Optimizing Tacrolimus Therapy in the Maintenance of Renal Allografts: 12-Month Results

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Background. The determination of optimal tacrolimus (TAC) trough levels is needed to prevent adverse effects of calcineurin inhibitors.

Methods. Stable transplant recipients currently receiving cyclosporine (CsA) were assigned randomly (1:1:1) to continue CsA (target trough level of 50–250 ng/mL); or convert to "reduced" TAC (target trough level 3.0–5.9 ng/mL) or "standard" TAC (target trough level 6.0–8.9 ng/mL).

Results. At 12 months, there was a significant improvement in renal function in the reduced TAC versus CsA group with lower serum creatinine ($P=0.004$) and cystatin C ($P<0.001$), and higher estimated creatinine clearance ($P=0.017$). However, there were no statistically significant differences in any renal parameter in the standard TAC versus CsA group. Total and low-density lipoprotein cholesterol were significantly reduced in both TAC groups versus the CsA group ($P<0.001$). Patient and graft survival and episodes of biopsy-confirmed acute rejection were similar for all treatment groups, and no statistically significant differences were observed between groups in the incidence of new-onset diabetes or cardiac conditions, or in the prevalence of hyperglycemia, hypertension, or hyperlipidemia among patients who did not have these conditions at baseline. Alopecia developed more commonly among TAC-treated patients than CsA-treated patients ($P<0.001$).

Conclusions. Compared with CsA continuation, conversion to reduced TAC target trough concentrations resulted in significantly improved renal function without increasing the risk of rejection. Conversion to TAC, regardless of target concentration, resulted in improved serum lipid profiles in kidney transplant recipients at 12 months.

Keywords: Optimizing, Tacrolimus, Kidney transplantation, 1 year.

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Calcineurin inhibitors (CNIs) such as tacrolimus (TAC) and cyclosporine (CsA) are effective in preventing short-term acute rejection; however, these drugs have inherent nephrotoxic properties when used long-term (*1*). Posttransplant renal function is a key indicator of long-term patient and graft outcome and poor function adversely impacts the risk for cardiac death (*2*, *3*). In recent years, numerous clinical trials have evaluated combinations of immunosuppressant regimens that spare or eliminate CNIs to maintain immunosuppression at a level sufficient to prevent acute rejection while reducing the risk for nephrotoxicity (*4*). The results of studies eliminating CNIs from immunosuppressant regimens have demonstrated an increased rate of acute rejection and have not consistently achieved better renal function (*5–7*). Switching from CsA to a maintenance regimen of sirolimus or mycophenolate mofetil (MMF) has resulted in similar patient survival in low-to-moderate risk patients (*8*, *9*), but long-term strategies that eliminate CNIs, although reversing or stabilizing the progression of chronic allograft nephropathy remain unproven, particularly in high-risk patients. CNI-sparing regimens have been associated with better renal function compared with standard regimens in kidney transplant recipients (*10–12*). The large SYMPHONY trial compared standard CsA/MMF-based immunosuppression without antibody induction to reduced-dose CsA/MMF, TAC/MMF, and sirolimus/MMF regimens that included daclizumab induction in de novo renal transplant recipients. Reduced-dose TAC/MMF was significantly superior at 1 year to all other groups with respect to glomerular filtration rate and biopsy-confirmed acute rejection (BCAR) ($P\leq0.001$), and to normal-dose CsA and sirolimus for graft survival ($P=0.007$) (*13*).

The present study was conducted to explore optimizing maintenance target TAC whole blood trough concentrations (reduced and standard doses) after conversion from CsA. The impacts on renal function, incidence of chronic graft dysfunction and cardiovascular risk factors, and quality of life in kidney transplant recipients were prospectively evaluated.

METHODS

This open-label, randomized, multicenter, three-arm, prospective study was designed to compare two TAC-based regimens (reduced [3.0–5.9 ng/mL] or standard [6.0–8.9 ng/mL] target whole blood trough concentrations) to continuation of a CsA-based regimen (target whole blood trough concentration of 50–250 ng/mL). The study was conducted at 41 investigative sites in the United States over a 36-month period; 12-month results are presented in this report. The study protocol was approved by an Institutional Review Board at each site. Study procedures were performed in accordance with the Helsinki Declaration. The first patient was enrolled

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on March 17, 2003 and enrollment ended on March 31, 2005. The cut-off date for inclusion in this 12-month clinical follow-up report was April 11, 2006.

