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ORIGINAL ARTICLE

Conversion to tacrolimus once-daily from ciclosporin in stable kidney transplant recipients: a multicenter study

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Summary

This 24-week, open, single-arm, prospective, multicenter study evaluated the effects of conversion from ciclosporin to Tacrolimus QD in adult kidney transplant patients. Stable patients receiving ciclosporin were converted to Tacrolimus QD at 0.1 mg/kg/day. Relative change in renal function (primary endpoint) was assessed using estimated creatinine clearance (eCrCl) with a noninferiority margin set at −10%. A total of 346 patients were enrolled; and 301 patients were treated per protocol (PPS) in the hyperlipidemia ($n = 42$), hypertrichosis ($n = 106$), hypertension ($n = 77$) and gingival hyperplasia ($n = 76$) groups. Relative change in eCrCl was −0.6% in all PPS patients (95% CI, −2.2; 0.9) and −5.3% in the hyperlipidemia (CI, −9.59; −0.97), 0.9% in the hypertrichosis (CI, −2.59; 4.45), −0.1% in the hypertension (CI, −3.8; 3.68), and −1% in the gingival hyperplasia groups (CI, −4.63; 2.65) (PPS), meeting noninferiority criteria. There was no acute rejection. Decreases in serum lipids and blood pressure were moderate but without meaningful change in the number of treatment medications. Substantial decreases in severity of ciclosporin-related cosmetic side effects were evident from investigator and patient self-report of symptoms. Renal function remained stable after conversion to Tacrolimus QD. The effect of conversion on cardiovascular parameters was not clinically meaningful, however, marked improvement in ciclosporin-related cosmetic side effects was observed.

(ClinicalTrials.gov number: NCT00481481)

Introduction

Conversion from ciclosporin to tacrolimus may be initiated not only because of refractory rejection, but also to reduce drug-related secondary clinical effects and undesirable cosmetic side effects.

Randomized studies have shown a significant reduction of triglycerides [1] and significantly lower incidences of new onset cardiac conditions and hyperlipidemia [2] at 5 years in patients converted to tacrolimus versus patients remaining on ciclosporin. Cardiovascular risk factors and Framingham risk scores improved at 6 months [3] with a sustained reduction in blood pressure (BP) and a sustained improvement in serum lipids at 2 years [4] in patients converted to tacrolimus versus patients remaining on ciclosporin. In a nonrandomized study, lowered

levels of total cholesterol and LDL cholesterol were identified as the most important effects of conversion at 6 months in patients with hyperlipidemia [5].

Ciclosporin-induced gingival hyperplasia and hypertrichosis may severely affect patient well being. The switch from ciclosporin to tacrolimus provided a significant decrease in the occurrence of symptoms and reports of symptom distress at 12 and 24 months [4]. In a 6-month prospective, multicenter study in which conversion was initiated because of ciclosporin side effects, strong or complete resolution of gingival hyperplasia was reported in 73% of patients and strong or complete resolution of hypertrichosis in 72% [6]. Ciclosporin-related cosmetic side effects have improved as early as 4 months after conversion [7,8].

Both tacrolimus and ciclosporin are associated with compromised renal function when used longer term. There is, however, evidence of stabilized [6] and improved [2,9–11] renal function following conversion to tacrolimus.

A prolonged-release tacrolimus formulation (Advagraf®, Astellas Pharma Europe Ltd, Staines, UK; referred to as Tacrolimus QD) allows once-daily dosing with the potential for improving treatment adherence. Clinical and pharmacokinetic data indicate similar safety and efficacy of Tacrolimus QD and twice-daily tacrolimus [12].

The effect of conversion from ciclosporin to Tacrolimus QD has not been evaluated. The primary objective of this prospective multicenter study therefore was to evaluate changes in renal function after 24 weeks following conversion from a ciclosporin-based to a Tacrolimus QD-based immunosuppressive regimen in stable kidney transplant patients. Secondary study objectives included the assessment of the safety profile of Tacrolimus QD and the effect of conversion on ciclosporin-related cosmetic side effects and cardiovascular risk parameters.

Patients and methods

Study design and patient population

The CONverting Ciclosporin to FK506E (Tacrolimus QD) in Renal TransplantatiOn (CONCERTO) clinical trial was a 24-week, multicenter, single-arm, nonrandomized, nonblinded study.

