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ORIGINAL ARTICLE

Comparative effects of sirolimus and cyclosporin on conduit arteries endothelial function in kidney recipients

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Summary

This study attempted to establish whether a calcineurin inhibitor (CNI)-free immunosuppressant regimen based on sirolimus (SRL) is associated with a preservation of conduit arteries endothelial function in kidney recipients or not. Twenty-nine kidney recipients were randomized to receive since transplantation SRL ($n = 15$) or cyclosporin A (CsA, $n = 14$) associated with mycophenolate mofetil (MMF) and steroids (6 months) in a parallel prospective study. Systolic, diastolic blood pressures, glomerular filtration rate (GFR) and radial artery flow-mediated dilatation (FMD) induced by postischaemic hyperaemia were assessed in a blind manner at one (M1) and 7 months (M7) after transplantation. Endothelium-independent dilatation was assessed by glyceryl trinitrate spray. There was no difference between the groups for all vascular parameters at M1. At M7, systolic blood pressure was lower (SRL: 119 ± 3 vs. CsA: 138 ± 4 mmHg, $P < 0.05$) and FMD was higher in SRL compared with CsA (SRL: 13.1 ± 0.9 vs. CsA: 9.9 ± 0.9%, $P < 0.05$) without any difference for hyperaemia, endothelium-independent dilatation and GFR (SRL: 66.7 ± 1.05 vs. CsA: 67.5 ± 1.22 ml/min). Our results demonstrate that a CNI-free regimen based on SRL and MMF prevents conduit artery endothelial dysfunction compared with CsA and MMF in kidney recipients suggesting a beneficial arterial wall effect that may also contribute to the decrease in systolic blood pressure.

Introduction

Cardiovascular diseases are the leading cause of premature death in renal transplant recipients [1,2]. Arterial endothelial dysfunction is an early event in the development of these diseases and is recognized as an independent predictor of adverse events in high-risk populations [3]. Transplant patients have impaired endothelial function affecting peripheral resistance and conduit arteries, as defined for the latter vessels by the decrease in the magnitude of the nitric oxide (NO)-dependent, flow-mediated dilatation (FMD) in response to postischaemic hyperaemia [4–7]. Calcineurin inhibitors (CNI) as cyclosporin A (CsA) have been suggested to play a role in the pathogenesis of this endothelial dysfunction [8–10]. Indeed, their long-term administration may be associated with the decrease in endothelium-derived NO availability, intrarenal vasoconstriction and stimulation of fibrogenic cytokines [11–19] that are involved in CNI-induced hypertension and chronic allograft dysfunction [20]. More recently, new CNI agents and dose minimization strategies have been proposed with a better tolerance and efficacy on renal function, but their effects on endothelial function remain a matter of debate [7,21–26]. Another approach consisted in the development of immunosuppressant regimens that spare or avoid CNI, such as those based on the mammalian target of rapamycin (mTOR) inhibitor, sirolimus (SRL) [20,27]. Its administration in

animals and humans is accompanied by beneficial vascular effects dominated by the decrease in arterial neo-intimal proliferation and allograft vasculopathy, although some *in vitro* experiments have also reported an oxidant effect that may compromise the endothelial NO availability [17,18,27–32]. In transplant patients, SRL is less frequently associated with the onset of hypertension, and its nephrotoxicity has also been demonstrated to be lesser than that of CNI when used at standard or lower doses [33–35]. However, to date, there are no available results concerning the endothelial function of peripheral conduit arteries in transplant patients treated with SRL. The aim of the study was thus to compare, in a randomized prospective study, the FMD of the radial artery in de novo renal transplant recipients receiving an immunosuppressant regimen based on standard doses of CsA or SRL since the transplantation.

Methods

Population

This study reports a subgroup of patients from a French multi-centre randomized prospective study designed to evaluate the tolerance and efficacy of a CNI-free regimen [34]. Twenty-nine de novo kidney transplant recipients from three centres participated to this observer-blinded study of endothelial function. None had a pretransplant exposure to CNI. All received a kidney transplant from a deceased donor. Exclusion criteria consisted of recipient age <18 years old, cold ischaemia time ≥36 h, donor age ≥65 years, graft from a living donor or donation after cardiac death, panel reactive antibodies of more than 80%, multiple organ transplants, any chronic disease requiring steroid therapy or history of cardiovascular events (e.g., stroke, coronary artery disease, peripheral vascular disease). Patients were randomly assigned prior to transplantation to receive either SRL-based therapy (Rapamune®; Wyeth, Paris-La Défense, France) or CsA-based therapy (Neoral®; Novartis, Rueil-Malmaison, France). The study complies with the Declaration of Helsinki and was approved by the relevant Committee for the Protection of Persons engaged in biomedical research. All participants gave written informed consent.