Selection and Description of Participants

Eligible patients were men and women deceased or living donor kidney transplant recipients more than or equal to 18 years of age, at least 6 months posttransplant, maintained on a CsA-based regimen since transplantation, with a functioning allograft and a Cockcroft-Gault estimate of creatinine clearance more than or equal to 35 mL/min within 4 weeks before randomization. Female patients could not be pregnant and agreed to practice effective birth control for the duration of the study. All patients were required to sign an Institutional Review Board-approved informed consent form before starting any study procedures. Patients excluded from participation in the study included those who were recipients of a solid organ other than the kidney, had BCAR requiring treatment within 3 months of randomization, had recurrent primary or de novo renal disease, had a urine protein more than 1.5 g over 24 hr or two successive urinalyses indicating albuminuria greater than 2+ within 6 months before enrollment, had a Cockcroft-Gault estimate of creatinine clearance less than 35 mL/min within 4 weeks of randomization, had a change in their adjunctive immunosuppressant therapy within 1 month of randomization, was a known carrier of the human immunodeficiency virus, had a known or suspected malignancy (except for treated squamous or basal cell skin cancers) less than 5 years before randomization or a history of posttransplant lymphoproliferative disease, or had known hypersensitivity to TAC or any of its excipients.

Treatment Plan

At the time of randomization, all patients were receiving CsA-based immunosuppression. Patients were assigned randomly, using an automated registration system, in a 1:1:1 ratio to receive 1 of 3 immunosuppressive regimens: CsA continuation with a target trough level of 50 to 250 ng/mL; conversion to TAC, initiated at 1/100th of the current CsA dose with a target trough level of 3.0 to 5.9 ng/mL; or conversion to TAC, initiated at 1/50th of the current CsA dose with a target trough level of 6.0 to 8.9 ng/mL. The target trough level was to be achieved within 4 weeks. As per protocol, dose changes to a patient's adjunctive immunosuppressant regimen, which could have included azathioprine, MMF, sirolimus, and corticosteroids, were not permitted during the study unless there was a medically justified reason. Attempts at steroid withdrawal were not allowed during the study; however, steroid doses could be reduced to a dose consistent with an institution's protocol. Episodes of rejection were treated with an increase in the dose of TAC or CsA, corticosteroids, or commercially available antilymphocyte therapy as per the standard practices of the individual study center. CsA and TAC doses were permitted to be adjusted to achieve target trough concentrations based on the investigator's clinical judgment. Induction agent status was not collected.

Study Endpoints and Assessments

The primary efficacy endpoint was the effect of conversion from CsA to TAC-based therapy (reduced and standard target trough levels) on renal function at 12 months based on the Cockcroft-Gault estimate of creatinine clearance and cystatin C. Secondary efficacy endpoints included estimated creatinine clearance and cystatin C at 6 months, serum creatinine at 6 and 12 months, incidence and severity of BCAR, and patient and graft survival. In addition, transforming growth factor beta-1 (TGF-β), C-reactive protein, and homocysteine were assessed at 6 and 12 months. Biopsies were performed before or within 24 hr of initiating treatment of rejection.

Safety assessments included serious adverse events, medical necessity to change randomized therapy, and adverse events of interest including hypertension (systolic blood pressure$\geq$140 mm Hg or diastolic blood pressure$\geq$90 mm Hg or treatment with medication), hyperlipidemia (serum cholesterol$\geq$ 200 mg/dL, low-density lipoprotein [LDL] cholesterol$\geq$130 mg/dL, triglycerides$\geq$150 mg/dL or treatment with medication), hyperglycemia (fasting blood glucose$\geq$126 mg/dL on at least one occasion or treatment with medication), diabetes (fasting blood glucose$\geq$126 mg/dL on two separate occasions or treatment with medication), and cardiac conditions in patients without these conditions at baseline; and cosmetic events (gingival hypertrophy, hypertrichosis [chronic renal failure "hirsutism"], alopecia), bone fracture, and other known immunosuppressant-associated events (hematologic disorders, infections, malignancies, lymphoma, and posttransplant lymphoproliferative disease).

Quality of life was assessed at 6 and 12 months using the Memphis Survey, a validated questionnaire used to evaluate the frequency and intensity of problems resulting from transplantation or use of immunosuppressant medications (*14*).

Clinical laboratory parameters including serum sodium, potassium, fasting glucose, blood urea nitrogen (BUN), creatinine, and complete blood count were evaluated at baseline, 6 and 12 months for patients in the CsA and TAC groups and additionally at weeks 1, 2, 4, 8, and 12 for patients in the TAC group. Lipids (total cholesterol, high density lipoproteins and LDL cholesterol and triglycerides), TGF-β, homocysteine, cystatin C, and C-reactive protein were also evaluated at baseline and months 6 and 12. Homocysteine was measured using a liquid chromatography-tandem mass spectrometry stable isotope dilution analysis (*15*), and C-reactive protein was quantitatively determined by latex particle-enhanced immunoturbidimetric assay. TGF-β was determined using a 4.5 hr solid phase enzyme-linked immunosorbent assay designed to measure Human TGF-B1 in serum and EDTA plasma (platelet poor) (The R&D Systems Inc. Human TGF-B1 Quantikine Immunoassay; Minneapolis, MN).