Stable adult kidney allograft recipients who were ≥12 months post-transplantation, had been treated with ciclosporin and met the inclusion criteria were eligible for enrollment. Patients must have been maintained on ciclosporin since the last transplantation and no changes had been made to either the ciclosporin dose or the immunosuppression regimen in the 4 weeks prior to enrollment. Eligible patients had a baseline serum creatinine <200 μmol/L and at least one of the following conditions: hyperlipidemia (total cholesterol >5.7 mmol/L [>220 mg/dL] despite treatment); hypertrichosis/hirsutism which required therapeutic intervention; hypertension stages I to III (systolic BP >140 mmHg and/or diastolic BP >90 mmHg despite treatment); gingival hyperplasia which required therapeutic intervention. Hypertrichosis and gingival hyperplasia are known cosmetic side effects of ciclosporin and there is evidence that total cholesterol and triglyceride levels are higher with ciclosporin than with tacrolimus [13–16].

Each patient meeting the inclusion criteria received a patient number and was enrolled in one of the four study groups (hyperlipidemia, hypertrichosis, hypertension, and gingival hyperplasia) according to the indication for conversion. Patients with more than one indication for conversion were allocated according to the following order: (i) hyperlipidemia, (ii) hypertrichosis, (iii) hypertension, and (iv) gingival hyperplasia. This order was specified in the statistical analysis plan prior to data analysis.

Immunosuppression

The initial dose of Tacrolimus QD was 0.1 mg/kg/day administered 12 h after the last ciclosporin dose. Tacrolimus blood concentration was monitored and dose adjustments made to reach a blood concentration of 10 ng/ml (range 5–15 ng/ml) for the first 4 weeks then progressively reduced to a target of 7 ng/ml (range 4–10 ng/ml) until week 24. Targeted ranges for tacrolimus blood concentration follow manufacturer's dosing recommendations for conversion as approved by regulatory authorities.

Study endpoints

Twenty-four weeks of treatment with Tacrolimus QD was considered an appropriate study duration to assess a response to a change in treatment. The primary endpoint was the relative change (in percentage) in estimated creatinine clearance (eCrCl) (Cockcroft-Gault method [17]) between baseline and week 24. The Modification of Diet in Renal Disease formula (MDRD) [18] was also used to assess renal function. Considering normal fluctuations in repeated measurements of renal function during which a change of 10 ml/min in eCrCl can be regarded as clinically meaningful, a relative change of less than 10% (6 ml/min from the population average) was considered appropriate to test for noninferiority.

The secondary endpoints assessed were absolute change in eCrCl (ml/min) between baseline and each visit until week 24; change in mean serum lipid levels (total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol) and change in the number of lipid-lowering medications

between baseline and week 24; change in mean arterial BP and change in the number of antihypertensive medications between baseline and week 24; investigator rating of severity of patient clinical status and the severity of ciclosporin-related side effects at baseline and week 24; patient self-report of severity of ciclosporin-related side effects at baseline and week 24 for patients with hypertrichosis and with gingival hyperplasia; frequency of biopsy-proven acute rejection (local evaluation using the Banff 97 classification system [19]).

Investigators descriptively rated the clinical status of patients and the severity of ciclosporin-related side effects using a five-point scale (not at all severe, barely severe, moderately severe, strongly severe, very strongly severe). There was no blinding of treatment group allocation. Hypertrichosis was assessed according to the Ferriman-Gallwey-Index [20]. Patients with hypertrichosis and gingival hyperplasia rated the severity of ciclosporin-related cosmetic side effects at week 24 or at study withdrawal compared to that at baseline also using a five-point scale (not at all severe, barely severe, moderately severe, strongly severe, very strongly severe).

The following safety endpoints were assessed: patient and graft survival; graft loss (defined as re-transplantation, nephrectomy, death, or dialysis ongoing at end of study); incidence of treatment-emergent adverse events; clinical laboratory (hematology, biochemistry, urinalysis); and vital signs. Patients were monitored for adverse events up to 28 days after the last dose of Tacrolimus QD.

Patients were assessed at each of five scheduled visits for possible graft rejection and adverse events. Vital signs and laboratory assessments were conducted at baseline and weeks 2, 4, and 24. Investigator and patient rating of ciclosporin-related side effects was made at baseline and at week 24.

Statistical analyses

A previous conversion study [6] was used as reference for the sample size estimation. A total of 380 patients were to be included in the trial: enrollment was stopped earlier than planned because of difficulty enrolling patients into some of the study groups.

The population treated per protocol (PPS) was used for the analysis of the primary endpoint and was defined as all patients from the full analysis set (FAS) not prematurely withdrawn and without a major protocol violation including violation of relevant inclusion/exclusion criteria, major deviation from protocol-compliant study drug administration, and use of prohibited concomitant medication. Use of the PPS in trials assessing noninferiority is advocated to avoid an increase of type I error, which could result from using the FAS [21]. The FAS was used to confirm results obtained using the PPS and for all other efficacy endpoints and was defined as all patients who had received at least one dose of Tacrolimus QD after conversion from ciclosporin and underwent at least one assessment visit thereafter. Safety results were assessed using the safety analysis population (SAF), which comprised all patients who took at least one dose of Tacrolimus QD. Unless specified otherwise in this paper, results are presented for the FAS; presentation of primary endpoint results includes those for the PPS and safety results are based on the SAF.

