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ORIGINAL ARTICLE

Renal function and safety in stable kidney transplant recipients converted from immediate-release to prolonged-release tacrolimus

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Keywords
calcineurin inhibitor, immunosuppressant, kidney transplantation, tacrolimus.

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Conflicts of Interest
R. Lauzurica is a clinical trial investigator for Astellas Pharma. J. Morales and J. van Hooff have served on advisory committees, received lecture fees and have been principal investigators for Astellas Pharma.

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Summary

This multicenter, open, phase IIIb study assessed short-term efficacy, safety and dose adjustments in adult stable renal transplant recipients converted from tacrolimus twice-daily (BID) to once-daily (QD). Patients receiving unchanged tacrolimus BID for ≥12 weeks were enrolled, and after 6-weeks, converted from tacrolimus BID to QD (morning dose) on a 1 : 1 (mg : mg) total daily dose basis, for a further 12 weeks. Primary endpoint: change in steady-state creatinine clearance between treatment phases. Secondary endpoints: biopsy-proven acute rejection (BPAR), patient and graft survival, safety. 128 patients enrolled (mean age 48.9 years; time post-transplant 48.9 months); 91 evaluated for the primary endpoint. Mean total daily dose was 0.06 mg/kg (BID) and 0.07 mg/kg (QD); 79.1% required one/no dose changes post-conversion to maintain recommended blood-trough levels; average dose increase was small (0.6–0.7 mg/day) with more dose increases in patients on the lowest tacrolimus BID doses. Renal function remained stable and non-inferiority of tacrolimus QD against tacrolimus BID was demonstrated. There were no BPAR episodes; patient and graft survival were 100%. Adverse events were few; none led to dose modifications/discontinuation. Tacrolimus BID to tacrolimus QD conversion is straightforward and does not compromise renal function in stable kidney transplant patients in the short term.

Introduction

Tacrolimus is available worldwide as an immediate-release immunosuppressive agent that is administered twice daily (Prograf® [tacrolimus BID], Astellas Pharma Europe Ltd, Staines, UK) for the prevention and treatment of allograft rejection in liver, kidney, and heart transplantation. A prolonged-release formulation of tacrolimus (Advagraf® [tacrolimus QD], Astellas Pharma Europe Ltd, Staines, UK) has been developed as an alternative to tacrolimus BID with once-daily morning dosing. Simplifying immunosuppressive regimens with once-daily morning dosing may help to improve adherence in transplant patients and therefore enhance patient outcomes [1–3].

Studies have demonstrated that tacrolimus QD is therapeutically equivalent to tacrolimus BID [4]. Two phase III, multicenter, randomized studies comparing tacrolimus BID and tacrolimus QD (with/without antibody induction) in *de novo* kidney transplant recipients demonstrated that both treatments resulted in good renal function and similar efficacy and safety at 12 months

[4,5]. Notably, patients receiving tacrolimus BID or QD had significantly better renal function compared with those receiving cyclosporine [5].

A similarly high degree of correlation between blood-trough levels and tacrolimus exposure has been established for tacrolimus QD and tacrolimus BID in four phase II studies in kidney, liver, and heart transplant recipients. Importantly, the relationship (slope of the line) between minimum plasma concentration (trough) and area under the curve has been shown to be almost identical for tacrolimus QD and tacrolimus BID. This is key in enabling the use of the same well-established therapeutic drug monitoring approaches and target levels for both formulations [6,7].

The primary objective of this multicenter, open, single-arm conversion, phase IIIb study was to examine the short-term consequences of conversion to a tacrolimus QD regimen by assessing renal function, measured by calculated creatinine clearance (CrCl), in stable kidney transplant patients converted on a 1 : 1 (mg : mg) basis from a tacrolimus BID regimen. Secondary objectives were to assess efficacy and other safety parameters.

Methods

Study population

Male and female patients (aged ≥18 years) were eligible to enter the study if they received a kidney transplant ≥12 months prior to enrollment, their tacrolimus BID dose had not changed for ≥12 weeks prior to enrollment, their tacrolimus whole-blood trough level measurements were in the range of 5–15 ng/ml, were clinically stable, and remained on the same concomitant immunosuppressive regimen for ≥12 weeks prior to enrollment. Female patients of childbearing age must have had a negative serum pregnancy test.

Exclusion criteria included previous non-renal organ transplant, an acute rejection (AR) episode within 12 weeks prior to enrollment (or within 24 weeks if anti-lymphocyte antibody treatment was required), new-onset malignancy after transplantation, receipt of prohibited concomitant therapy within 28 days of enrollment, proteinuria >2 g/24 h or CrCl (Cockcroft–Gault) <40 ml/min or 'creeping creatinine' (serum creatinine increase ≥20% over the 6 months prior to enrollment), and liver cirrhosis or liver function enzymes ≥2 times the upper limit of the normal range.