Statistical Analyses

A sample size of 300 patients was calculated to provide approximately 80% power to detect an 8 mL/min change in mean estimated creatinine clearance (if the CsA group mean$\pm$standard deviation [SD] was 68$\pm$24 mL/min) and a 0.21 mg/L change in mean cystatin C (if the CsA group mean$\pm$SD was 1.6$\pm$0.6 mg/L) between the two TAC groups combined and the CsA group (2-sided alpha=5%); and an 11 mL/min or 0.28 mg/L difference among any pairwise comparisons between the three groups with alpha set at 1.67% (to account for multiple comparisons).

All randomized patients who had data available from at least one clinical visit postenrollment were included in the analyses. Differences in means of continuous variables (e.g., age and weight) across the three treatment groups were analyzed using

analysis of variance techniques. The chi-square test or Fisher's exact test were used as appropriate for comparisons of categorical variables (e.g., gender, number of patients who developed diabetes, number of patients with a laboratory value above a certain threshold) across the three treatment groups. Differences in medians of continuous variables (such as laboratory values) across the three treatment groups were tested using the Kruskal-Wallis test. Pairwise comparisons of median laboratory values between each TAC group and the CsA group were made using the Kruskal-Wallis test; similar pairwise comparisons of median laboratory values between the reduced TAC group and the standard TAC group were performed using the Wilcoxon rank-sum test. The signed-rank test was used to test whether the median of a continuous variable was significantly different from zero within a treatment group.