Relative change in eCrCl was analyzed using an ANOVA model with ciclosporin-related side effect and study center as fixed factors. To adjust for multiple comparisons, the Bonferroni-Holm method was used to control the familywise two-sided error rate at the $\alpha = 0.05$ level. The last observation carried forward (LOCF) procedure was used for missing data. Study centers were pooled based on the number of recruited patients: small (≤5 patients enrolled), medium (6–15 patients enrolled), and large (>15 patients enrolled).

Descriptive methods were used to analyze secondary endpoints and investigator and patient rating scales. Kaplan–Meier analysis and confidence intervals (Greenwood formula) were used to calculate time to death and acute rejection.

Ethics

The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines and in accordance with local and national regulatory requirements and laws. All relevant study documents were approved by the Institutional Review Board responsible for the study center. All patients provided signed informed consent and were free to withdrawal from the study at any time.

Results

The study was conducted between April 2007 and April 2009 at 48 clinical sites in 12 European countries. The pooling of study centers resulted in 24 small centers, 22 medium centers, and two large centers.

The number of enrolled patients was 346, three of these patients were not converted (Table 1). A further three patients were inappropriately enrolled (no documented indication for conversion) but received a dose of Tacrolimus QD. These three patients are included in the total SAF which comprised 343 patients. The FAS comprised 339 patients and 301 patients were treated per protocol (PPS).

Approximately 91% of patients (315 of 343 patients) completed the study (Table 1). In total, 4.7% (16 of 343

Table 1. Disposition of kidney transplant recipients converted from ciclosporin to Tacrolimus QD.

	Hyperlipidemia	Hypertrichosis	Hypertension	Gingival hyperplasia	Total
Enrolled	49	114	93	87	346
Not converted	0	0	0	3	3
SAF	49 (100)	114 (100)	93* (100)	84 (100)	343*
Inappropriate enrollment	–	–	–	–	3*
Completed	44 (89.8)	108 (94.7)	85 (91.4)	78 (92.9)	315
Premature discontinuation	5 (10.2)	6 (5.3)	8 (8.6)	6 (7.1)	25
Adverse event	5 (10.2)	4 (3.5)	3 (3.2)	4 (4.8)	16
Consent withdrawn	0 (0)	2 (1.8)	4 (4.3)	0 (0.0)	6
Noncompliance	0 (0)	0 (0)	1 (1.1)	1 (1.2)	2
FAS	49	114	92	84	339
PPS	42	106	77	76	301

SAF: (safety analysis set) all patients who took at least one dose of Tacrolimus QD.
FAS: (full analysis set) all patients who had received at least one dose of Tacrolimus QD and underwent at least one assessment after conversion.
PPS: (per protocol set): all patients not prematurely withdrawn and without a major protocol violation including violation of relevant inclusion/exclusion criteria, major deviation from protocol-compliant study drug administration, and use of prohibited concomitant medication.
Data are presented as number (percentage) unless otherwise indicated.
*One patient assigned to the hypertension group had a missing baseline estimated creatinine clearance and received one dose of Tacrolimus QD. Three patients were enrolled in the study but did not exhibit ciclosporin-related side effects and were therefore not assigned to a group; they received one dose of Tacrolimus QD. All four patients received study drug and are therefore counted in the total SAF.

patients) withdrew because of an adverse event, which included five patients with hyperlipidemia, four with hypertrichosis, three with hypertension, and four with gingival hyperplasia. Ciclosporin was re-initiated in three patients prematurely withdrawn from the study.

Patient demographics were generally similar across the groups (Table 2). The median time since transplant was 87 months (range 6–292 months) or approximately 7 years. On average, patients had experienced the indication for conversion for approximately 5 years prior to study enrollment. Because of the severity of the indication for conversion, four patients were admitted to the study although the time since transplantation was <12 months (two patients in the hypertrichosis group, one patient each in the gingival hyperplasia and hypertension groups).

Ciclosporin blood concentration was similar across groups prior to enrollment. At week −1, the median ciclosporin blood concentration was 106 (range, 27–370) ng/ml and median daily dose was 2.3 (range, 1–7) mg/kg ($N = 343$). The majority of patients were on a triple-drug immunosuppressive regimen which included steroids for about 67% and MMF for about 76% of patients. More than half of the study population was receiving lipid-lowering medications and/or antihypertensive medications at enrollment.