Study protocol

Patients were investigated at one (M1) and seven (M7) months after kidney transplantation. Both treatment arms received antithymocyte globulins during 5 days (1.5 mg/kg/day, Thymoglobulin®; Genzyme, Saint-Germain en Laye, France), mycophenolate mofetil 2 g/day (MMF, Cellcept®; Roche, Neuilly sur Seine, France) from day 0 and then adapted according to clinical events and a 6-month course of steroids with a progressive dose reduction and a complete discontinuation after at least the 6th month. In addition, a standardized protocol for the treatment of hypertension (<130/80 mmHg) and hyperlipemia (LDL cholesterol <1 g/l) was suggested.

In the CNI-free group, patients began SRL treatment within 48 h after transplantation with a loading dose of 15 mg/day for 2 days followed by a dose of 10 mg/day adjusted to maintain a trough whole-blood concentration between 10 and 15 ng/ml (HPLC-MS). In the CNI group, patients began CsA within 48 h after transplantation at 6–8 mg/kg/day to maintain during the following 3 months a trough whole-blood concentration (C0) between 150 and 250 ng/ml, which was reduced to between 75 and 150 ng/ml from the 4th month onwards (monoclonal TDX).

Instrumentation

During each experiment day, patients arrived at the laboratory at 9 AM, 2 h after a light breakfast. Measurements were taken while they were in a supine position in a quiet, air-conditioned room (22–24 °C). Brachial artery blood pressure and heart rate were measured by means of a brachial cuff oscillometric device (Dinamap 8103, Critikon, Creteil, France). Radial artery internal diameter, blood flow and digital arterial pressure were continuously measured using a high-precision echo-tracking device (NIUS 02, Asulab, Neuchâtel, Switzerland) coupled to a Doppler system (Doptek, Deltex, Chichester, UK) and a finger photoplethysmograph (Finapres System, Ohmeda, Englewood, CO, USA) as previously described [36,37]. Furthermore, graft function was assessed by an estimated glomerular filtration rate (GFR) calculated by using Nankivell formula [34].

Endothelium-dependent flow-mediated dilatation

Arterial blood pressure and heart rate were measured at baseline after C0 determination and 30 min resting. Radial artery blood flow and diameter were recorded for 5 min. Then, an arterial occlusion cuff placed at the wrist (i.e., distal to the site of radial artery measurements) was inflated for 10 min at least 50 mmHg above systolic blood pressure and was deflated to allow reactive hyperaemia [36–38]. All parameters were recorded continuously throughout cuff inflation and during hyperaemia. Baseline and peak measurements represented mean values obtained during 15 and 3 cardiac cycles, respectively. The continuous measurement of radial artery parameters allows to precisely estimate the maximal values of diameter and flow occurring after cuff deflation. Thus, radial artery FMD was calculated as the percent change of radial

artery diameter in response to postischaemic hyperaemia with the peak diameter after cuff deflation and the basal diameter before cuff inflation [37]. Moreover, because the modifications in the hyperaemic stimulus influence the magnitude of radial artery FMD, we also measured the characteristical parameters of this stimulus: the peak flow representing the maximal value of flow after cuff deflation and the duration of the increase in flow ($t_{1/2}$: time elapsing between peak hyperaemia and return to 50% of this peak) [37,38]. By using this procedure, according to a standard deviation of 55 μm for the mean difference between repeated measures, 13 patients per group enabled a single observer to detect a difference in FMD of 63 μm with a 80% power at the two-sided 5% significance level.

Endothelium-independent dilatation

After radial artery diameter and flow had returned to baseline, the patients received sublingual glyceryl trinitrate (GTN: 0.3 mg) to evaluate the radial artery endothelium-independent dilatation.

Statistics

Results are expressed as mean ± SEM. The differences between groups were analysed for qualitative variables by chi-square test and for quantitative variables by standard one-way ANOVA and Kruskal–Wallis nonparametric test. In addition, the analysis of the radial artery FMD was repeated by using ANCOVA analysis with pertinent variables as covariates. A value of $P < 0.05$ was considered statistically significant.