Patients were excluded from entering the tacrolimus QD phase for any of the following during the tacrolimus BID phase: change in dose of tacrolimus BID or concomitant immunosuppressants, mean tacrolimus blood-trough levels not within 5–15 ng/ml, an AR episode, CrCl <40 ml/min, or liver function enzymes ≥2 times the upper limit of the normal range.

Patients were discontinued from the study for: intolerable adverse event (AE), graft loss, AR during tacrolimus BID treatment, violation of inclusion or exclusion criteria, interruption of study medication for >7 consecutive days or permanent discontinuation of study medication, non-compliance, start of prohibited concomitant medication, pregnancy, lack of efficacy, withdrawal of consent, or if the patient was lost to follow-up.

Study design

This was a multicenter, open, phase IIIb study of the safety and efficacy of a tacrolimus QD-based immunosuppressive regimen in stable kidney transplant patients converted from a tacrolimus BID-based immunosuppressive regimen. The study was conducted at 15 centers in six European countries (Spain, Poland, Germany, United Kingdom, France, and The Netherlands), in accordance with the Declaration of Helsinki, and the Independent Ethics Committee from each study center granted approval for the study and its amendments prior to implementation. Each patient provided written informed consent prior to study enrollment.

Patients had a 6-week run-in period with tacrolimus BID, and were then converted to tacrolimus QD on a 1 : 1 (mg : mg) total daily dose basis; patients remained on tacrolimus QD for 12 weeks. During the tacrolimus BID treatment phase (week −6 to day −1), tacrolimus BID was administered twice daily (morning and evening). In the tacrolimus QD treatment phase (day 1 to week 12), tacrolimus QD was administered once daily (morning). Tacrolimus whole-blood trough levels were monitored.

Tacrolimus target whole-blood trough levels in the range of 5–15 ng/ml were recommended throughout the study. Dose modifications were only made if indicated by clinical signs or if mean tacrolimus blood-trough levels changed by >20% compared with the tacrolimus BID treatment phase. Whole-blood trough levels were monitored locally by MEIA (IMX®), EMIT, or HPLC-MSMS analysis. Blood samples (2 ml) were taken before the morning dose of tacrolimus at all scheduled visits and as clinically indicated.

Endpoints

The primary endpoint was renal function, assessed as change in mean steady-state CrCl (calculated using the Cockcroft–Gault formula) between the tacrolimus BID and tacrolimus QD treatment phases. Mean CrCl during steady-state phase was defined as mean calculated CrCl from week −6 to day −1 for the tacrolimus BID treatment phase and from week 6 to week 12 for the tacrolimus QD treatment phase. Mean CrCl over the duration of the study was also calculated using the Modification of Diet in Renal Disease (MDRD) formula [8].

Secondary efficacy endpoints comprised frequency of biopsy-proven acute rejection (BPAR), patient survival, and graft survival. An AR episode with clinical or laboratory signs was defined to be a BPAR if it was associated with a positive biopsy finding (Banff grade I, II, or III) [9]. Graft loss was defined as re-transplantation, nephrectomy or death, or as dialysis ongoing at study end or at premature patient discontinuation (unless superseded by follow-up information).

Secondary safety endpoints comprised the incidence of AEs (including abnormal laboratory measurements), serious AEs (SAEs), change in blood pressure (BP) between day −1 and week 12 using 24-h arterial BP measurements, and change in glycated hemoglobin (HbA_{1c}) between day −1 and week 12. BP was measured using a Boso TM-2430 PC sphygmomanometer with Profile-manager 2 software.

Statistical analyses

The safety analysis set (SAF) included all patients who received at least one dose of study drug and for whom any data were reported after the first dose of medication. The full analysis set (FAS) comprised all patients who received at least one dose of study medication in each treatment phase with sufficient recording for deriving the primary variable at least once during each treatment phase. The per-protocol set (PPS) included all patients in the FAS without major protocol violations, which included: no calculated CrCl value during the tacrolimus BID steady-state phase (week −6 to day −1) and/or no calculated CrCl value during the tacrolimus QD steady-state phase (week 6 to week 12); violation of inclusion or exclusion criteria, which may affect the primary endpoint; non-adherence to tacrolimus and dose adjustment rules; use of prohibited concomitant medication for ≥7 consecutive days; and change of immunosuppressive regimen for ≥7 consecutive days.

The analysis for the primary endpoint was performed on the PPS and was repeated for the FAS to assess the robustness of the results. Patient demographics, baseline characteristics and immunosuppressive therapy, including tacrolimus trough levels were also assessed for the PPS. All safety analyses were based on the SAF.

Assuming 20% of patients would be excluded from the PPS, approximately 125 patients were planned for enrollment to reach a power >90% for assessing non-inferiority of tacrolimus QD. The non-inferiority margin was predefined as 10% of the reference mean (tacrolimus BID) (considered to be clinically meaningful).