Adjustments in the daily dose of Tacrolimus QD were permitted to maintain targeted blood concentration of tacrolimus. An interruption in administration of Tacrolimus QD was rarely necessary to maintain blood levels while increases and especially decreases in daily dose were more often required (Table 3). During the first 4 weeks, when blood concentrations were set at 5–15 ng/ml, dose increases were required in approximately 15% of patients and decreases in 83%. Trough levels during this time ranged from 9 to 11 ng/ml. After week 4, to comply with a tapering of blood concentration to 7 ng/ml, dose increases were required in 38% and decreases in 81%. The average trough level after week 4 was 7.5 ng/ml. The average number of dose adjustments needed to achieve targeted concentration during the study was 3.2 (median was 3).

The mean (SD) daily dose of MMF at any time during the study was 1.3 (0.5) g.

There were no episodes of acute rejection.

Renal function

The mean relative change in eCrCl at week 24, the primary endpoint, was −0.6% in all patients included in the PPS ($n = 301$) and similar at −0.8% in all patients included in the FAS ($n = 339$) (Table 4). These results are in agreement with the definition for determining non-inferiority of Tacrolimus QD against ciclosporin. There were no apparent differences in results using the MDRD formula to assess renal function. Serum creatinine remained stable after conversion: the absolute median

Table 2. Demographic and baseline characteristics of kidney transplant recipients converted from ciclosporin to Tacrolimus QD.

Characteristic	Hyperlipidemia (*n* = 49)	Hypertrichosis (*n* = 114)	Hypertension (*n* = 92)	Gingival hyperplasia (*n* = 84)
Age, mean (SD) y	53 (10.8)	49 (12.3)	57 (10.4)	48 (12.8)
Male	25 (51)	51 (44.7)	65 (70.7)	61 (72.6)
Race, White	46 (93.9)	110 (96.5)	89 (96.7)	82 (97.6)
Duration of adverse condition, median (range), mo	48 (2–215)	66 (0–247)*	112 (0–447)*	17 (0–207)*
Time since transplant, median (range), months	84 (12–277)	86 (6–250)†	97 (11–292)†	67 (10–270)†
Number of transplants:				
1	44 (89.8)	108 (94.7)	84 (91.3)	76 (90.5)
2	5 (10.2)	6 (5.3)	8 (8.7)	7 (8.3)
3	0	0	0	1 (1.2)
Deceased donor	48 (98)	105 (92.1)	87 (95.6)	79 (94)
ABO, donor/recipient identical	47 (95.9)	103 (90.4)	85 (92.4)	74 (88.1)
Serum creatinine, mean (SD), μmol/l	127.6 (31.2)	123.6 (28.4)	135.8 (34)	128.4 (35.9)
Total cholesterol, mean (SD), mmol/l	6.4 (1.0)	5 (1.1)	5 (0.8)	4.9 (0.9)
Blood pressure, mean	101/82	100/82	109/87	96/79
Pre-existing type 2 diabetes	5 (10.2)	1 (0.9)	6 (6.5)	6 (7.1)
Pre-existing type 1 diabetes	1 (2.0)	4 (3.5)	4 (4.3)	4 (4.8)
Pre-existing cardiac disorder	7 (14.3)	12 (10.5)	29 (31.5)	11 (13.1)
Ciclosporin concentration, median (range) ng/ml	108.5 (36–231)	98.6 (42–370)	108.0 (30–248)	104.7 (27–300)
Adjunct immunosuppressive agents:				
MMF	35 (71.4)	90 (78.9)	74 (80.4)	62 (73.8)
Everolimus	0	0	0	1 (1.2)
Corticosteroids	39 (79.6)	71 (62.3)	62 (67.4)	55 (65.5)
AZA	9 (18.4)	9 (7.9)	8 (8.7)	12 (14.3)

MMF, mycophenolate mofetil; AZA, azathioprine

Data are presented as number (percentage) unless otherwise indicated. Data are for the full analysis set (FAS): patients who had received at least one dose of Tacrolimus QD and underwent at least one assessment after conversion.

*****Duration of adverse condition was <1 month and hence reported as 0 months.

†Two patients in the hypertrichosis group and one patient each in the hypertension and gingival hyperplasia groups were admitted to the study because of the severity of their indication for conversion although the time since transplantation was <12 months.

Table 3. Doses and adjustments of daily doses of Tacrolimus QD required to maintain defined trough range, safety analysis set (*N* = 343).

