Randomized, Open-Label, Phase IV, Korean Study of Kidney Transplant Patients Converting From Cyclosporine to Prolonged-Release Tacrolimus Plus Standard- or Reduced-Dose Corticosteroids

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ABSTRACT

Background. This 24-week, multicenter, randomized, exploratory, comparative, open-label, phase-IV study assessed the safety and efficacy of prolonged-release tacrolimus (PR-T) with reduced-dose versus standard-dose corticosteroids in stable kidney transplant recipients in Korea after converting from cyclosporine-based therapy.

Methods. At baseline, patients were converted from cyclosporine-based to PR-T-based immunosuppression and randomized (1:1) to receive either corticosteroids maintained at prestudy dose (standard-dose group) or tapered from week 4 to 50% of the prestudy dose by week 12 (reduced-dose group). Patients were seen at baseline and weeks 1, 4, 12, and 24. The primary endpoint was change in estimated glomerular filtration rate (Modification-of-Diet-in-Renal-Disease-4) between baseline and week 24. Secondary endpoints included either acute rejection or patient-reported satisfaction with PR-T. Adverse events (AEs) were recorded.

Results. Overall, 150 patients were randomized into a reduced-dose group (n = 73) and a standard-dose group (n = 77). At week 24, mean ± standard deviation for corticosteroid dose was 2.5 ± 0.9 mg and 5.0 ± 1.3 mg, respectively. Mean change in estimated glomerular filtration rate from baseline to week 24 was +1.5 ± 9.1 mL/min/1.73 m^2 (P = .1567) and +3.4 ± 10.6 mL/min/1.73 m^2 (P = .0065), respectively, and not significantly different between groups. There were no acute rejection episodes. Most

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respondents (>70%) considered PR-T more convenient than cyclosporine. AE incidence was similar between groups. The most common AEs experienced by ≥3% of patients in either treatment group were gastrointestinal events (20.8% and 28.6% of patients receiving reduced- and standard-dose corticosteroids, respectively). Most AEs in both treatment groups were mild or moderate in severity.

Conclusion. Renal function was maintained following conversion from cyclosporine to PR-T, irrespective of corticosteroid regimen; PR-T enables reduced corticosteroid dosage.

SINCE its introduction in the early 1990s, oral tacrolimus has become the mainstay of immunosuppressive therapy following solid organ transplantation. However, while >90% of kidney transplant recipients are now prescribed tacrolimus at the time of transplantation, approximately 10% continue to receive cyclosporine as their primary calcineurin inhibitor [1]. In clinical practice, the latter patients may subsequently be converted from cyclosporine to tacrolimus due to refractory rejection and also to address cosmetic side effects associated with cyclosporine [2]. As such, assessing the safety and efficacy of conversion from cyclosporine to different tacrolimus-based regimens remains of interest.

A once-daily, prolonged-release tacrolimus formulation was first approved in 2007 and is now available in many countries for immunosuppressive therapy following solid organ transplantation [3]. It was anticipated that nonadherence to immunosuppressive regimens, which is associated with de novo donor-specific antibody development, antibody-mediated rejection, and poor graft survival in kidney transplant recipients [4–6], may be reduced with once-daily tacrolimus dosing compared with twice-daily, immediate-release tacrolimus [7,8]. This has the potential to improve transplant outcomes [4–6].

In the European CONCERTO study, converting stable kidney transplant recipients from a twice-daily, cyclosporine-based to a once-daily, prolonged-release tacrolimus–based immunosuppressive regimen was associated with clinical effectiveness, stable renal function, and a good safety profile over 24 weeks of follow up [2]. However, this study did not examine the clinical impact of changing the dose of adjunct immunosuppressive agents before and after conversion to prolonged-release tacrolimus. As tacrolimus has a more potent immunosuppressive action than cyclosporine [9], it may be possible to decrease the dosing of concomitant immunosuppressive drugs, potentially reducing their associated side effects. While the long-term side effects of corticosteroid use following renal transplantation (eg, hypertension and post-transplantation diabetes mellitus) are well known [10], a recent Cochrane Collaboration systematic review suggested that the benefits of corticosteroid avoidance or withdrawal remain unclear [11]. To our knowledge, there are no studies reporting the efficacy of reduced corticosteroid-dosing in patients converting from cyclosporine-based to prolonged-release tacrolimus–based regimens in Korea. Furthermore, little is known regarding the safety of prolonged-release tacrolimus with reduced-dose corticosteroids.

This study investigated the safety and efficacy of prolonged-release tacrolimus in conjunction with either a standard-dose or a 50% reduced-dose corticosteroid regimen in patients with stable kidney transplants in Korea after converting from immunosuppressive treatment with a cyclosporine plus corticosteroid-based regimen.

MATERIALS AND METHODS

Study Design and Patients

This was a 24-week, multicenter, randomized, exploratory, comparative, open-label, phase IV study conducted at 19 medical centers in Korea (ClinicalTrials.gov: NCT02034747; protocol number ADV-KT-13-01). All study materials were reviewed and approved by the Institutional Review Board at each study site (see Table S1 for approval numbers). The study was conducted in accordance with Korean Good Clinical Practice, the International Council for Harmonisation guidelines, and the Declaration of Helsinki. Written informed consent to participate in the study was obtained from all patients.

The study included adult patients aged ≥20 years with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 who had received a kidney transplant (including retransplants) ≥12 months prior to study enrollment. Only patients who had received cyclosporine and corticosteroids (with or without concomitant mycophenolic acid [MPA]) as immunosuppressive therapy following transplantation and whose cyclosporine dosage had remained unchanged for ≥4 weeks prior to enrollment were included. Patients were required to be clinically stable, as assessed by the study investigator, and females of childbearing potential with a negative serum pregnancy test at enrollment were required to use contraception during the study.

Patients were excluded from the study if they had received an organ transplant other than a kidney, experienced an acute rejection episode ≤12 weeks before enrollment, had an acute rejection episode requiring antilymphocyte antibody therapy ≤24 weeks before enrollment, or received their transplant from a full human leukocyte antigen-identical donor. Patients with underlying focal segmental glomerulosclerosis or membranoproliferative glomerulonephritis type II were excluded, as were those who had cirrhosis or an unstable medical condition that was likely to affect the study objectives. Participants in other clinical trials or patients who had received any investigational drug ≤28 days before enrollment were also ineligible. Full inclusion and exclusion criteria are listed in the supporting information (Table S2).