Results

Patients

Twenty-nine patients were enrolled in the study, 14 in the CsA group and 15 in the SRL group. At the M1 visit, all patients continued the study. There was no significant difference between groups for demographic parameters, donor age, cold ischaemia time and HLA mismatches (Table 1). During the next follow-up period, two patients discontinued the study in the SRL group after withdrawing their consent and a patient committed suicide in the CsA group before the M7 visit.

Table 1. Demographic characteristics of the patients at randomization.

Parameters	CsA (n = 14)	SRL (n = 15)
Age (years)	47 ± 4	50 ± 2
Gender (M/F)	10/4	9/6
Body mass index (kg/m^2)	22.8 ± 1.0	24.7 ± 1.1
Duration of dialysis (months)	24 ± 5	22 ± 5
Type of dialysis (HD/peritoneal)	2/12	6/9
Hypertension (n, %)	11 (79)	11 (73)
Dyslipidaemia (n, %)	2 (14)	6 (40)
Smoker (current/stop/never)	1/4/9	1/4/10
Type 2 diabetes mellitus (n, %)	1 (7)	1 (7)
Donor age (years)	45 ± 4	41 ± 4
Cold ischaemia time (h)	20 ± 1	21 ± 1
HLA mismatches	3.8 ± 0.3	4.4 ± 0.2

Values are mean ± SEM.
CsA, cyclosporin A; SRL, sirolimus; M, male; F, female; HD, haemodialysis; HLA, human leucocyte antigens.

Immunosuppressive regimen

Trough levels of SRL and cyclosporin remained in the targeted ranges at M1 (SRL: 11.2 ± 1.1 ng/ml, CsA: 171 ± 9 ng/ml) and M7 (SRL: 14.5 ± 2.1 ng/ml, CsA: 139 ± 10 ng/ml) with no significant difference between groups for the mean daily doses of MMF at M1 (SRL: 1.93 ± 0.07 g/day of MMF vs. CsA: 2.00 ± 0.00 g/day of MMF) and M7 (SRL: 1.79 ± 0.10 g/day of MMF vs. CsA: 1.88 ± 0.09 g/day of MMF). At the M7 visit, steroid therapy was withdrawn in all the study patients for 3 weeks with no difference between groups for the mean duration of treatment (SRL: 27 ± 1 weeks, CsA: 28 ± 1 weeks). The number of acute rejection episodes confirmed by renal graft biopsy was three in the SRL group (grade 1) and two in the cyclosporin group (grade 1) with no steroid-resistant episode.

Concomitant medications

At the M1 visit, there was no significant difference between groups as regards the number of patients receiving antihypertensive (SRL: 6/15 vs. CsA: 7/14) or lipid lowering treatments, the latter mainly consisting of HMG-CoA reductase inhibitors (SRL: 4/15 vs. CsA: 2/14). At the M7 visit, the number of patients receiving antihypertensive medications was similar in both groups (SRL: 9/13 vs. CsA: 10/13) but, compared with CsA, more patients were on monotherapy in the SRL group (SRL: 7/9 vs. CsA: 2/10, $P < 0.05$), which consisted of beta blockers. In addition, there was no difference between groups as regards the number of patients treated with angiotensin converting enzyme inhibitors/receptor blockers (SRL: 1/13 vs. CsA: 2/13). Moreover, there was still no significant difference found between groups concerning HMG-CoA reductase inhibitor treatments (SRL: 10/13 vs. CsA: 6/13).

Systemic haemodynamics and biological parameters

There was no significant difference between groups at the M1 visit for systolic, diastolic blood pressures and heart

Table 2. Haemodynamics and biological parameters.