	Mean (SD) trough level during time period, ng/ml	Mean (SD) daily dose during time period, mg/kg	Dose adjustments during time period, *n* (%)		
			Increase	Decrease	Interruption
Week 1	11 (6.6)	0.09 (0.02)	19 (5.5)	26 (7.6)	4 (1.2)
Week 2	10.4 (5.5)	0.09 (0.02)	18 (5.2)	89 (25.9)	1 (0.3)
Week 3	9.9 (5.3)	0.08 (0.03)	34 (9.9)	121 (35.3)	3 (0.9)
Week 4	8.9 (3.4)	0.08 (0.03)	14 (4.1)	47 (13.7)	0
Month 2	7.8 (2.6)	0.07 (0.03)	63 (18.4)	143 (41.7)	2 (0.6)
Month 3	7.3 (2.9)	0.07 (0.03)	25 (7.3)	43 (12.5)	1 (0.3)
Month 4	7.5 (2.5)	0.07 (0.04)	18 (5.2)	28 (8.2)	0
Month 5	7.6 (2.2)	0.07 (0.03)	10 (2.9)	40 (11.7)	1 (0.3)
Month 6	7.2 (2.6)	0.07 (0.03)	13 (3.8)	22 (6.4)	0

change was 0.0 μmol/l (range, −88.4–125 μmol/l) for all patients included in the FAS. The change in proteinuria was not of clinical relevance.

Cardiovascular parameters

Lipid parameters improved after conversion in patients in the hyperlipidemia group but changes after conversion were modest in the total study population (Fig. 1). In patients in the hyperlipidemia group, total cholesterol changed by −0.82 mmol/l (95% CI, −1.0 to −0.6 mmol/l), LDL-cholesterol changed by −0.43 mmol/l (95% CI, −0.7 to −0.2 mmol/l), HDL-cholesterol by −0.09 mmol/l (95% CI, −0.2 to −0.0 mmol/l), and triglycerides by −0.44 mmol/l (95% CI, −0.7 to −0.2 mmol/l). There was no meaningful change in the number of patients taking

Table 4. Change in estimated creatinine clearance (eCrCl) per Cockcroft–Gault method between baseline and week 24 in patients converted from ciclosporin to tacrolimus QD.

	Hyperlipidemia		Hypertrichosis		Hypertension		Gingival hyperplasia		All	
eCrCl	PPS (n = 42)	FAS (n = 49)	PPS (n = 106)	FAS (n = 114)	PPS (n = 77)	FAS (n = 92)	PPS (n = 76)	FAS (n = 84)	PPS (n = 301)	FAS (n = 339)
Relative change, mean (SEM)	−5.28% (2.2)	−4.97% (2.3)	0.93% (1.4)	1.27% (1.5)	−0.06% (1.6)	−1.44% (1.6)	−1.0% (1.6)	−0.33% (1.7)	−0.63% (13.5)	−0.81% (15.3)
95% CI*, ml/min	−9.6; −1.0	−9.5; −0.4	−2.6; 4.5	−2.5; 5.1	−3.8; 3.7	−5.1; 2.2	−4.6; 2.7	−4.5; 3.9	−2.2; 0.9	−2.4; 0.8
Absolute change, mean (SD), ml/min	−3.6 (9.9)	−3.6 (10)	0 (8.7)	0.1 (8.7)	−0.3 (8.2)	−1.1 (8.6)	−0.7 (7.5)	−0.8 (9.3)	−0.8 (8.5)	−1.0 (9.1)

PPS: all patients from the FAS not prematurely withdrawn and without a major protocol violation.
FAS: all patients who had received at least one dose of Tacrolimus QD and underwent at least one assessment after conversion.
CI, confidence interval.
Last observation carried forward method used for missing data.
*Confidence intervals are adjusted for multiplicity testing using Bonferroni-Holm method to control familywise two-sided error rate at $\alpha = 0.05$ level (corresponding to a 95% confidence interval).

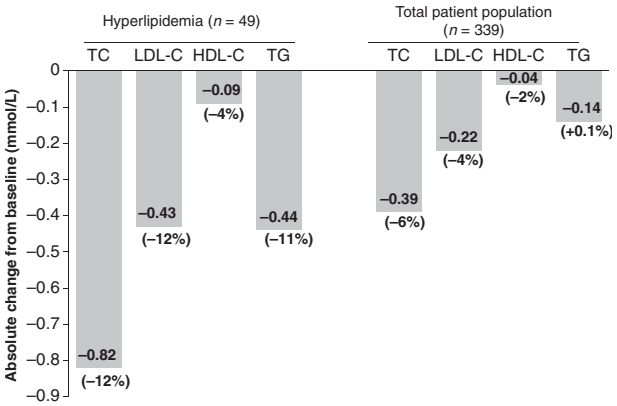

Figure 1 Absolute mean change from baseline at end of study in serum lipid levels in patients with hyperlipidemia as the primary indication for conversion and in the total patient population. At week 24 after conversion, decreases in mean absolute values for total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were evident in the hyperlipidemic group (n = 49). Changes in mean absolute lipid values in the overall population of patients (n = 339) were modest. Data are for the full analysis set: patients who had received at least one dose of Tacrolimus QD and underwent at least one assessment after conversion. TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; TG, triglycerides. Data presented in parentheses represent mean relative change in serum lipids from baseline at week 24.