Study Procedures

The study included 6 scheduled visits: screening (between day -30 and day 0), baseline (day 0), week 1 (±3 days), week 4 (±7 days), week 12 (±7 days), and week 24 (±14 days). Patient and donor

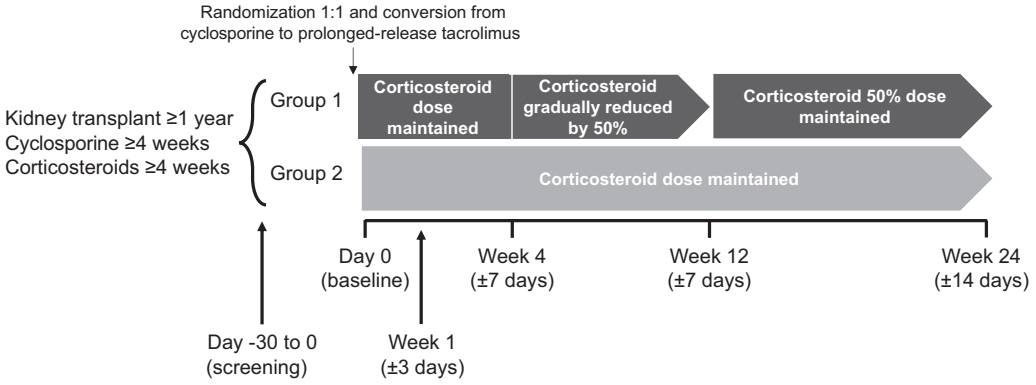

Fig 1. Overview of the study design.

demographics and characteristics were collected during screening. At baseline, patients' medical histories were reviewed, a physical examination was conducted, and cyclosporine trough levels were measured. Eligible patients were then randomized at baseline (1:1) to receive 1 of 2 treatment regimens: prolonged-release tacrolimus (Advagraf, Astellas Pharma Europe BV, Meppel, Netherlands) plus corticosteroid gradually reduced from week 4 to 50% of the pre-enrollment dose by week 12 (reduced-dose group); or prolonged-release tacrolimus plus corticosteroid maintained at the pre-enrollment dose (standard-dose group) (Fig 1).

Vital signs, laboratory parameters, and tacrolimus trough blood concentration were measured throughout the study (the latter not at baseline). Information on concomitant medication use and rejection episodes was also collected. eGFR (Modification of Diet in Renal Disease-4) and creatinine (Cockcroft–Gault [12]) was assessed at baseline, week 12, and week 24. Adverse events (AEs) were recorded throughout follow-up and, at week 24, a further physical examination was carried out.

At week 24, each patient's satisfaction with their treatment regimen was assessed using a 5-item questionnaire. Patients responded to the following questions: 1. Is it more convenient for you to take your drug after converting to once-daily, prolonged-release tacrolimus? 2. Has the number of missed doses decreased after converting to prolonged-release tacrolimus (comparing missed doses in the previous 24 weeks using prolonged-release tacrolimus versus the entire time receiving cyclosporine)? 3. Have you ever missed or discontinued cyclosporine doses due to the inconvenience of twice-daily dosing before participating in the study? 4. When you missed a cyclosporine dose, was it usually in the morning or evening? and 5. Before participating in the study, what would be the biggest reason for missing a cyclosporine dose at the scheduled time?

Study Treatment

At baseline, patients were converted from their cyclosporine-based regimen to oral once-daily, prolonged-release tacrolimus, administered at an initial daily dose of 0.05–0.07 mg/kg. Prolonged-release tacrolimus was given in the morning, at least 1 hour before or 2 to 3 hours after breakfast and 24 hours after the last dose of cyclosporine. The tacrolimus dose was subsequently adjusted in order to achieve target whole blood trough levels of 5 to 15 ng/mL during the first 4 weeks and 3 to 10 ng/mL thereafter.

Corticosteroid treatment was continued, using the same agents and at the same dose as each patient had received prior to study entry. In only the reduced-dose group, the corticosteroid dose was tapered from week 4, such that the patient received 50% of their prestudy daily dose by week 12. After this time, the corticosteroid dose was maintained at the reduced level until the end of the study.

Endpoints

The primary efficacy endpoint was change in the eGFR from baseline (before conversion) to week 24. The secondary efficacy endpoints were change in the eGFR from baseline to week 12, the change in creatinine clearance from baseline to weeks 12 and 24, and the incidence of acute rejection. Acute rejection episodes were suspected when serum creatinine was 30% higher than baseline or had increased by $\geq$0.3 mg/dL from baseline at the second of 2 or more consecutive evaluations showing an increase in serum creatinine and on the basis of findings from nuclear medicine or ultrasound tests. When acute rejection was suspected, biopsies were evaluated according to the Banff 2007 classification [13]. A further secondary endpoint was patient-reported satisfaction with prolonged-released tacrolimus-based immunosuppressive therapy, based on the questionnaire.

The incidence of AEs was recorded, regardless of their association with the study drug. Assessments included change from baseline to week 24 in vital signs (systolic and diastolic blood pressure) and laboratory parameters (glucose, glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides). Physical changes from baseline were also recorded at week 24, as was the presence of hypertrichosis and gingival hyperplasia at baseline and week 24.

Data and Statistical Analysis

As this was an exploratory study, a formal sample size calculation was not performed. The aim was to recruit 75 patients into each study group (ie, 150 patients in total). Patients were assigned to a treatment arm in the order of study entry, by the predefined allocation code of block randomization. The randomization table applied a sequence of random numbers (random number of each treatment group) produced by a randomization program, generated by the statistician, before the study started.

The full-analysis set (FAS) included all patients who received at least 1 dose of prolonged-release tacrolimus following conversion from cyclosporine and had eGFR data at baseline and at least 1 time point post baseline. Those in the FAS who completed the study according to the protocol and who had $\geq$80% treatment adherence for taking their prescribed medication were included in the per-protocol set (PPS). Treatment adherence was calculated

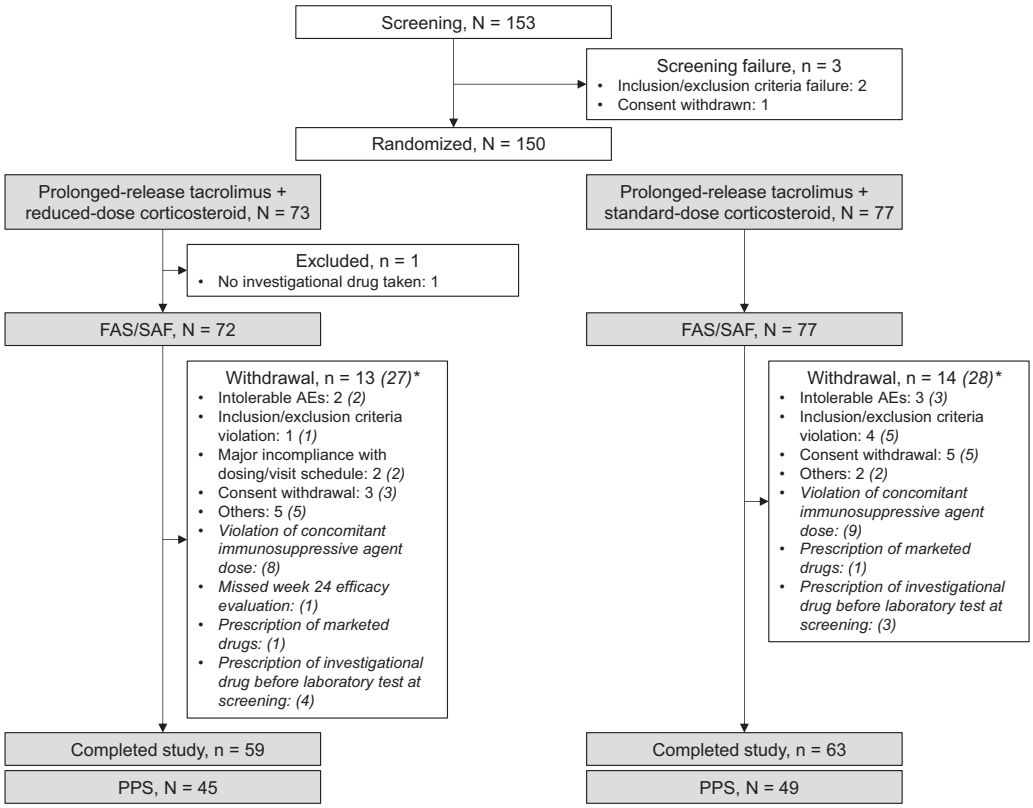

Fig 2. Patient flow through the study. *Numbers in italicized parentheses *(n)* denote the numbers of patients excluded from the PPS. AE, adverse event; FAS, full-analysis set; PPS, per-protocol set; SAF, safety-analysis set.