	M1		M7	
Parameters	CsA (n = 14)	SRL (n = 15)	CsA (n = 13)	SRL (n = 13)
Systolic blood pressure (mmHg)	138 ± 4	136 ± 2	138 ± 4	119 ± 3*†
Diastolic blood pressure (mmHg)	76 ± 3	78 ± 2	70 ± 3†	70 ± 2†
Heart rate (bpm)	84 ± 5	86 ± 3	85 ± 3	85 ± 4
GFR (ml/min)	66 ± 5	64 ± 6	68 ± 3	67 ± 5
Haemoglobin (g/dl)	12.7 ± 1.0	12.1 ± 1.1	13.5 ± 1.1	13.4 ± 0.8
Plasma glucose (g/l)	1.16 ± 0.01	1.00 ± 0.07	0.95 ± 0.04	1.04 ± 0.07
Total cholesterol (g/l)	2.29 ± 0.12	2.82 ± 0.13*	1.74 ± 0.16†	2.04 ± 0.19*†
LDL cholesterol (g/l)	1.44 ± 0.11	1.65 ± 0.15	1.11 ± 0.12†	1.18 ± 0.12†
HDL cholesterol (g/l)	0.55 ± 0.03	0.72 ± 0.09	0.46 ± 0.06†	0.53 ± 0.09†
Triglycerides (g/l)	1.38 ± 0.15	1.96 ± 0.29*	1.15 ± 0.14	1.49 ± 0.19*
Basal radial artery diameter (mm)	2.37 ± 0.13	2.40 ± 0.10	2.39 ± 0.13	2.33 ± 0.10
Basal radial artery flow (ml/min)	12 ± 3	19 ± 4	12 ± 2	16 ± 5

Values are mean ± SEM.
*$P < 0.05$ vs. CsA, †$P < 0.05$ vs. M1.
M1, month 1 visit; M7, month 7 visit; CsA, cyclosporin A; SRL, sirolimus; GFR, glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein.

rate (Table 2). In addition, GFR, plasma haemoglobin, glucose, LDL and HDL cholesterol did not differ significantly between groups, but total cholesterol and triglycerides were higher in the SRL group compared with CsA group ($P < 0.05$). At the M7 visit, diastolic blood pressure decreased similarly in the two groups ($P < 0.05$), while the decrease in systolic blood pressure ($P < 0.05$) was more marked in the SRL group compared with CsA group ($P < 0.05$). There was no significant change in the heart rate, GFR, plasma haemoglobin and glucose. Total, LDL and HDL plasma cholesterols decreased similarly in the two treatment groups (all $P < 0.05$) with no significant change in triglycerides. Total cholesterol and triglycerides thus remained higher in the SRL group compared with CsA group at M7 ($P < 0.05$).

Flow-mediated dilatation and GTN-dependent dilatation

There was no significant difference between groups at the M1 visit for radial artery diameter and flow measured at baseline before cuff inflation (Table 2). During reactive hyperaemia, peak flow and $t_{1/2}$ were similar in CsA and SRL groups (Fig. 1 top). The radial artery FMD was also similar between groups at M1 (Fig. 2).

At the M7 visit, there was no significant change in baseline radial artery diameter and flow compared with the M1 visit, and thus there was no difference between groups for these parameters (Table 2). In the same manner, the peak flow and $t_{1/2}$ measured during reactive hyperaemia were similar in the CsA and SRL groups demonstrating the absence of a difference between groups in the flow stimulus of FMD (Fig. 1 bottom). In contrast, the radial artery FMD, i.e., the endothelium-dependent conduit artery vasomotor function, was lower in the CsA group compared with SRL at the M7 visit (Fig. 2, $P < 0.01$). This difference between groups in FMD at M7 persisted after adjustment for systolic blood pressure, pulse pressure, GFR, peak blood flow and $t_{1/2}$, plasma lipids or the presence of lipid lowering treatments (all $P < 0.05$). In addition, when comparing SRL and CsA-treated patients matched for systolic (SRL 125 ± 3 vs. CsA 130 ± 3 mmHg) and diastolic blood pressures (SRL 71 ± 3 vs. CsA 69 ± 3 mmHg) at M7 ($n = 8$ in each group), the difference in radial artery FMD remained significant (SRL 14.2 ± 1.1 vs. CsA 9.2 ± 1.1%, $P < 0.05$).

The radial artery endothelium-independent dilatation in response to GTN was similar in the two groups at the M1 and M7 visits demonstrating the absence of a difference between groups in the ability of the vascular smooth muscle cells to relax in response to exogenous NO (Fig. 3).

Discussion

The main finding of this randomized prospective study was that a CNI-free immunosuppressant regimen based on SRL prevents peripheral conduit artery endothelial dysfunction compared with CsA in kidney recipients.