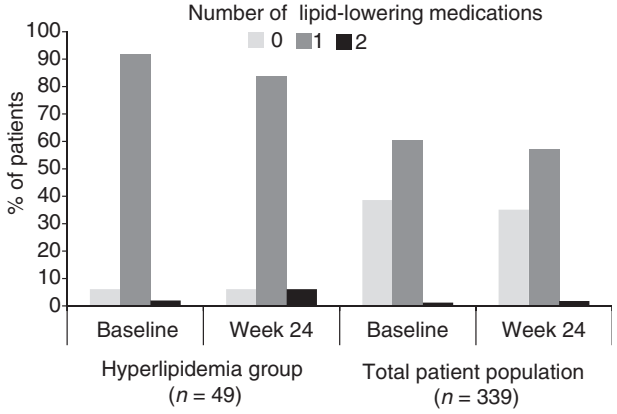

Figure 2 Comparison of the number of medications taken for treatment of hyperlipidemia at baseline and week 24 in patients with hyperlipidemia and the total study population. There was no measureable change between baseline and week 24 in the number of lipid-lowering medications taken by patients in the hyperlipidemia group or in the total patient population. Data presented are for the full analysis set.

one or two lipid-lowering medications in either the hyperlipidemia group or in the total study population (Fig. 2).

Arterial BP decreased by 8.2 mmHg (95% CI, −10.6 to −5.8 mmHg) after conversion in patients with hypertension (n = 92) and decreased by 5.0 mmHg (95% CI, −6.3 to −3.7 mmHg) in the total study population (n = 339).

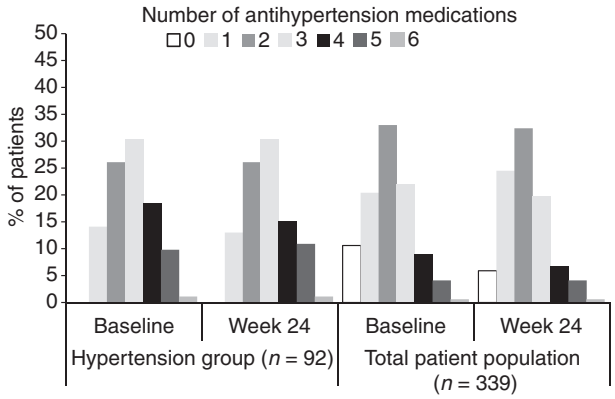

Figure 3 Comparison of the number of medications taken for treatment of hypertension at baseline and week 24 in patients with hypertension and the total study population. There was no measureable change between baseline and week 24 in the number of antihypertensive medications taken by patients in the hypertensive group or in the total patient population. Data presented are for the full analysis set.

There was no meaningful change in the number of antihypertensive medications being taken by patients in the hypertensive group or by patients in the total study population (Fig. 3).

The clinical status of patients converted to Tacrolimus QD because of hyperlipidemia and hypertension showed improvement, as rated by investigators, at week 24 compared to baseline (Fig. 4). At week 24, the severity of hyperlipidemia was strongly/very strongly severe in 6% of 49 patients compared to 32% at baseline. Similarly, the severity of hypertension was strongly/very strongly severe in 23% of 92 patients at week 24 compared to 35% at baseline.

Ciclosporin-related cosmetic side effects

Hypertrichosis and gingival hyperplasia were rated by investigators and patients as markedly improved after conversion to Tacrolimus QD. At week 24, investigators rated symptoms of hypertrichosis as strongly/very strongly severe in 5% of 114 patients compared to 45% at baseline (Fig. 4). Similarly, symptoms of gingival hyperplasia were rated as strongly/very strongly severe in 4% of 84 patients at week 24 compared to 51% at baseline.