using the following equation: Treatment compliance (%) = (Dose of the drug actually taken/Dose of the drug expected to be taken) × 100. The safety-analysis set (SAF) included all patients who received prolonged-release tacrolimus at least once during the study. Efficacy analyses were conducted using the FAS, and results were confirmed in the PPS. Safety and demographic data were analyzed in the SAF.

Continuous data are presented with descriptive statistics, and categorical data are shown as frequencies and percentages, with between-group differences evaluated by χ^2 test or Fisher exact tests, as appropriate. Changes in eGFR and creatinine clearance were analyzed using a paired *t* test, and between group differences were assessed using Student *t* test. In the case of missing data or study discontinuation, the participant's most recent efficacy observations (excluding baseline measurements) were imputed according to the last observation carried forward (LOCF) method, including for analysis of the primary endpoint. $P < .05$ was considered statistically significant; type 1 error was not controlled for in the study. All analyses were conducted using SAS Version 9.4 (SAS Institute, Inc, Cary, NC, United States).

RESULTS

Patient Disposition and Baseline Characteristics

The date of first patient enrollment was November 21, 2013, and the last patient's final visit was November 7, 2015. Overall, 153 patients were screened for this study (Fig 2). Three patients failed the screening due to consent withdrawal and inclusion and exclusion criteria violation. Of the remaining 150 patients, 73 were randomized to reduced-dose and 77 to standard-dose corticosteroids. As 1 patient in the group receiving reduced-dose corticosteroids did not take prolonged-release tacrolimus, the FAS and SAF was composed of 149 patients (reduced-dose group, n = 72; standard-dose group, n = 77); 94 patients formed the PPS (reduced-dose group, n = 45; standard-dose group, n = 49) (Fig 2).

Patient and donor baseline characteristics are shown in Table 1. There were no statistically significant differences between patient baseline parameters, except that the mean ± standard deviation (SD) age of patients receiving reduced- versus standard-dose corticosteroids was lower (49.9 ± 10.1 years vs 54.0 ± 10.0 years, respectively; $P = .0143$). Over half of the patients in both groups were male (66.7% and 58.4%, respectively). Glomerulonephritis was the most common known cause of renal failure in patients receiving reduced- or standard-dose corticosteroids (36.1% and 22.1%, respectively). Living donor kidney transplantation predominated (>80%) in both groups. The mean ± SD time since kidney transplantation was similar in patients receiving reduced- and standard-dose corticosteroids (140.2 ± 84.7 months and 138.2 ± 79.0 months, respectively; $P = .8835$) (Table 1).

Table 1. Baseline Patient and Donor Demographics and Characteristics (SAF)

Parameter	Prolonged-Release Tacrolimus + Reduced-Dose Corticosteroids (n = 72)	Prolonged-Release Tacrolimus + Standard-Dose Corticosteroids (n = 77)
Patient characteristics		
Sex, male	48 (66.7)	45 (58.4)
Age, mean ± SD, y	49.9 ± 10.1	54.0 ± 10.0
Median (range)	50.0 (31.0–73.0)	53.0 (34.0–77.0)
Time since kidney transplantation, mean ± SD, mo	140.2 ± 84.7	138.2 ± 79.0
Median (range)	131.4 (20.3–301.3)	129.6 (18.3–343.1)
BMI, mean ± SD, kg/m^2	23.4 ± 2.9	23.4 ± 3.0
Cause of renal failure		
Glomerulonephritis	26 (36.1)	17 (22.1)
Nephrosclerosis	13 (18.1)	15 (19.5)
Diabetic nephropathy	2 (2.8)	8 (10.4)
Polycystic disease	3 (4.2)	3 (3.9)
Uropathy	1 (1.4)	0 (0)
Systemic vasculitis	0 (0)	1 (1.3)
Other	6 (8.3)	3 (3.9)
Unknown	21 (29.2)	30 (39.0)
Hepatitis B virus, positive	1 (1.4)	2 (2.6)
Data missing	3 (4.2)	5 (6.5)
Hepatitis C virus, positive	1 (1.4)	0 (0)
Data missing	5 (6.9)	9 (11.7)
Cytomegalovirus IgG, positive	32 (44.4)	43 (55.8)
Data missing	27 (37.5)	24 (31.2)
Epstein-Barr virus VCA IgG, positive	24 (33.3)	27 (35.1)
Data missing	44 (61.1)	46 (59.7)
Major-type HLA mismatch*		
0–3 mismatches	41 (56.9)	43 (55.8)
4–6 mismatches	19 (26.4)	25 (32.5)
Data missing	12 (16.7)	9 (11.7)
Donor characteristics		
Sex, male	41 (56.9)	46 (59.7)
Data missing	5 (6.9)	2 (2.6)
Age, mean ± SD, y	39.2 ± 11.7	37.7 ± 11.7
Median (range)	39.5 (15.0–60.0)	36.5 (19.0–61.0)
Data missing	14 (19.4)	9 (11.7)
Donor type, living	58 (81.7)†	62 (80.52)

Data are n (%), unless otherwise stated. Percentages may not add up to 100% because of rounding errors.
Abbreviations: BMI, body mass index; SAF, safety-analysis set; SD, standard deviation; VCA, viral capsid antigen.
*Analysis was conducted only when HLA type was available in both patient and donor; data are for the total number of mismatches in major HLA type (HLA-A, HLA-B, HLA-DR).
†Donor status was unknown for 1 patient receiving prolonged-release tacrolimus + reduced-dose corticosteroids.

Immunosuppression

The mean ± SD trough blood concentration of cyclosporine at baseline, before conversion to prolonged-release tacrolimus, was 102.2 ± 97.8 ng/mL and 111.0 ± 97.4 ng/mL in patients receiving reduced- and standard-dose corticosteroids, respectively. Prior to conversion, MPA and prednisolone were the most common concomitant immunosuppressive drugs in the reduced-dose corticosteroid group (81.9% and 76.4% of patients, respectively) and in the standard-dose corticosteroid group (84.4% and 66.2%, respectively). Compared with preconversion, a similar proportion of patients received these drugs postconversion.