These results were obtained from the radial artery, a model of peripheral conduit artery [37,38], in middle-age patients, first transplant population with a short duration on dialysis and no previous history of cardiovascular diseases. Therefore, this population showed limited confounding diseases on endothelial function, although

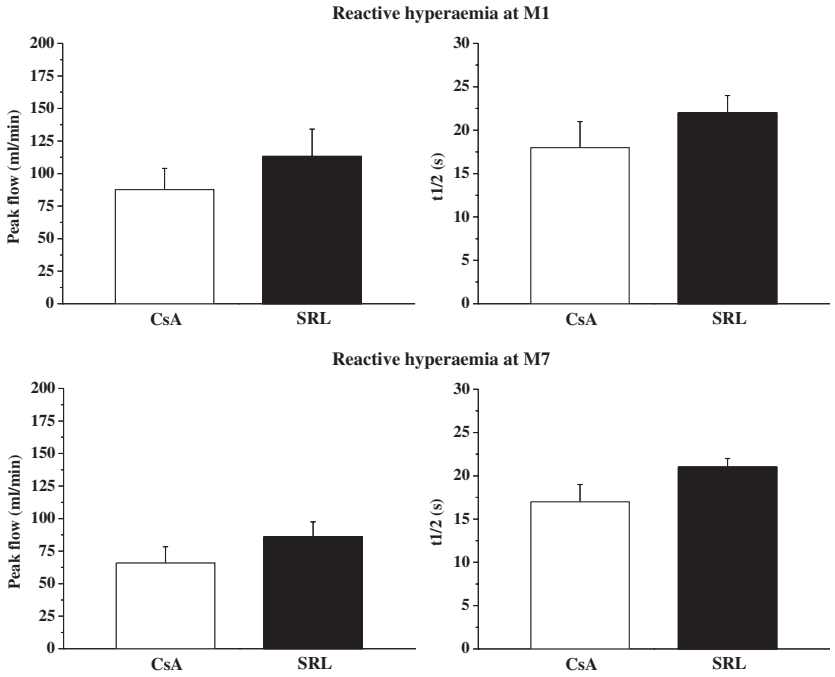

Figure 1 Bar graphs show the maximal increase in radial artery blood flow and the duration of the increase in flow ($t_{1/2}$: time to return to 50% of peak hyperaemia) during reactive hyperaemia at the M1 (up) and M7 (down) visits obtained in kidney recipients treated with cyclosporin A (open bars) and sirolimus (filled bars). These parameters were similar in the two groups at the M1 and M7 visits demonstrating the absence of difference between groups in the magnitude and duration of the flow stimulus during postischaemic hyperaemia. Values are mean ± SEM.

significant cardiovascular risk factors were present. In all patients, FMD was evaluated by the continuous and simultaneous measurement of radial artery diameter and blood flow velocity throughout the procedure [36,37]. This method was chosen to characterize accurately the modification of the vasomotor endothelial function after treatment with particular attention focused on changes in the hyperaemic stimulus, by determining the peak flow and the duration of the increase in flow that are major determinants of FMD [37,38]. Furthermore, immunosuppressant regimens were chronically administered and their vascular effects were, for the first time to our knowledge, compared according to a randomized parallel prospective study design with a follow-up duration period of 6 months and a blind evaluation of vascular parameters. Moreover, after a similar immunosuppressant induction, patients were allocated at an early stage to CsA plus MMF or SRL plus MMF with no prior confounding treatment with CsA. Plasma values of CsA and SRL were monitored during the study and confirmed that the therapeutical goals were reached and maintained. In addition, all patients received a parallel 6-month course of steroids with a similar drug withdrawal between groups, 1 month before the second investigation visit. Furthermore, standardized protocols were proposed concerning the concomitant treatments for hypertension and hyperlipemia to reduce their potential impact on vascular function.

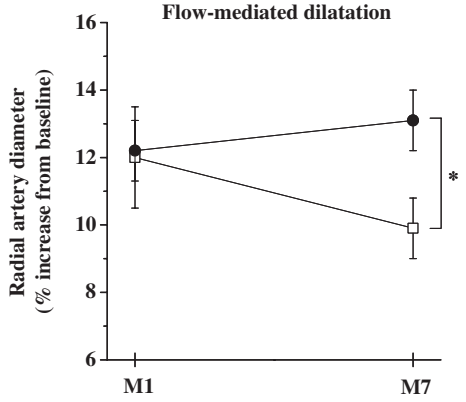

Figure 2 Flow-mediated dilatation (% increase in radial artery diameter from baseline) obtained at the M1 and M7 visits in kidney recipients treated with cyclosporin A (CsA) (□) and sirolimus (SRL) (●). The radial artery flow-mediated dilatation was similar in the two groups at the M1 visit but was lower at M7 visit in the CsA group compared with SRL demonstrating a lower endothelium-dependent conduit artery vasomotor function in this group. Values are mean ± SEM. *$P < 0.05$ vs. CsA.