Patient self-report of ciclosporin-related cosmetic side effects also indicated alleviation of severity of symptoms after conversion (Fig. 5). Although 48% of 114 patients with hypertrichosis rated the severity of symptoms as strong/very strong at baseline, the frequency decreased to 6% at week 24 (Fig. 5). Patients also identified a lessening of the severity of gingival hyperplasia: 53% of 84 patients with gingival hyperplasia indicated that the severity of symptoms was strong/very strong at baseline compared to 5% at week 24 (Fig. 5).

Safety

There was one death from lymphoma in the gingival hyperplasia group. One patient (hypertension group) had graft failure on day 35 after conversion. This patient received a kidney transplant 14 months before study entry and had had marginal graft function before and throughout the study.

In total, 224 of 343 patients (65%) experienced an adverse event and 47 patients (14%) a serious adverse event. The most commonly occurring adverse event was diarrhea (67 of 343 patients, 19.5%). Diarrhea was also the most common adverse event associated with premature study discontinuation (6 of 343 patients, 1.7%). The

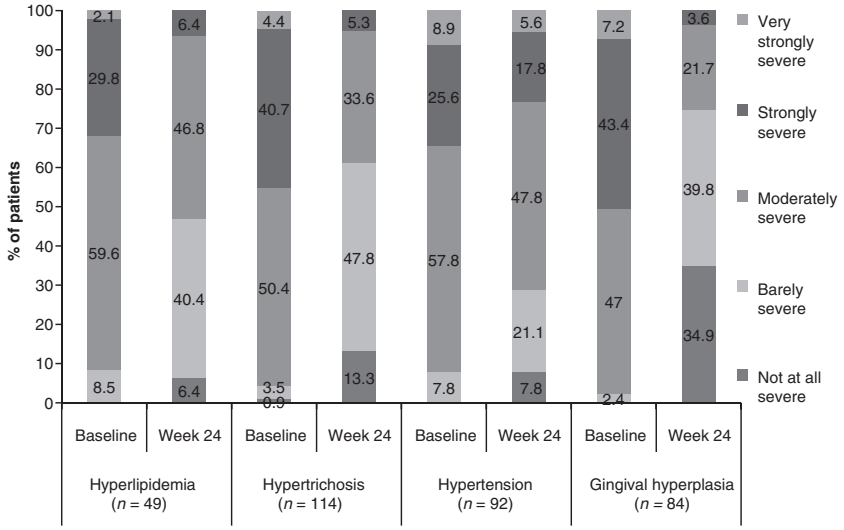

Figure 4 Investigator rating of resolution or improvement of the indication for conversion at week 24 compared with baseline. A clear lessening in severity of the indication for conversion was demonstrated by the ratings provided by investigators at baseline and at week 24. Data presented are for the full analysis set.

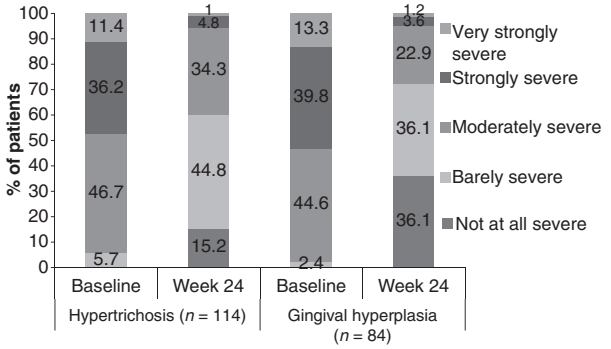

Figure 5 Patient self-rating of severity of gingival hyperplasia or hypertrichosis at baseline and at week 24 after conversion to Tacrolimus QD. The severity of hypertrichosis and gingival hyperplasia markedly decreased between baseline and week 24 as demonstrated by patient self-ratings of severity. Data presented are for the full analysis set.

most common serious adverse event was infection (not further classified) with an incidence of 6% (21 patients). Study drug-related events were reported in 124 of 343 patients (36%) and serious study drug-related events in 17 of 343 patients (5%). The most commonly occurring tacrolimus-related adverse event was tremor with an incidence of 7% (23 of 343 patients).

Three patients required insulin for treatment of new-onset diabetes mellitus (one patient each with hyperlipidemia, hypertrichosis, and gingival hyperplasia). Insulin was discontinued during the study in two of these patients. One patient (hyperlipidemia group) required insulin at week 24. Two patients developed type 2 diabetes during the study: one patient (hyperlipidemia group) recovered; the condition persisted in the other patient (hypertension group) but was controlled through dietary interventions. Values for both blood glucose and HbA1c remained unchanged between baseline and week 24.

Discussion

In conducting this study, we assumed that a relative change in eCrCl would not be greater than 10% at week 24 following conversion from ciclosporin to Tacrolimus QD, which it was. The change in eCrCl indicated that Tacrolimus QD was noninferior to ciclosporin in this study setting. Because the time since transplantation was relatively long in our population (median 7 years) we would not have expected an improvement in renal function after conversion.

