hepatitis C virus; PRA, panel reactive antibody; ADPKD, autosomal dominant polycystic kidney disease.

Table 2. Causes of monotherapy.

Cause	*N* (%)
Minimization of immunosuppression (local protocol)	70 (50.7)
Converted to sirolimus	60 (43.4)
Cancer	39
Squamous cell carcinoma	9
Basal cell carcinoma	7
Breast cancer	1
Kaposi's sarcoma	4
Colon cancer	2
Pancreatic cancer	1
Renal cell carcinoma	2
Thyroid	2
Lymphoma	5
Lung cancer	1
Prostatic cancer	1
Non specified malignancy	4
Other	21
CNI nephrotoxicity	3
Chronic allograft nephropathy	8
Post-transplant diabetes	1
MMF intolerance	3
Steroid witdrawal	5
Renal artery stenosis	1
Unknown	8 (5.8)

Table 3. Immunosuppressive treatment previous to monotherapy.

Treatment	*n* = 138
SRL + MMF	24
SRL + MMF + ST	1
SRL + Aza	8
SRL + Aza + ST	1
SRL + ST	47
Tac + SRL	28
CsA + SRL + ST	2
CsA + SRL	6
Aza + ST	1
ST	1
Tac + MMF	2
TaC + MMF + ST	1
Tac	2
CsA + Aza	1
CsA	13

SRL, sirolimus; MMF, mycophenolate mofetil; ST, steroids; Aza, azathioprine; Tac, tacrolimus; CsA, cyclosporine.

and at 12 months it was 543.7 ± 794 mg/24 h (Table 4). Baseline, 11% of patients had proteinuria higher than 1 g/day whereas the proportion was 20.4% at 12 months after initiation of monotherapy. Use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) increased from 30% at the beginning of monotherapy to 45% of the patients at the end of the follow-up. Two patients experienced an acute rejection after starting SRL monotherapy. This was confirmed by biopsy in one case (Banff grade I). Neither of these patients had had previous acute rejection episodes. Both cases were successfully treated with pulsed corticosteroids, and SRL-based therapy was maintained in one of them.

No significant changes in lipid profile, glycemia, or hemoglobin levels occurred (Table 5). No changes were observed for body mass index or weight. During follow-up, two patients died of cardiovascular disease (already diagnosed before they started monotherapy), One of them had discontinued monotherapy 5 months earlier because of edema. The use of statins increased from 53.8% to 66.9% ($P < 0.006$) and the use of erythropoietin from 12.5% to 18% (P = ns). Two patients died because of previously diagnosed post-transplant malignancy (one pancreatic cancer and one lung cancer). No new cardiovascular events or malignancies were diagnosed.

Table 4. Renal function, proteinuria, SRL dose, and trough levels.

	Six months before SRL monotherapy	Baseline	One month after initiation of SRL monotherapy	Six months after initiation of SRL monotherapy	Twelve months after initiation of SRL monotherapy	36 months of follow-up after initiation of SRL monotherapy
Creatinine (mg/dl)	1.62 (0.8–3.6) *n* = 138	1.7 (0.7–4.8) *n* = 138	1.66 (0.7–3.8) *n* = 138	1.69 (0.7–5.2) *n* = 130	1.72 (0.6–5.7) *n* = 125	1.73 (0.7–5.2) *n*= 56
Proteinuria (mg/24 h)	351.1 ± 927 *n* = 138	499.7 ± 1257 *n* = 138	529.7 ± 1086 *n* = 138	608.9 ± 1117 *n* = 130	543.7 ± 794 *n* = 125	634.5 ± 453 *n* = 56
MDRD (ml/min/1.73 m^2)	48.43 ± 16 *n* = 138	46.83 ± 18 *n* = 138	46.38 ± 18 *n* = 138	48.59 ± 19 *n* = 130	47.76 ± 19 *n* = 125	45.5 + 18 *n* = 56
SRL trough levels (μg/l)	NA	10.7 (4.9–24) *n* = 138	10.8 (4.5–24) *n* = 138	10.3 (3.9–25.1) *n* = 130	9.6 (3.5–22) *n* = 125	8.5 (4.1–9.7) *n* = 56
SRL dose (mg/24 h)	3.4 (1–10) *n* = 117	3.7 (1.5–9) *n* = 138	3.5 (0.4–12) *n* = 138	3.1 (0.4–10) *n* = 130	3.1 (0.4–10) *n* = 125	3.0 (0.5–5) *n* = 56

MDRD, modification of diet in renal disease; SRL, sirolimus; NA, not available.

Table 5. Hemoglobin, MCV, glycemia, and lipid profile.