After conversion from cyclosporine, the mean daily dose of prolonged-release tacrolimus during the entire follow-up period was similar in patients receiving reduced- or standard-dose corticosteroids (0.06 ± 0.02 mg/kg and 0.05 ± 0.02 mg/kg, respectively). Mean tacrolimus trough blood levels were similar between the treatment groups and remained stable during follow up, including after corticosteroid dose reduction in the reduced-dose group (Fig 3).

In the patients receiving reduced-dose corticosteroids, the mean ± SD corticosteroid daily dose was 5.0 ± 1.7 mg at baseline and, following protocol dose reduction, was approximately 50% lower at week 12 (2.7 ± 1.0 mg) through to week 24 (2.5 ± 0.9 mg) (Fig 4). In patients receiving standard-dose corticosteroids, the mean ± SD corticosteroid dose was similar at baseline and week 24 (5.1 ± 1.4 mg vs 5.0 ± 1.3 mg, respectively) (Fig 4). There was no significant difference in corticosteroid dose between the treatment groups at baseline and week 1 ($P = .5897$ and $P = .6807$, respectively).

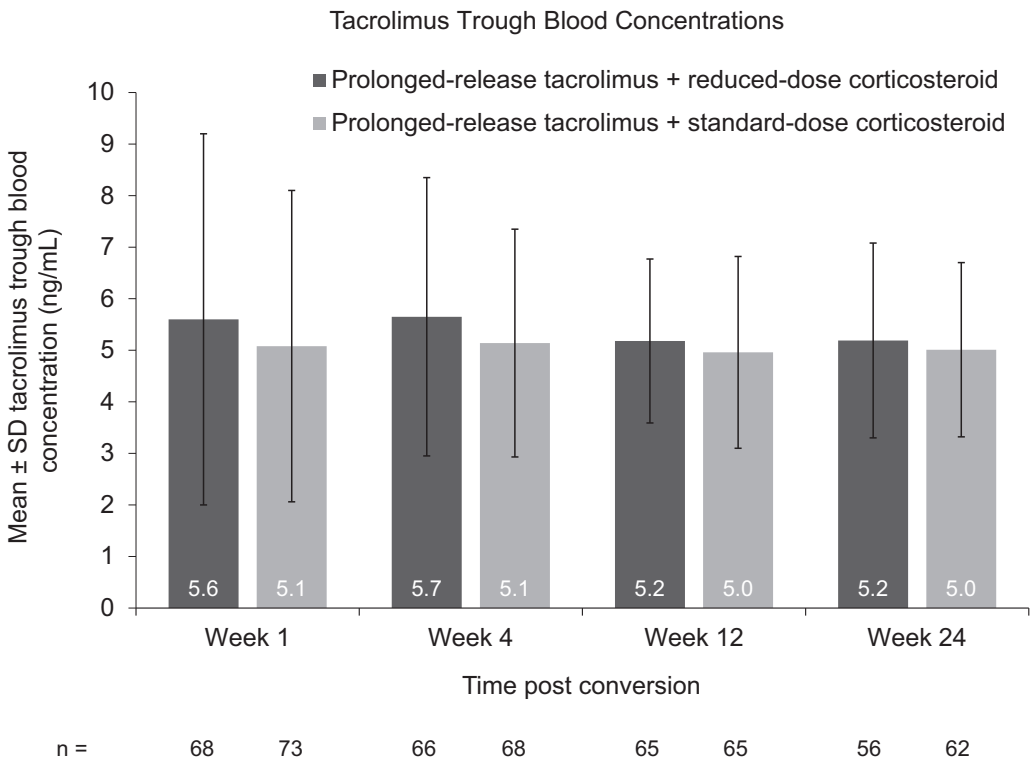

Fig 3. Mean tacrolimus trough blood concentrations after conversion from cyclosporine-based immunosuppression to treatment with once-daily, prolonged-release tacrolimus plus reduced- or standard-dose corticosteroids (safety-analysis set). Not all patients had data for all visits and parameters assessed. SAF, safety-analysis set; SD, standard deviation.

However, at weeks 4, 12, and 24, corticosteroid dose was significantly lower in patients receiving reduced- versus standard-dose corticosteroids (all $P < .0001$).

Renal Function

In patients receiving prolonged-release tacrolimus with reduced-dose corticosteroids, mean ± SD eGFR (FAS, LOCF) was similar at baseline and week 24 (61.8 ± 17.5 mL/min/1.73 m^2 vs 63.3 ± 19.2 mL/min/1.73 m^2, respectively; $P = .1567$) (Table 2). In patients receiving prolonged-release tacrolimus with standard-dose corticosteroids, mean eGFR (LOCF) significantly increased between baseline and week 24 (62.5 ± 15.0 mL/min/1.73 m^2 vs 65.9 ± 18.3 mL/min/1.73 m^2; $P = .0065$). The difference between treatment groups at baseline and week 24 was not statistically significant. Results followed a similar pattern in the PPS (Table 2).

The change in mean ± SD eGFR (FAS, LOCF) from baseline to week 12 was not statistically significant for patients receiving prolonged-release tacrolimus with reduced-dose corticosteroids (61.8 ± 17.5 mL/min/1.73 m^2 vs 63.0 ± 18.3 mL/min/1.73 m^2, respectively; $P = .1582$). However, in patients receiving standard-dose corticosteroids, eGFR significantly increased between baseline and week 12 (62.5 ± 15.0 mL/min/1.73 m^2 vs 66.2 ± 19.8 mL/min/1.73 m^2; $P = .0164$) (Table S3). The difference between treatment groups at baseline and week 12 was not statistically significant (Table S3). Results followed a similar pattern in the PPS (Table S3).

There was no significant change in mean creatinine clearance (FAS, LOCF) from baseline to week 12 for patients receiving prolonged-release tacrolimus with either reduced-dose corticosteroids or standard-dose corticosteroids (mean ± SD change, +0.7 ± 7.0 mL/min and +1.5 ± 8.4 mL/min, respectively) (Table S4). Neither was there a significant change between baseline and week 24 (+0.9 ± 8.4 mL/min and +1.8 ± 8.2 mL/min, respectively). The change in creatinine clearance did not significantly differ between treatment groups at baseline, week 12, or week 24 (Table S4). A similar pattern was observed for the PPS, except that mean ± SD eGFR significantly increased between baseline and week 24 in the group receiving standard-dose corticosteroids (60.9 ± 15.4 mL/min vs 63.0 ± 18.4 mL/min, respectively; $P = .0266$) (Table S4).

Acute Rejection

There were no episodes of acute rejection during the study.