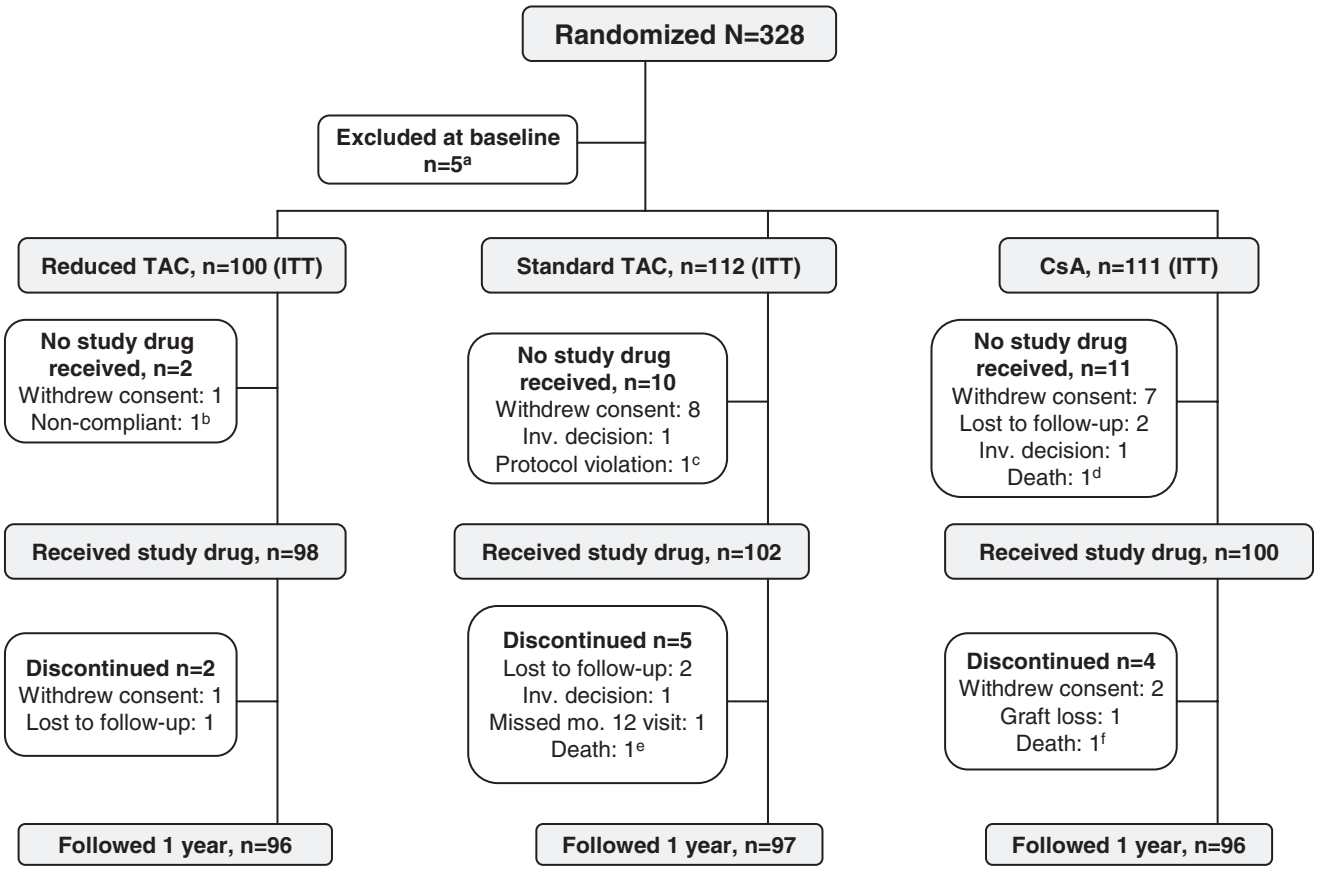
RESULTS

Patient Population Characteristics

Figure 1 displays the patient disposition. There were no significant differences across treatment groups in patient demographics or other baseline characteristics (Table 1). Female and black patients comprised 34% and 27% of the baseline population. The median time to enrollment was 4 years posttransplant. Neoral was the most commonly used CsA at baseline, with 66% of patients receiving it. Eleven percent of patients were receiving azathioprine, 2% were receiving sirolimus, and 94% were receiving corticosteroids.

Study Drug and Other Immunosuppressant Exposure

There was a statistically significant difference in the median total daily TAC dose between the standard TAC (median, 5.5 mg/day) and the reduced TAC groups (median, 3.0 mg/day) ($P<0.001$) at 12 months. Statistically significant differences in median TAC trough levels were observed between the reduced TAC and standard TAC groups throughout the 12-month study period ($P<0.001$ at months 1, 2, 3, 6, and 12). However, there was wide interpatient variability in trough levels in the two TAC groups, and relatively large percentages of patients in the reduced TAC group had levels



TAC=tacrolimus (target trough levels: reduced, 3.0-5.9 ng/mL; standard, 6.0-8.0 ng/mL); ITT=intent to treat.
[a]Excluded at 1 site because of improper informed consent and randomization.
[b]Patient only completed baseline visit, would not return phone calls.
[c]Cockroft-Gault score calculated incorrectly.
[d]Cause of death was respiratory arrest at month 5, no laboratory or clinic visits after baseline.
[e]Cause of death unknown, patient died in a community hospital at month 7.
[f]Cause of death was metastatic melanoma at month 8.

FIGURE 1. Patient disposition.

TABLE 1. Patient demographics and other baseline characteristics

	Reduced TAC n=100	Standard TAC n=112	CsA n=111	*P*-value[a]
Age (yr), mean±SD	49.7±12.6	48.3±12.2	51.3±12.1	0.188
Female gender, n (%)	39 (39%)	31 (28%)	40 (36%)	0.191
Black race, n (%)[b]	28 (28%)	30 (27%)	30 (27%)	0.979
Donor age (yr), mean±SD	35.1±13.4	37.7±14.6	37.3±14.9	0.407
Deceased donor transplant	58 (58%)	50 (45%)	60 (54%)	0.131
Time to enrollment after transplant (mos), median	52.6	48.8	50.4	0.657
Medical conditions present at baseline	n=100	n=111	n=111	
Diabetes	35 (35%)	42 (38%)	38 (34%)	0.875
Hyperlipidemia	88 (88%)	91 (82%)	91 (82%)	0.375
Hypertension	91 (91%)	104 (94%)	100 (90%)	0.672
Cardiac condition	26 (26%)	25 (23%)	23 (21%)	0.668

[a] Based on Fisher exact test.
[b] Other races include whites and patients of Native American, Asian, and Pacific Islander ethnic origin.
TAC, tacrolimus (reduced trough level 3.0–5.9 ng/mL; standard trough level 6.0–8.9 ng/mL); CsA, cyclosporine.