	Six months before SRL monotherapy	Baseline	One month after initiation of SRL monotherapy	Sixth months after initiation of SRL monotherapy	Twelve months after initiation of SRL monotherapy	36 months of follow-up after initiation of SRL monotherapy
Hemoglobin (g/dl)	12.4 ± 1.7 *n* = 138	12.3 ± 1.8 *n* = 138	12.1 ± 1.9 *n* = 138	11.9 ± 1.7 *n* = 5130	12.4 ± 1.6 *n* = 4125	12.2 ± 1.1 *n* = 56
MCV (fl)	84 ± 6.5 *n* = 97	82.5 ± 12.9 *n* = 88	82 ± 6.6 *n* = 57	80 ± 5.2 *n* = 98	82 ± 9.4 *n* = 90	82 ± 9 *n* = 56
Glycemia (mg/dL)	94.9 ± 23.5 *n* = 107	95 ± 25 *n* = 101	96.5 ± 32 *n* = 56	96 ± 30 *n* = 104	96.5 ± 37 *n* = 96	94.3 ± 29 *n* = 56
Total cholesterol (mg/dl)	204.4 ± 41.4 *n* = 104	203.9 ± 43.4 *n* = 101	214.4 ± 39.5 *n* = 56	208 ± 41.25 *n* = 104	208.5 ± 44.4 *n* = 94	210 ± 45 *n* = 56
Triglycerides (mg/dl)	132.4 ± 108 *n* = 104	143.9 ± 166 *n* = 101	144.5 ± 186 *n* = 56	139.4 ± 109 *n* = 104	144.4 ± 98 *n* = 94	154 ± 78 *n* = 56

MCV, mean corpuscular volume; SRL, sirolimus.

Patient and graft survival after initiation of monotherapy was 97.1% and 94.2% respectively at the end of the follow-up. There were no changes in the results for blood pressure, new cardiovascular events, or malignant neoplasm.

At the end of the follow-up, 118 patients remained on monotherapy. Six patients discontinued SRL as a result of the following adverse events: anemia (one patient), edema (one), proteinuria (two), pneumonitis (one) and infection (one). Two patients discontinued because of the need of programmed surgery. Other eight patients discontinued SRL treatment for different reasons (unknown one, graft loss four, transplant glomerulopathy one, relapse of membranoproliferative glomerulonephritis one, acute rejection one). Mouth ulcers were the most common adverse event, occurring in 5.8% of patients; none of them discontinued treatment with SRL. Other adverse events included infections in 3.6% of patients (herpes zoster, pneumonia, oral herpes and urinary tract infection), dyslipidemia (1.4%), anemia (1.4%), leukopenia (0.7%), edema (0.7%) and pneumonitis (0.7%)

Discussion

In recent years, the incidence of acute rejection has decreased significantly among kidney transplant recipients [8], thus leading to an improvement in patient and graft survival at 1 year after transplantation. However, this improvement has not been observed in the long term [9], as a result of chronic allograft nephropathy [5] and death with a functioning graft attributable to cardiovascular disease [10,11] or cancer [12]. Immunosuppressive treatment, essentially CNIs and corticosteroids, also threaten long-term graft and patient survival. The adverse effects

of CNIs are well known, and include chronic allograft nephropathy [13], cardiovascular disease [10], and cancer [14]. In addition, long-term treatment with corticosteroids can result in arterial hypertension, diabetes, and dyslipidemia [15]. Over the years, different strategies, particularly discontinuation of CNIs [16–18] or corticosteroids [19], have been designed to minimize the impact of these adverse effects. However, there is no general consensus on the best long-term strategy.

The safety profile, absence of nephrotoxicity, and antiproliferative effect [20] of SRL make it a good therapeutic option for maintenance treatment in the long term. Diekmann *et al.* [21] published a pilot experience on SRL monotherapy. This study had some limitations, such as a small sample size and a short follow-up. In the present study, data from 138 Spanish and Portuguese renal transplant patients from different centers were included. Only two out of the 138 patients whom we analysed experienced acute rejection, and both were managed using pulsed corticosteroids; one of them continued maintenance SRL therapy, and the other changed to another immunosuppressive regimen. The other patients presented good renal function throughout follow-up. We are not able to ensure that baseline GFR or other factors influenced outcomes. Other previous studies demonstrated that baseline proteinuria and GFR are predictors of outcomes in patients converted to a SRL-based regimen [22–24].

A slight increase in proteinuria values was observed, probably because most of these patients were converted from CNIs to SRL. Trough levels were very stable during the follow-up. The safety profile of SRL was good, as seen in relatively low incidence of dropouts and SRL-associated complications. Our study has some limitations. This is a retrospective study, in which initiation of monotherapy was done in different ways, and for different reasons. Nevertheless, despite our methodological limitations, the large number of patients collected for this analysis enhances its value.

Finally, mammalian target of rapamycin (mTOR) inhibitors can also play a role in the prevention of cancer, and their effect during the post-transplantation period is well known. In this sense, data from the Rapamune Maintenance Regimen Study confirmed that therapy with SRL was associated with a lower incidence of malignancy [18]. Recently, the CONVERT study published by Schena *et al.* [22] showed that conversion from CNIs to SRL resulted in a significant decrease in the incidence of cancer. It is known that the m-TOR pathway is activated in many cancer-related processes [25] and there is increasing evidence that mTOR inhibitors play an important role in the treatment of cancer. Therefore, SRL monotherapy and withdrawal of CNIs could lead to a lower incidence of cancer in the long term.

In conclusion, the results of our retrospective study show that SRL monotherapy is useful for prevention of late acute rejection, preservation of renal function, and allows a good safety profile. Moreover, it has a positive impact on cardiovascular morbidity and mortality and in cancer. SRL monotherapy can be a therapeutic alternative in selected renal transplant patients, resulting in improved renal function and better patient survival.

Authorship

JRP participated in data collection and paper writing. EMAT participated in data collection and paper writing. AF collected data and helped in paper writing. JMM collected data and helped in paper writing. JCR collected data. FD participated in paper writing. GA wrote the paper. JMC designed the study, analysed data and participated in paper wiriting.

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