Patient Satisfaction

Of respondents to the satisfaction questionnaire, 50 of 71 (70.4%) and 61 of 74 (82.4%) receiving reduced- or standard-dose corticosteroids, respectively, considered that their medication became more convenient to take after

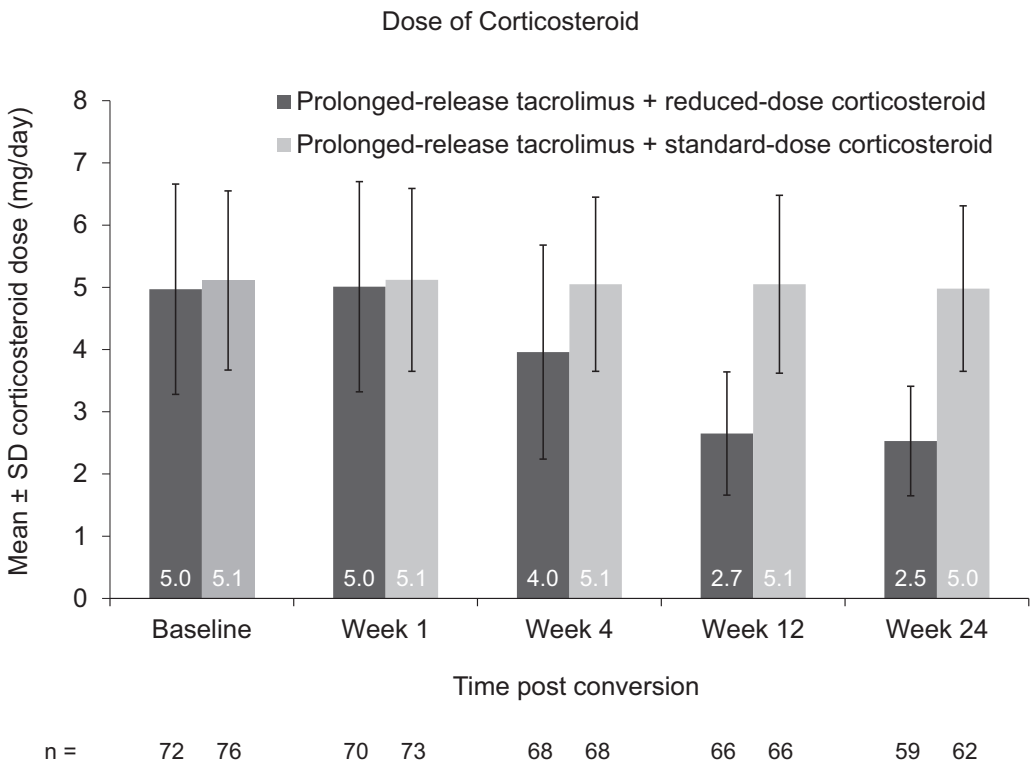

Fig 4. Mean corticosteroid dose from baseline up to week 24 (safety-analysis set). Not all patients had data for all visits and parameters assessed. SAF, safety-analysis set; SD, standard deviation.

converting from twice-daily cyclosporine to once-daily, prolonged-release tacrolimus (responses of "yes" or "definitely yes"). Additionally, 31 of 71 (43.7%) and 35 of 74 (47.3%) receiving reduced- or standard-dose corticosteroids, respectively, reported that the number of doses of their immunosuppressive medication that they missed had decreased after converting to prolonged-release tacrolimus (Table S5). Of the patients responding "Morning" or "Evening" to the question "When you missed a cyclosporine dose, was it usually in the morning or evening?" 44 of 69 (63.8%) missed the evening versus the morning dose. The most common reason for missing a dose of cyclosporine prior to conversion was difficulty taking the drug at the scheduled time because of lifestyle and social life.

Safety

Overall, 58.3% of patients receiving prolonged-release tacrolimus with reduced-dose corticosteroids experienced a total of 98 AEs. This was similar to the incidence of AEs in patients receiving prolonged-release tacrolimus with standard-dose corticosteroids (64.9% of patients experiencing 109 AEs). The most common AEs experienced by ≥3% of patients in either treatment group were gastrointestinal events (20.8% and 28.6% of patients receiving reduced- and standard-dose corticosteroids, respectively), particularly diarrhea (9.7% and 14.3%) (Table 3). Most AEs in both treatment groups were mild or moderate in severity. Serious AEs were reported for 8.3% (6 events) and 10.4% (11 events) of patients receiving reduced- and standard-dose corticosteroids, respectively. AEs that were "probably related" or "possibly related" to the investigational drug occurred in 15.3% (17 events) and 13.0% (15 events) of patients, respectively.

Two patients (2.8%) receiving reduced-dose corticosteroids were withdrawn from the study due to AEs (diarrhea, and renal impairment and urticaria). Three patients (3.9%) receiving standard-dose corticosteroids were withdrawn from the study due to AEs (diarrhea in 2 patients and altered alanine aminotransferase and aspartate aminotransferase in 1 patient). There were no deaths during the study.

Hypertrichosis and Gingival Hyperplasia

Of the 3 patients who had hypertrichosis at baseline, 2 patients (1 each in the reduced- and standard-dose groups) did not have the condition at week 24, and the severity of hypertrichosis improved from severe at baseline to mild at week 24 for the third patient (standard-dose group). Of the 5 patients who had gingival hyperplasia at baseline (2 and 3 patients in the reduced- and standard-dose groups, respectively), no patients had the condition at week 24. There were no new cases of hypertrichosis or gingival hyperplasia in either treatment group after conversion to prolonged-release tacrolimus.

Table 2. Mean Change in eGFR From Baseline to week 24 in Patients Receiving Prolonged-Release Tacrolimus With Either Reduced- or Standard-Dose Corticosteroids (FAS and PPS)

FAS	Prolonged-Release Tacrolimus + Reduced-Dose Corticosteroids (n = 72)		Prolonged-Release Tacrolimus + Standard-Dose Corticosteroids (n = 77)		*P* Value (Reduced- Vs Standard-Dose Group)
	n	eGFR, Mean ± SD, mL/min/1.73 m^2	n	eGFR, Mean ± SD, mL/min/1.73 m^2	
Baseline	72	61.8 ± 17.5	77	62.5 ± 15.0	.7997
Week 24	58*	63.2 ± 19.3	63	64.9 ± 17.5	.5988
Week 24 (LOCF)	72	63.3 ± 19.2	77	65.9 ± 18.3	.4090
Difference (baseline - week 24 [LOCF])	72	1.5 ± 9.1	77	3.4 ± 10.6	.2538
P value for difference (baseline - week 24 [LOCF]) within group		.1567		.0065	

PPS	Prolonged-Release Tacrolimus + Reduced-Dose Corticosteroids (n = 45)		Prolonged-Release Tacrolimus + Standard-Dose Corticosteroids (n = 49)		*P* Value (Reduced- Vs Standard-Dose Group)
	n	eGFR, Mean ± SD, mL/min/1.73 m^2	n	eGFR, Mean ± SD, mL/min/1.73 m^2	
Baseline	45	62.3 ± 17.3	49	59.8 ± 14.3	.4584
Week 24	45	64.3 ± 19.8	49	63.6 ± 17.2	.8593
Difference (baseline - week 24)	45	2.0 ± 9.1	49	3.8 ± 10.0	.3774
P value for difference (baseline - week 24) within group		.1402		.0103	

Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full-analysis set; LOCF, last observation carried forward; PPS, per-protocol set; SD, standard deviation.
*59 patients in the FAS completed the study, but week 24 eGFR data were missing for 1 patient.

Vital Signs, Laboratory Parameters, and Physical Examination

The change in systolic blood pressure between baseline and week 24 was similar between treatment groups (Fig 5). While diastolic blood pressure was similar at baseline and week 24 within each treatment group, diastolic blood pressure was higher in the reduced- versus standard-dose group at week 24.