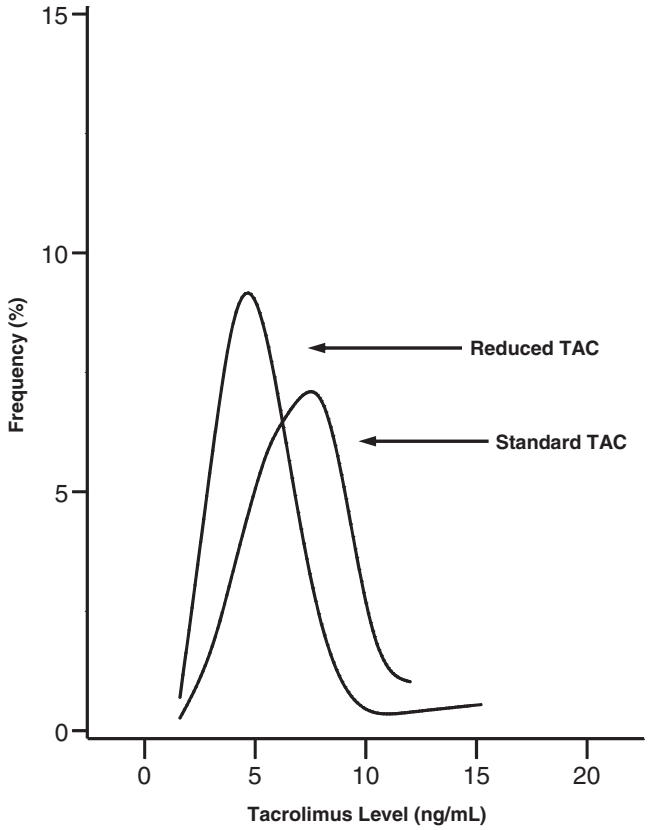


FIGURE 2. Frequency (%) distribution of TAC blood trough levels at 12 months for the reduced and standard TAC groups.

above target range (26.8% at month 1, 24.5% at month 12) and relatively large percentages of patients in the standard TAC group had levels below the target range (35.6% at month 1, 34.4% at month 12), resulting in overlap between the two groups throughout the study (Fig. 2). Median trough CsA levels in patients in the CsA group were 147 ng/mL on day 0, 118 ng/mL on day 182 and 130 ng/mL on day 365; 75% of these patients had mean levels of 194 ng/mL on day 0, 173 ng/mL on day 182 and 167.5 ng/mL on day 365. The proportions of patients in the CsA and reduced and standard TAC groups receiving MMF were 76.6% (85/111), 73.0% (73/100), and 73.9% (82/111) at baseline and 77.3% (75/97), 71.9% (69/96), and 66.0% (64/97) at month 12, respectively. The proportions of patients in the CsA and reduced and standard TAC groups receiving Myfortic were 2.1% (2/97), 3.1% (3/96), and 4.1% (4/97) at month 12.

Clinical Results

Patient and Graft Survival

A total of three patients died within the first 12 months. Two patients in the CsA group died, one because of metastatic melanoma and the other because of respiratory arrest. One patient in the standard TAC group died because of an unknown reason; the patient died in a community hospital and attempts to obtain information related to cause of death were unsuccessful. One patient in the CsA group experienced graft loss because of rejection.

Rejection

There was no statistical difference between treatment groups in the incidence of BCAR or biopsy-confirmed treated rejection in the first 12 months; BCAR was experienced by two patients in the reduced TAC group (grade 1B and 2A), two patients in standard TAC group (grade 1A and 1B), and three patients in the CsA group (grade 1A, 1B, and 2A). All of the episodes of BCAR were managed with corticosteroids, either alone or in combination with antilymphocyte therapy or an increase in CsA dose (one patient). Biopsy-confirmed chronic allograft nephropathy was present as an incidental finding in two patients in the reduced TAC group, two patients in the standard TAC group, and one patient in the CsA group.

Renal Function

At 12 months, a more favorable median change from baseline in cystatin C ($P<0.001$), estimated creatinine clearance ($P=0.017$), and serum creatinine ($P=0.004$) was observed for the reduced TAC group compared with the CsA group (Table 2). Additionally, among patients with an estimated creatinine clearance less than or equal to 50 mL/min at baseline, significantly fewer patients in the reduced TAC group (13/48, 27%) than in the CsA group (22/45, 49%; $P=0.035$) had an estimated creatinine clearance less than or equal to 40 mL/min at 12 months. No statistically significant differences in the change from baseline in estimated creatinine clearance, cystatin C, or serum creatinine were observed

TABLE 2. Renal function tests and cardiovascular factors: median change from baseline to 12 months[a]

	(n) Median			*P* value[b] Reduced TAC vs. CsA	*P* value[b] Standard TAC vs. CsA	*P* value[c] Reduced vs. standard TAC
	Reduced TAC	Standard TAC	CsA			
Est. creatinine clearance (mL/min)	(96) 1.65	(97) −0.60	(96) −0.80	0.017	0.212	0.239
Cystatin C (mg/L)	(91) −0.09	(93) 0.02	(88) 0.06	<0.001	0.083	0.041
Serum creatinine (mg/L)	(96) −0.10	(97) 0.00	(97) 0.00	0.004	0.152	0.151
Total cholesterol (mg/dL)	(91) −25.0	(91) −20.0	(86) 2.50	<0.001	<0.001	0.538
LDL (mg/dL)	(80) −17.5	(83) −17.0	(73) 5.00	<0.001	<0.001	0.654
HDL (mg/dL)	(88) −3.00	(86) −3.00	(80) −3.00	0.854	0.966	0.945
Triglycerides (mg/dL)	(89) −13.0	(91) −18.0	(85) −11.0	0.504	0.283	0.694
TGF-β (ng/mL)	(90) −0.79	(87) −0.69	(83) −1.09	0.861	0.324	0.399
Homocysteine (umol/L)	(90) 0.00	(88) 1.00	(83) 1.00	0.569	0.774	0.753
C-reactive protein (mg/L)	(92) −0.30	(92) −0.15	(88) 0.00	0.184	0.464	0.360