Studies have demonstrated the feasibility of conversion from ciclosporin to tacrolimus and the benefits of conversion from tacrolimus BID to tacrolimus QD. This is the first study, however, to demonstrate the safety of conversion from ciclosporin to Tacrolimus QD. Because renal function has been shown to be similar with the two formulations of tacrolimus [12,22,23], we assumed that we would observe outcomes in line with results on renal function from ciclosporin to tacrolimus BID conversion studies which was the case. For example, at 6 months after conversion renal function remained stable in renal allograft recipients with stable function at the time of conversion [5,6,13]. Further out from transplantation, at 24 months, serum creatinine remained unchanged in patients converted to tacrolimus while values increased in patients maintained on ciclosporin ($P < 0.05$ for the difference between groups) [4]. Our findings showed stable renal function at 24 weeks. Despite what might be considered a relatively short study time, we would expect function to continue to remain stable longer term with Tacrolimus QD in this population.

We had anticipated greater difficulty in managing the conversion because of reduced tacrolimus predose blood concentration levels and increased dose requirements reported in conversion [16] and *de novo* [12,22] studies of Tacrolimus QD. The situation we experienced was quite the opposite: during the first 4 weeks, decreases rather than increases in daily dose were more commonly required to attain the protocol-defined trough range of 5–15 ng/ml. The targeted tacrolimus concentration range during the first 4 weeks was intentionally set high because of our concern that under-dosing might lead to acute rejection during conversion. While this initially higher drug concentration did provide benefit in preventing rejection and did not seem to adversely affect renal function, we might have seen a more pronounced nephrological response had the initial Tacrolimus QD dose been lower.

A small but encouraging benefit of conversion on cardiovascular parameters was the decrease in arterial BP observed in the hypertension group. Decreases in the total study population were not as great. We did not find a corresponding decrease in the number of antihypertensive medications taken by patients. Decreases in serum lipids in the hyperlipidemia group were modest but greater than those observed in the total population. Here, too, there was no corresponding decrease in the number of lipid-lowering medications taken by patients (data were not collected on changes in doses). Clinically, these results indicate a potential benefit in terms of reducing existing cardiovascular risk parameters after conversion to Tacrolimus QD from ciclosporin. There is evidence that conversion to tacrolimus from ciclosporin reduces cardiovascular risk factors through a reduction in serum lipids [3,6,13–15] and in mean BP [4,13] with a reduction in the number of lipid-lowering medications taken by patients [6].

The rate of adverse events leading to premature study discontinuation was low and treatment tolerability was very good. One patient died and one graft was lost. The switch to Tacrolimus QD from ciclosporin did not

replace one side effect with another. The overall incidence of tremor was low as was the incidence of new onset diabetes after transplantation (two patients). Premature study discontinuation caused by diarrhea occurred early (between days 9 and 16) and we suspect this was caused by higher doses of MMF, as given concomitantly with ciclosporin, not being reduced soon after conversion to Tacrolimus QD. In terms of patient outcomes, the benefits of conversion we observed must be weighed against the possible onset of tacrolimus-related side effects. Results for this predominantly white, middle-aged male population may not be replicable in other populations.

Of interest are the results of investigator and patient report of a reduction in the severity of hypertrichosis and gingival hyperplasia after conversion. This study was not designed to show that the conversion to Tacrolimus QD had caused the reduction in these side effects; it is unlikely, however, that the degree of the reduction in severity would have occurred under continued administration or at a lower dose of ciclosporin. Resolution of cosmetic side effects has been similarly reported [6,8] and we assume that improvements in physical appearance and physical comfort positively impacted on our patients' well being.

The lack of a reference arm, a clear limitation of our study, precludes us from drawing any firm conclusions on the influence of conversion to Tacrolimus QD on renal function in comparison to patients maintained on ciclosporin. The use of a reference arm could have negated any regression to the mean which can occur when measuring changes from baseline in conditions as stipulated in our study. In our opinion, the inclusion of a control group (i.e., patients remaining on ciclosporin despite drug-related adverse effects) would have compromised best medical treatment for the sake of study design.

In conclusion, conversion to Tacrolimus QD from ciclosporin was both safe and effective in stable kidney transplant patients. Renal function remained stable at week 24 after conversion. There was remarkable improvement in ciclosporin-related cosmetic side-effects but marginal change in cardiovascular risk parameters following conversion to Tacrolimus QD.

Authorship

All named authors participated in the design of the study and in the performance of the research, in developing and reviewing the paper, and in the decision to submit the paper.

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