The mean decrease in glucose was similar between treatment groups. HbA1c decreased between baseline and week 24 in patients receiving prolonged-release tacrolimus with reduced-, but not standard-dose, corticosteroids (mean ± SD change -0.1% ± 0.4% and +0.2% ± 0.6%, respectively) (Fig 5). The cholesterol profiles showed improvement from baseline in both treatment groups at week 24 (Fig 5). No clinically meaningful changes, however, were found for pulse rate (data not reported) or triglyceride levels.

Between baseline and week 24, there were 4 reports of a change from normal to abnormal in physical appearance, all of which were reported as AEs. One patient in each treatment group experienced a dermatologic change; there was 1 change in general appearance in a patient receiving reduced-dose corticosteroids and 1 musculoskeletal change in a patient receiving standard-dose corticosteroids.

DISCUSSION

This is the first study to investigate the safety and efficacy of prolonged-release tacrolimus in conjunction with either a standard-dose or a 50% reduced-dose corticosteroid regimen in Korean patients with stable kidney transplants after converting from immunosuppressive treatment with a cyclosporine plus a corticosteroid-based regimen. In this study, patients in both treatment groups had stable and comparable renal function over 24 weeks of treatment, as assessed by eGFR and creatinine clearance, and there were no episodes of acute rejection. Patients reported that treatment with prolonged-release tacrolimus was more convenient than with their previous twice-daily cyclosporine-based regimen. Furthermore, prolonged-release tacrolimus with either reduced- or standard-dose corticosteroids was associated with a good safety profile.

In this study, renal function was supported following conversion from cyclosporine to prolonged-release tacrolimus. Similarly, Rostaing et al [2] reported that conversion of patients from cyclosporine to prolonged-release tacrolimus, without per protocol changes in corticosteroid dose, was associated with stable creatinine clearance over 24 weeks of treatment (mean ± SD change of -1.0 ± 9.1 mL/min between conversion and week 24). Supporting the role of tacrolimus in maintaining renal function, publications comparing tacrolimus- with cyclosporine-based immunosuppression in de novo kidney transplant recipients reported better renal function (eGFR and creatinine levels) with tacrolimus-based therapy [14–16]. Indeed, prolonged-release tacrolimus–based immunosuppression improved renal function versus cyclosporine-based immunosuppression over 4 years of treatment in de novo kidney transplant recipients, as measured by eGFR (Cockcroft–Gault and Modification of Diet in Renal Disease-4) [16]. Importantly,

Table 3. AEs Reported by ≥3% of Patients in Either Treatment Group, Regardless of Relationship With Study Drug (SAF)

MedDRA Preferred Term	Prolonged-Release Tacrolimus + Reduced-Dose Corticosteroids (n = 72)	Prolonged-Release Tacrolimus + Standard-Dose Corticosteroids (n = 77)
Gastrointestinal disorders	15 (20.8)	22 (28.6)
Diarrhea	7 (9.7)	11 (14.3)
Gastroesophageal reflux disease	3 (4.2)	3 (3.9)
Nausea	1 (1.4)	3 (3.9)
Abdominal discomfort	0 (0.0)	3 (3.9)
Skin and subcutaneous tissue disorders	14 (19.4)	8 (10.4)
Alopecia	6 (8.3)	2 (2.6)
Pruritus	4 (5.6)	4 (5.2)
Rash	3 (4.2)	0 (0.0)
Urticaria	3 (4.2)	0 (0.0)
Infections and infestations	11 (15.3)	19 (24.7)
Nasopharyngitis	5 (6.9)	6 (7.8)
Upper respiratory tract infection	3 (4.2)	5 (6.5)
Nervous system disorders	7 (9.7)	4 (5.2)
Headache	5 (6.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	4 (5.6)	5 (6.5)
Renal and urinary disorders	4 (5.6)	1 (1.3)
Respiratory, thoracic, and mediastinal disorders	4 (5.6)	0 (0.0)
General disorders and administration site conditions	3 (4.2)	2 (2.6)
Eye disorders	2 (2.8)	3 (3.9)
Investigations	2 (2.8)	6 (7.8)
Metabolism and nutrition disorders	2 (2.8)	5 (6.5)
Injury, poisoning, and procedural complications	1 (1.4)	3 (3.9)

Data are n (%).
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAF, safety-analysis set.

there was no decline in renal function when the dose of corticosteroid was reduced by 50% compared with maintaining the dose of corticosteroids. However, maintaining the corticosteroid dose was associated with a significant improvement in eGFR between baseline and week 24. There were no episodes of acute rejection in our study. Given that most patients were receiving concomitant MPA during the study, the stability or improvement in eGFR during follow up and the acceptable safety profile indicated that standard immunosuppressive therapy with tacrolimus plus corticosteroids and MPA remains a valuable recommendation for rejection prophylaxis in kidney transplant recipients.

Most of the patients who completed the patient satisfaction questionnaire in our study considered that taking their medication became more convenient after conversion from twice-daily cyclosporine to once-daily, prolonged-release tacrolimus. Patients also tended to miss the evening rather than the morning dose of cyclosporine prior to conversion. These findings are in concordance with reports that kidney transplant recipients prefer once-daily dosing [17] and are more likely to take their morning than their evening dose of immunosuppressive medication [8,17]. Furthermore, in our study, over 40% of patients reported missing fewer doses of their immunosuppressive medication after converting from cyclosporine to prolonged-release tacrolimus. This is consistent with a previous report, in which nonadherence to medication was improved after stable heart transplant patients were converted from immediate-release tacrolimus or cyclosporine to prolonged-release tacrolimus [18,19]. Collectively, these data suggest that reducing the number of doses of medication may be sufficient reason for converting patients from twice-daily cyclosporine- to once-daily, prolonged-release tacrolimus–based immunosuppression.

There did not appear to be any harmful effects of converting patients from cyclosporine-based to prolonged-release tacrolimus–based immunosuppression, and the incidence of AEs was similar between reduced- and standard-dose corticosteroid groups. However, as this was only a 24-week study, it is possible that differences in the incidence of AEs between corticosteroid dosing groups might emerge over a longer period of follow up. Notably, some publications have suggested that cyclosporine is associated with the development of hypertrichosis and gingival hyperplasia [16,20,21]. In our study, patients who had hypertrichosis and/or gingival hyperplasia at baseline with cyclosporine-based immunosuppression experienced an improvement in or no longer had the condition by week 24 after conversion to prolonged-release tacrolimus. This suggests that in routine clinical practice, converting kidney