[a] All randomized patients who had at least one laboratory value and at least one postbaseline clinical visit were included in the analyses.
[b] *P*-values based on the Kruskal-Wallis test and adjusted using the least significant difference test to account for multiple pairwise comparisons.
[c] *P*-value based on the Wilcoxon rank sum test.
TAC, tacrolimus (target trough levels: reduced, 3.0–5.9 ng/mL; standard, 6.0–8.9 ng/mL); CsA, cyclosporine.

between the standard TAC and CsA groups. The decrease from baseline at 12 months in cystatin C was significantly greater in the reduced TAC group than in the standard TAC group ($P=0.041$) (Table 2).

No statistically significant differences in change from baseline in TGF-β were observed between treatment groups in this study. However, only a small proportion of OPTIMA study patients experienced renal function deterioration (seven patients experienced BCAR and five patients experienced biopsy-confirmed chronic allograft nephropathy).

Cardiovascular Factors and Significant Conditions

At 12 months, statistically significant differences with respect to reductions from baseline in total and LDL cholesterol were observed for both TAC groups compared with the CsA group ($P<0.001$) (Table 2). No significant difference with respect to the change from baseline in total or LDL cholesterol between the reduced and standard TAC groups was observed. There were no significant differences for any of the comparisons in change from baseline in high-density lipoproteins cholesterol, triglycerides, TGF-β, homocysteine or C-reactive protein levels.

There were no statistically significant differences across treatment groups in the incidence of new onset diabetes after transplantation (NODAT) (reduced TAC 3/63, 4.8%; standard TAC 2/66, 3.0%; CsA 3/66, 4.5%; $P=0.909$). No statistically significant differences across treatment groups were present with respect to the prevalence of hypertension, hyperlipidemia, or hyperglycemia among patients who did not have these conditions at baseline.

Infections and Malignancies

There were no statistical differences across treatment groups in the incidence of infections (reduced TAC 16/100, 16.0%; standard TAC 33/112, 29.5%; CsA 23/111, 20.7%; $P=0.060$) or malignancies (reduced TAC 9/100, 9.0%; standard TAC 6/112, 5.4%; CsA 3/111, 2.7%; $P=0.142$) in the first 12 months. There were four patients (three standard TAC, one CsA) who tested positive for cytomegalovirus (CMV) within the first 12 months; of these, three patients (two standard TAC, one CsA) had donors who tested positive for CMV, and one of the two standard TAC patients also tested positive for CMV pretransplant. The majority of malignancies were basal and squamous cell carcinomas. Malignancies, other than basal and squamous cell carcinoma, occurred in four patients in the reduced TAC group (prostate cancer, breast carcinoma, renal cell carcinoma, and melanoma); one patient in the standard TAC group (lymphoma); and two patients in the CsA group (metastatic melanoma [this patient had a history of melanoma] and mesothelioma).

Adverse Events

The proportion of patients who discontinued their randomized therapy because of adverse events was similar across treatment groups within the first 12 months (reduced TAC 1/100, 1.0%; standard TAC 8/112, 7.1%; CsA 7/111, 6.3%; $P=0.065$). Nine TAC-treated patients (one reduced TAC, eight standard TAC) crossed over to CsA, and of six CsA-treated patients who converted, four converted to TAC and two to sirolimus. One patient in the reduced TAC group converted because of hyperglycemia. Among the standard TAC patients, two were converted because of gastrointestinal (GI) side effects, two because of alopecia, one because of hyperglycemia, one because of hypertriglyceridemia, one because of a generalized rash, and one voluntarily withdrew. Of the six patients in the CsA group who converted, two converted because of CsA toxicity; one converted because of renal dysfunction; one because of gingival hypertrophy, hypertrichosis, and hypercholesterolemia; one because of hypertrichosis; and one because of refractory rejection. One additional patient in the CsA group who did not convert to another immunosuppressant, discontinued CsA because of renal dysfunction and subsequently died after 8 months of follow-up.

The incidences of hypertrichosis, gingival hypertrophy, and bone fracture were similar across treatment groups at 12 months in patients who did not have these conditions at baseline. Significantly more patients in both TAC groups than in the CsA group developed alopecia

(reduced TAC 12/93, 12.9%; standard TAC 16/102, 15.7%, CsA 0/103, 0%; $P<0.001$). Serious adverse events were experienced by 18 patients within the first 12 months, nine in the reduced TAC group, six in the standard TAC group, and three in the CsA group. One patient experienced a serious adverse event that was considered definitely related to treatment; a patient in the standard TAC group tested positive for disseminated CMV within 8 weeks of enrollment in the study.