In this context, at the M1 visit, there was no significant difference between groups for all the measured parameters demonstrating the homogeneity of the population at this initial visit except for the total cholesterol and plasma triglycerides that were higher after SRL than CsA as expected because of the hyperlipemic effect of mTOR inhibitors [39]. Furthermore, FMD was of higher magnitude than usually reported in haemodialysis patients [4,36]. Whether the anti-inflammatory effect of glucocorticoids administered since the transplantation may have enhanced FMD and masked a possible negative influence

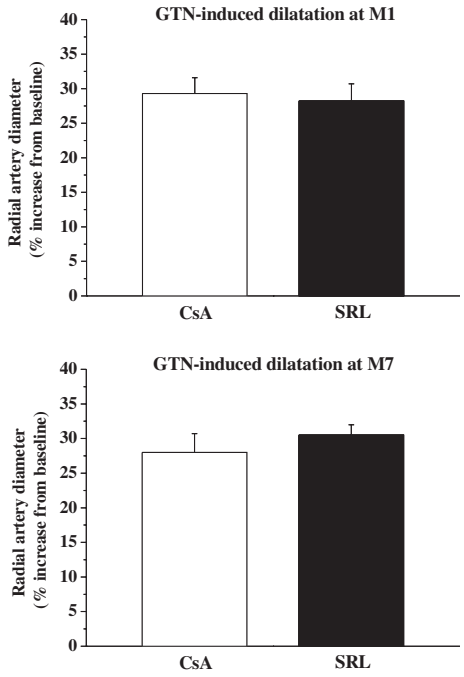

Figure 3 Endothelium-independent, glyceryl trinitrate (GTN)-induced dilatation (% increase in radial artery diameter from baseline) obtained at the M1 and M7 visits in kidney recipients treated with cyclosporin A (open bars) and sirolimus (filled bars). Values are mean ± SEM. The radial artery response to GTN was similar in the two groups at the M1 and M7 visits demonstrating the absence of difference between groups in the ability of the vascular smooth muscle cells to relax in response to exogenous NO.

of 1 month CsA administration on this response remains unknown. However, this appears unlikely because, although glucocorticoids can increase endothelial-derived relaxing factors availability through nontranscriptional mechanisms, their repeated administration in humans has been associated in most studies with endothelial dysfunction and oxidative stress [40–44]. In contrast, the magnitude of the endothelial response in both groups may be rather related to the improvement in GFR after successful transplantation, which appears to play a key role in the early maintenance of endothelial function [23,45].