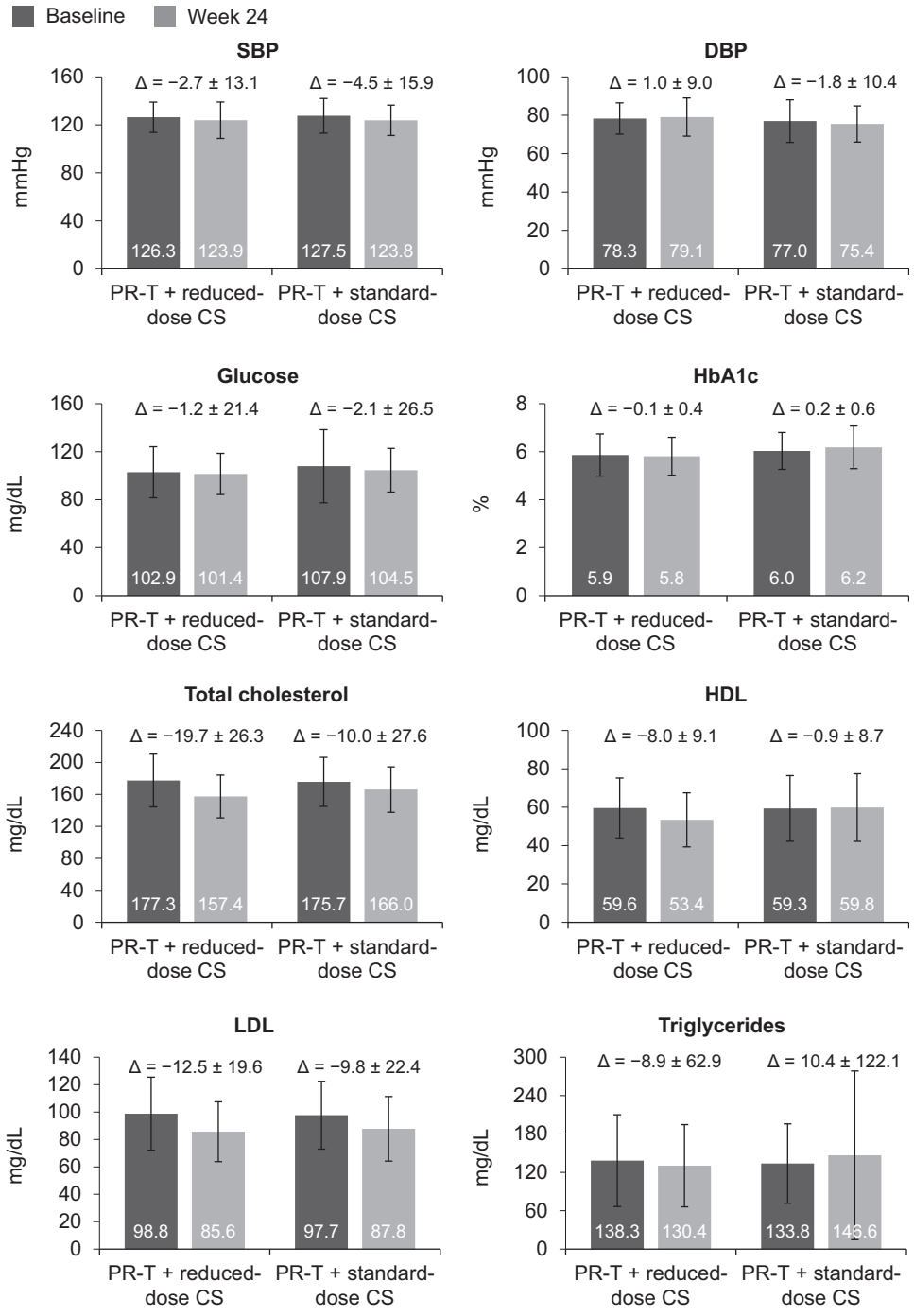

Fig 5. Mean change in vital signs and laboratory parameters from baseline to week 24 (safety-analysis set). Data are mean ± standard deviation. Δ is the change between baseline and week 24. Not all patients had data for all visits and parameters assessed. Numbers of patients in the reduced-dose group at baseline and week 24 and for change between baseline and week 24 are as follows: SBP, n = 72, n = 58, n = 58, respectively; DBP, n = 72, n = 58, n = 58, respectively; glucose, n = 71, n = 58, n = 58, respectively; HbA1c, n = 66, n = 57, n = 53, respectively; total cholesterol, n = 71, n = 58, n = 58, respectively; HDL, n = 68, n = 57, n = 54, respectively; LDL, n = 68, n = 58, n = 55, respectively; triglycerides, n = 69, n = 58, n = 56, respectively. Numbers of patients in the standard-dose group at baseline and week 24 and for change between baseline and week 24: SBP, n = 77, n = 63, n = 63, respectively; DBP, n = 77, n = 63, n = 63, respectively; glucose, n = 76, n = 63, n = 62, respectively; HbA1c, n = 69, n = 57, n = 52, respectively; total cholesterol, n = 77, n = 63, n = 63, respectively; HDL, n = 74, n = 62, n = 59, respectively; LDL, n = 74, n = 62, n = 59, respectively; triglycerides, n = 74, n = 62, n = 59, respectively. CS, corticosteroid; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PR-T, prolonged-release tacrolimus; SAF, safety-analysis set; SBP, systolic blood pressure; SD, standard deviation.

transplant recipients from cyclosporine- to tacrolimus-based maintenance immunosuppression may improve cyclosporine-related AEs.

Although our study was not powered to examine changes in cardiovascular and metabolic factors between baseline and follow up, reducing the dose of the corticosteroid may improve LDL and HDL cholesterol levels and HbA1c. Further evaluation of these outcomes in future studies may, therefore, be warranted, particularly as other studies have shown reductions in HDL levels following corticosteroid withdrawal in kidney transplant patients receiving tacrolimus [22,23]. A number of mechanisms have been suggested by which glucocorticoids could increase HDL cholesterol [24]; therefore, if the corticosteroid dose is reduced, reductions in HDL cholesterol might be expected.

This study had several limitations, such as the open-label design, which could influence reporting or measurement of the outcomes and introduce bias. Furthermore, lack of a formal power calculation to determine the sample size might reduce the sensitivity of analyses conducted. Analyses of eGFR did not adjust for baseline eGFR values. While this approach was acceptable when analyzing LOCF data (ie, as most patients had week 12 data), it is possible that a treatment effect could be observed in the non-LOCF analysis if baseline eGFR values were taken into account. Therefore, despite similar baseline eGFR values between treatment groups, statistical analysis of non-LOCF data should be interpreted with caution. The study had a duration of 24 weeks, but longer-term follow up may be necessary for a more complete evaluation, especially as corticosteroid treatment has been associated with long-term side effects [10]. It was not possible to determine whether the patients who missed cyclosporine doses were the same patients who missed fewer doses after conversion to prolonged-release tacrolimus. Furthermore, the patient satisfaction questionnaire required patients to recall their cyclosporine treatment 24 weeks previously, which may be associated with recall bias. Finally, as this study was conducted in Korean kidney transplant recipients, the findings may not be generalizable to other patient populations.

As tacrolimus is a more potent immunosuppressive agent than cyclosporine [9], we considered that a reduced corticosteroid dose might be tolerable as part of a prolonged-release tacrolimus–based regimen. Results of previous attempts to minimize or withdraw corticosteroid therapy for kidney transplant recipients in order to reduce the long-term side effects associated with corticosteroid use [25] have been controversial [11]. For example, corticosteroid withdrawal during cyclosporine-based immunosuppression increased the risk of acute rejection or graft failure [26,27], while corticosteroid reduction in the presence of tacrolimus was tolerable [22,28,29] but potentially associated with an increased risk of graft rejection [30]. In our study, we found no clinically relevant changes in renal function and safety parameters when converting patients with stable kidney transplants from cyclosporine to prolonged-release tacrolimus plus a 50% reduced-dose versus standard-dose corticosteroids. However, this was a short-term study of 24 weeks duration. As long-term use of high-dose corticosteroids is associated with a variety of side effects, a 50% reduction of corticosteroid might be considered a clinical option for kidney transplant recipients converting from a cyclosporine-based to a prolonged-release tacrolimus–based immunosuppressive regimen.