Quality of Life

Based on results of the Memphis Survey, there were no statistically significant differences across treatment groups at 12 months in the median change from baseline in the following areas related to quality of life: emotional burden, life/role responsibilities, mobility, or miscellaneous (e.g., changes in appetite, sleep habits, weight gain, hair growth, sexual interest). Within the miscellaneous category, a statistically significant difference across treatment groups ($P=0.018$) was observed for enlarged gums; the mean score for enlarged gums increased in the CsA group (indicating a lower quality of life in this area), whereas, it decreased in both TAC groups. A statistically significant difference ($P=0.037$) in the median change from baseline in GI distress score was observed across treatment groups, with a statistically significant ($P=0.031$) increase from baseline in GI distress score observed in the reduced TAC group indicating a lower quality of life in this area.

Results of 2-Year Follow-Up

The OPTIMA study was terminated after all patients completed 1 year. In the subset of patients who completed 2 years of follow-up (reduced TAC: 58/100; standard TAC: 57/112; CsA: 56/111), multiple parameters demonstrated significantly ($P<0.05$, Kruskal-Wallis test) better mean change from baseline at month 24 for both the reduced (BUN: −4.41 mg/dL; serum creatinine: +0.09 mg/dL; Cystatin C: −0.13 mg/L) and standard TAC (BUN: −2.75 mg/dL; serum creatinine: +0.09 mg/dL; Cystatin C: −0.05 mg/L) groups versus the CsA group (BUN: +2.39 mg/dL; serum creatinine: +0.12 mg/dL; Cystatin C: +0.21 mg/L).

DISCUSSION

The stable renal transplant recipients in this clinical trial were characteristic of the U.S. transplant population (*16*) and included a good representation of blacks (approximately 27%) and women (approximately 34%).

Despite clear protocol-defined initial target trough levels (reduced dose TAC: 3–6 ng/mL, standard dose TAC: 6–9 ng/mL), the achieved trough levels overlapped substantially after 1 year (Fig. 2), with the median trough levels at 4.9 and 6.9 ng/mL, respectively. Similarly in the SYMPHONY study, TAC trough levels were maintained at the high end or above the target range (*13*). The results of SYMPHONY and OPTIMA suggest that clinicians tend to treat conservatively. OPTIMA was designed with a wide range of target CsA trough levels, given the possible variability of these levels after several years posttransplant. This variability should not have introduced a significant bias because the CsA dose was stable at study entry and stable for most CsA patients throughout the study (median daily CsA doses were 200 mg at every time point from baseline through month 12; the mean dose at baseline was 221 mg compared with 210 at month 12).

Conversion from CsA to TAC was safe and well-tolerated, and patient and graft survival and incidence of BCAR were similar across treatment groups. Conversion from CsA to reduced TAC resulted in improved renal function based on estimated creatinine clearance and serum creatinine, consistent with results of previous comparison studies of TAC and CsA (*17*, *18*). A more favorable change from baseline in cystatin C was observed in the reduced TAC group compared with the CsA group or the standard TAC group in this study. Cystatin C is proposed to be superior to serum creatinine as a marker of renal function, because studies have demonstrated it to be more sensitive for detecting small changes in glomerular filtration rate and delayed graft function (*19*). Further comparison studies of cystatin C versus serum creatinine as a marker of renal function are warranted. Although there were statistically significant differences in median dose and trough concentrations between the two TAC dose groups in OPTIMA, the overlap between these groups (Fig. 2) for TAC exposure may explain the lack of significant differences between the reduced and standard doses at 12 months other than those results with cystatin C.

In a previous study, significantly lower lipid levels have been reported among patients receiving TAC immunosuppression compared with those receiving CsA (*19*). The results of the present study were consistent with those reported previously, in that total and LDL cholesterol levels were demonstrated to be significantly lower in both TAC groups compared with the CsA group (*20*). Reduced TAC doses did not significantly affect other nonimmune safety endpoints, including the markers of inflammation and cardiovascular disease homocysteine and C-reactive protein.

Historically, TAC has been associated with a higher incidence of NODAT than CsA (*21*); however, no significant difference in the incidence of NODAT between TAC-treated (5.7%) and CsA-treated (3.3%) patients ($P=0.453$) was observed in a more recent retrospective review of 435 kidney transplant recipients (*22*). Similarly, in this study, we found no statistically significant difference in the incidence of NODAT between the TAC group and the CsA group at 12 months. These recent results are likely reflective of better patient management and the advent of new adjunctive agents in recent years. Early trials maintained higher TAC levels (median trough levels of 12–15 ng/mL) (*21*). The similar incidence of NODAT could also be related to patients in this study being at least 4 years posttransplant.