At the M7 visit, diastolic blood pressure decreased similarly in the two groups probably as a result of the persistent improvement in renal function, the steroids withdrawal and the adjustment of the antihypertensive treatment. Of interest, this result was more frequently obtained by using a polytherapy in the CsA group compared with SRL, as expected from the hypertensive effect of CNI [19,20]. However, systolic blood pressure decreased after SRL but not after CsA thus, suggesting a beneficial effect of the SRL-based immunosuppressive regimen on the conduit arteries mechanical properties. Although we did not directly evaluate the mechanics of these arteries, this effect could have resulted from the decrease in conduit artery stiffness, a major vascular determinant of systolic pressure [46,47]. As regards the radial artery parameters, the FMD was lower after CsA compared with SRL, whereas baseline values of diameter and flow and postischaemic hyperaemia did not differ between groups. This decreased FMD was thus not explained by the differences between groups in the hyperaemic stimulus. In addition, it was not related to a modification in vascular smooth muscle cell sensitivity to NO as GTN-induced dilatation was similar between groups. Moreover, this effect did not result from a difference in the number of acute rejection episodes, which was previously reported to influence endothelial function [48]. Therefore, this result demonstrates that this SRL-based regimen allows to maintain the endothelial vasomotor function in contrast to CsA after chronic administration in kidney recipients. In addition, because the difference in FMD between groups persisted after adjustment for the main confounding factors, i.e. GFR, systolic and pulse pressures and plasma lipids or the presence of lipid-lowering treatment [5,24,49], this result strongly suggests a beneficial arterial wall effect of SRL-based regimen that may also have contributed to the decrease in systolic blood pressure. To our knowledge, this beneficial effect on peripheral artery endothelial function has never been previously reported before but was suggested from animal experiments [28] and more recently in humans, by the attenuation in the progression of coronary vasculopathy in cardiac transplants after conversion from CsA to SRL [29]. Similarly, a recent open study showed higher epicardial coronary dilatation to acetylcholine in cardiac transplant patients receiving SRL compared with CNI, which suggests a better endothelial function in these patients, although observed with a concomitant enhancement of vascular smooth muscle cell reactivity to GTN [50]. Moreover, Saurina *et al.* reported a decrease in plasma endothelin-1, a marker of endothelial activation in kidney recipients with chronic allograft dysfunction after conversion from CsA to SRL [18]. Furthermore, although the high doses of SRL, used to prevent early rejection episodes in absence of CsA, were associated with adverse events in the tolerance and kidney efficacy study [34], we did not observe an alteration in the endothelial function of conduit arteries under our experimental conditions but rather a prevention of the decrease in FMD compared with the CNI group. In contrast, these beneficial effects were not observed after CsA withdrawal in the brachial artery [6] nor after conversion from CsA to azathioprine in forearm resistance arteries [45], despite a blood pressure decrease and a better lipid profile. However, these apparent discrepancies

may be explained by the differences in study populations. In particular, the kidney recipients previously explored compared with our patients were transplanted and exposed to CsA since several years and exhibited a severe endothelial dysfunction at inclusion, which could be irreversible even after a change in treatment [6,45].

As regards the mechanisms involved in our study, the prevention of the endothelial dysfunction in the SRL group may result from the absence of endothelial CsA related toxicity [8–19], as previously shown at the arteriolar level in azathioprine-treated patients [8]. Nevertheless, the doses of CsA we used were not particularly high and were reduced after the 4th month of transplantation (C0 M7: 139 ± 10 ng/ml) [34,35]. Therefore, because CsA is not always associated with endothelial dysfunction [5,51,52] and conversion to CNI-free regimen may be insufficient to restore endothelial function [6,45], additional mechanisms may be involved. This includes a direct beneficial effect of SRL on vascular endothelium [17,28], although controversial [30–32], or a vascular synergistic effect of SRL and MMF preventing endothelin-1 release and oxidative stress [53,54]. This latter mechanism has been described for SRL and MMF and may be more effective with SRL than with CsA when administered at standard doses [17,53,54]. This hypothesis is supported by the fact that exposure to MMF has probably been more important in the SRL group than in the CsA group because CsA increases the biliary excretion of the active metabolite of MMF [55]. In the same manner, whether such difference in FMD between groups may be observed when comparing SRL with new CNI agents as tacrolimus, especially after doses minimization, remains to be determined [21,26]. This is of interest because such strategies are increasingly used, and no studies [7,23–25] except one [22] demonstrated a significant difference between the effect of CsA and tacrolimus on conduit arteries vasomotor function, whereas no study comparing tacrolimus and SRL has been performed at this level. Finally, because endothelial dysfunction is one of the main cardiovascular risk factor after transplantation and although the study includes a small number of patients, our results may be useful for the prevention and management of cardiovascular diseases in kidney recipients.

In conclusion, this study demonstrates that a CNI-free immunosuppressant regimen based on SRL and MMF prevents conduit arteries endothelial dysfunction in comparison to CsA and MMF in kidney recipients. This could be related to a direct arterial wall beneficial effect of this immunosuppressant regimen that may have also contributed to the decrease in systolic blood pressure. This beneficial effect of SRL associated with MMF could be useful to prevent the development of cardiovascular complications after kidney transplantation while preserving renal function.

Authorship

RJ: conceived and designed the research, interpreted the data and drafted the manuscript. IE: conceived and designed the research, acquired the data and made critical revision of the manuscript. MI, BHL and SB: acquired the data. JB: interpreted the data and made critical revision of the manuscript. YL: conceived and designed the research and made critical revision of the manuscript. CT: handled funding and supervision and made critical revision of the manuscript. MG: conceived the research, handled funding and supervision and made critical revision of the manuscript.

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