CONCLUSIONS

In this study, renal function was maintained following conversion from a cyclosporine-based to prolonged-release tacrolimus–based therapy, irrespective of corticosteroid regimen, enabling the reduction of corticosteroid dosage. Coupled with a comparable incidence of AEs between the corticosteroid regimens, prolonged-release tacrolimus–based immunosuppressive regimens with reduced-dose corticosteroids may be a viable treatment option in clinical practice. Patients reported that after conversion from twice-daily cyclosporine to once-daily, prolonged-release tacrolimus, their medication became more convenient. No new safety signals were detected with prolonged-release tacrolimus.

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SUPPLEMENTAL DATA

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REFERENCES

[1] Hart A, Smith JM, Skeans MA, Gustafson SK, Stewart DE, Cherikh WS, et al. OPTN/SRTR 2015 annual data report: kidney. Am J Transplant 2017;17(Suppl 1):21–116.

[2] Rostaing L, Sánchez-Fructuoso A, Franco A, Glyda M, Kuypers DR, Jaray J. Conversion to tacrolimus once-daily from ciclosporin in stable kidney transplant recipients: a multicenter study. Transpl Int 2012;25:391–400.

[3] Caillard S, Moulin B, Buron F, Mariat C, Audard V, Grimbert P, et al. Advagraf, a once-daily prolonged release tacrolimus formulation, in kidney transplantation: literature review and guidelines from a panel of experts. Transpl Int 2016;29:860–9.

[4] Sellarés J, de Freitas DG, Mengel M, Reeve J, Einecke G, Sis B, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant 2012;12:388–99.

[5] Wiebe C, Gibson IW, Blydt-Hansen TD, Pochinco D, Birk PE, Ho J, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. Am J Transplant 2015;15:2921–30.

[6] Gaynor JJ, Ciancio G, Guerra G, Sageshima J, Hanson L, Roth D, et al. Graft failure due to noncompliance among 628

kidney transplant recipients with long-term follow-up: a single-center observational study. Transplantation 2014;97:925–33.

[7] Morales JM, Varo E, Lázaro P. Immunosuppressant treatment adherence, barriers to adherence and quality of life in renal and liver transplant recipients in Spain. Clin Transplant 2012;26:369–76.

[8] Kuypers DR, Peeters PC, Sennesael JJ, Kianda MN, Vrijens B, Kristanto P, et al. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. Transplantation 2013;95:333–40.

[9] Henry ML. Cyclosporine and tacrolimus (FK506): a comparison of efficacy and safety profiles. Clin Transplant 1999;13:209–20.

[10] Veenstra DL, Best JH, Hornberger J, Sullivan SD, Hricik DE. Incidence and long-term cost of steroid-related side effects after renal transplantation. Am J Kidney Dis 1999;33:829–39.

[11] Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC. Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev 2016;8:CD005632.

[12] National Kidney Foundation. Cockcroft-Gault formula. 2016. Available from https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc. Published 2016. Accessed March 15, 2017.

[13] Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, et al. Banff 07 classification of renal allograft pathology: updates and future directions. Am J Transplant 2008;8:753–60.

[14] Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562–75.

[15] Kaplan B, Schold JD, Meier-Kriesche H-U. Long-term graft survival with neoral and tacrolimus: a paired kidney analysis. J Am Soc Nephrol 2003;14:2980–4.

[16] Silva Jr HT, Yang HC, Meier-Kriesche H-U, Croy R, Holman J, Fitzsimmons WE, et al. Long-term follow-up of a phase III clinical trial comparing tacrolimus extended-release/MMF, tacrolimus/MMF, and cyclosporine/MMF in de novo kidney transplant recipients. Transplantation 2014;97:636–41.

[17] Ichimaru N, Kakuta Y, Abe T, Okumi M, Imamura R, Isaka Y, et al. Treatment adherence in renal transplant recipients: a questionnaire survey on immunosuppressants. Transplant Proc 2008;40:1362–5.

[18] Doesch AO, Mueller S, Konstandin M, Celik S, Erbel C, Kristen A, et al. Increased adherence after switch from twice daily calcineurin inhibitor based treatment to once daily modified released tacrolimus in heart transplantation: a pre-experimental study. Transplant Proc 2010;42:4238–42.

[19] Doesch AO, Mueller S, Akyol C, Erbel C, Frankenstein L, Ruhparwar A, et al. Increased adherence eight months after switch from twice daily calcineurin inhibitor based treatment to once daily modified released tacrolimus in heart transplantation. Drug Des Devel Ther 2013;7:1253–8.

[20] Kramer BK, Montagnino G, del Castillo D, Margreiter R, Sperschneider H, Olbricht CJ, et al. Efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation: 2 year follow-up results. Nephrol Dial Transplant 2005;20:968–73.

[21] Silva Jr HT, Yang HC, Abouljoud M, Kuo PC, Wisemandle K, Bhattacharya P, et al. Erratum: One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. Am J Transplant 2007;7:595–608.

[22] Vanrenterghem Y, van Hooff JP, Squifflet J-P, Salmela K, Rigotti P, Jindal RM, et al. Minimization of immunosuppressive therapy after renal transplantation: results of a randomized controlled trial. Am J Transplant 2005;5:87–95.

[23] Boots JMM, van Duijnhoven EM, Christiaans MHL, Wolffenbuttel BHR, van Hooff JP. Glucose metabolism in renal transplant recipients on tacrolimus: the effect of steroid withdrawal and tacrolimus trough level reduction. J Am Soc Nephrol 2002;13:221–7.

[24] García-Gómez C, Nolla JM, Valverde J, Narváez J, Corbella E, Pintó X. High HDL-cholesterol in women with rheumatoid arthritis on low-dose glucocorticoid therapy. Eur J Clin Invest 2008;38:686–92.

[25] Taber DJ, Hunt KJ, Gebregziabher M, Srinivas T, Chavin KD, Baliga PK, et al. A comparative effectiveness analysis of early steroid withdrawal in black kidney transplant recipients. Clin J Am Soc Nephrol 2017;12:131–9.

[26] Ahsan N, Hricik D, Matas A, Rose S, Tomlanovich S, Wilkinson A, et al. Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil–a prospective randomized study. Steroid Withdrawal Study Group. Transplantation 1999;68:1865–74.

[27] Sinclair NR. Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts. The Canadian Multicentre Transplant Study Group. CMAJ 1992;147:645–57.

[28] Vitko S, Klinger M, Salmela K, Wlodarczyk Z, Tyden G, Senatorski G, et al. Two corticosteroid-free regimens–tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil–in comparison with a standard triple regimen in renal transplantation: results of the Atlas study. Transplantation 2005;80:1734–41.

[29] Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg 2008;248:564–77.

[30] Pascual J, Quereda C, Zamora J, Hernández D. Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. Transplantation 2004;78:1548–56.