Safety findings in the CsA and both TAC groups were consistent with the known safety profiles of the two CNIs (*4*). Overall, patients in both TAC groups and the CsA group had a comparable quality of life, although patients in both TAC groups had significantly lower incidences of enlarged gums and patients in the reduced TAC group displayed significantly worsened GI distress from baseline. Diarrhea and other GI events are associated with both CNI inhibitors and MMF. MMF doses were not reduced at the time of conversion from CsA. Because mycophenolate acid levels were not measured, it is not possible to rule out a

higher mycophenolate acid exposure in the reduced TAC group.

In conclusion, conversion from CsA to TAC resulted in significantly improved renal function when target trough concentrations were between 3.0 and 5.9 ng/mL, and a better serum lipid profile regardless of TAC concentration in kidney transplant recipients at 12 months. However, the TAC levels in the standard-dose arm approached those in the reduced-dose arm and the similar TAC exposure was associated with similar efficacy and safety outcomes in the two treatment groups.

APPENDIX

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REFERENCES

1. Olyaei AJ, de Mattos AM, Bennett WM. Nephrotoxicity of immunosuppressive drugs: New insight and preventive strategies. *Curr Opin Crit Care* 2001; 7: 384.
2. Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002; 62: 311.
3. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation* 2003; 75: 1291.
4. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med* 2004; 351: 2715. [Erratum in: *N Engl J Med* 2005; 352: 1056].
5. Wong W, Venetz JP, Tolkoff-Rubin N, et al. 2005 immunosuppressive strategies in kidney transplantation: Which role for the calcineurin inhibitors? *Transplantation* 2005; 80: 289.
6. Abramowicz D, del Carmen Rial M, Vitko S, et al. Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen: Results of a five-year, prospective, randomized study. *J Am Soc Nephrol* 2005; 16: 2234.
7. Kasiske BL, Chakkera HA, Louis TA, et al. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. *J Am Soc Nephrol* 2000; 11: 1910.
8. Flechner SM, Goldfarb D, Solez K, et al. Kidney transplantation with sirolimus and mycophenolate mofetil-based immunosuppression: 5-year results of a randomized prospective trial compared to calcineurin inhibitor drugs. *Transplantation* 2007; 83: 883.
9. Dudley C, Pohanka E, Riad H, et al. Mycophenolate mofetil substitution for cyclosporine A in renal transplant recipients with chronic progressive allograft dysfunction: The "creeping creatinine" study. *Transplantation* 2005; 79: 466.
10. Gallagher MP, Hall B, Craig J, et al. A randomized controlled trial of cyclosporine withdrawal in renal-transplant recipients: 15-year results. *Transplantation* 2004; 78: 1653.
11. Hernández D, Miquel R, Porrini E, et al. Randomized controlled study comparing reduced calcineurin inhibitors exposure versus standard cyclosporine-based immunosuppression. *Transplantation* 2007; 84: 706.
12. Frimat L, Cassuto-Viguier E, Charpentier B, et al. Impact of cyclosporine reduction with MMF: A randomized trial in chronic allograft dysfunction. The 'reference' study. *Am J Transplant* 2006; 6: 2725.
13. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; 357: 2562.
14. Hathaway D, Winsett R, Prendergast M, et al. The first report from the patient outcomes registry for transplant effects on life (PORTEL): Differences in side-effects and quality of life by organ type, time since transplant and immunosuppressive regimens. *Clin Transplant* 2003; 17: 183.
15. Magera MJ, Lacey JM, Casetta B, et al. Method for the determination of total homocysteine in plasma and urine by stable isotope dilution and electrospray tandem mass spectrometry. *Clin Chem* 1999; 45: 1517.
16. 2006 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1996–2005. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD.
17. Vincenti F, Jensik SC, Filo RS, et al. A long-term comparison of

tacrolimus (FK506) and cyclosporine in kidney transplantation: Evidence for improved allograft survival at five years. *Transplantation* 2002; 73: 775.
18. Waid T for the CRAF Study Group. Tacrolimus as secondary intervention vs. cyclosporine continuation in patients at risk for chronic renal allograft failure. *Clin Transplant* 2005; 19: 573.
19. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. *Am J Kidney Dis* 2002; 40: 221.
20. McCune TR, Thacker LR II, Peters TG, et al. Effects of tacrolimus on hyperlipidemia after successful renal transplantation. *Transplantation* 1998; 65: 87.
21. Pirsch JD, Miller J, Deierhoi MH, et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation* 1997; 63: 977.
22. First MR, Gerber DA, Hariharan S, et al. Posttransplant diabetes mellitus in kidney allograft recipients: Incidence, risk factors, and management. *Transplantation* 2002; 73: 379.