Comparison of the primary endpoint, change in steady-state CrCl, was based on the lower limit of the two-sided 95% CI for the relative difference of means between tacrolimus BID and tacrolimus QD, which should lie above −10% of the tacrolimus BID mean for concluding non-inferiority. Kaplan–Meier analyses were conducted for patient survival, graft survival, and time to first BPAR, as appropriate.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 6.1.

Results

Study population

Of 128 patients enrolled (127 in the SAF; 115 in the FAS [overall population]; 91 in the PPS), 114 completed the study; patient disposition is shown in Fig. 1.

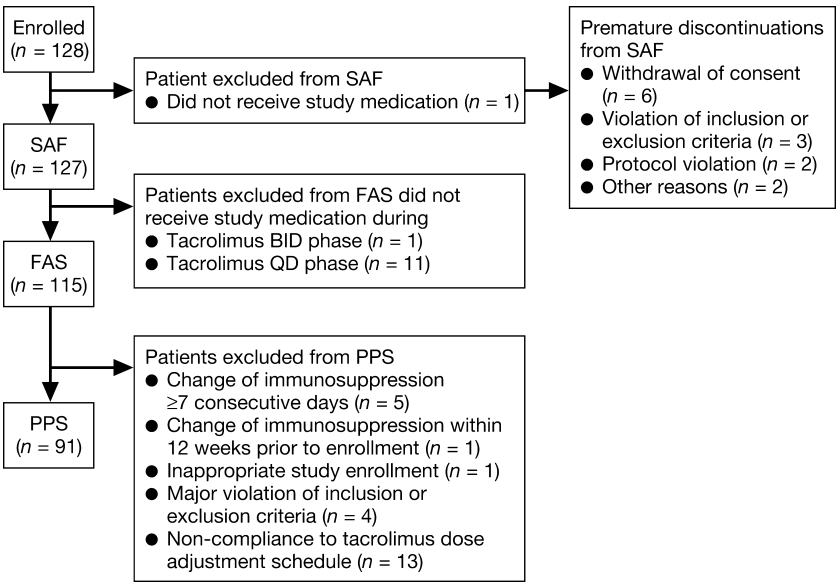

Figure 1 Patient disposition. SAF, safety analysis set; FAS, full analysis set; PPS, per-protocol set.

Table 1. Patient demographics and baseline characteristics (PPS and FAS).

Patient demographics and baseline characteristics	PPS Number of subjects *n* = 91	FAS Number of subjects *n* = 115
Age, mean years (± SD)	48.9 (± 11.8)	49.0 (± 12.3)
Caucasian, *n* (%)	90 (98.9)	113 (98.3)
Male, *n* (%)	67 (73.6)	85 (73.9)
Height, mean cm (± SD)	171.1 (± 9.7)	171.0 (± 9.5)
Weight, mean kg (± SD)	76.4 (± 12.0)	76.6 (± 12.8)
Deceased organ donation, *n* (%)	73 (80.2)	90 (78.3)
Living organ donation, *n* (%)	18 (19.8)	25 (21.7)
Number of kidney transplants, *n* (%):		
1	83 (91.2)	104 (90.4)
2	7 (7.7)	10 (8.7)
3	1 (1.1)	1 (0.9)
Time since last transplant, mean months (± SD)	48.9 (± 28.6)	46.8 (± 28.7)
Time range since last transplant	12–133 months	12–133 months

FAS, full analysis set; PPS, per-protocol set; SD, standard deviation.

Demographic and baseline characteristics for the PPS and FAS are presented in Table 1. Mean time since transplant was approximately 4 years prior to study entry. The most common reasons for renal failure leading to the need for transplantation were glomerulonephritis (30.8% [PPS], 33.0% [FAS]), polycystic kidney disease (18.7% [PPS], 16.5% [FAS]), unknown reasons (13.2% [PPS], 13.9% [FAS]), and uropathy (12.1% [PPS], 12.2% [FAS]).

Tacrolimus administration and exposure

The mean (± standard deviation [SD]) total daily dose of tacrolimus was stable at 4.4 (± 2.4) mg during the 6-week tacrolimus BID treatment phase (FAS). Following conversion to tacrolimus QD, the mean total daily dose was 4.4 (± 2.2) mg in week 1, increasing slightly to 5.1 (± 2.6) mg by week 12. In relation to body weight, the mean (± SD) total daily dose was stable at 0.06 (± 0.03) mg/kg during the BID phase, 0.06 (± 0.03) mg/kg in week 1 and 0.07 (± 0.03) mg/kg at week 12 of the tacrolimus QD treatment phase (FAS, Fig. 2a).

During the 6-week tacrolimus BID phase, the median whole-blood trough levels ranged between 6.4 and 7.1 ng/ml. Following conversion to tacrolimus QD, the median trough level fell slightly, from 6.7 ng/ml at day −1 before switch to 6.0 ng/ml at week 1, and then stabilized to lie between 5.8 and 6.7 ng/ml for the remainder of the study (FAS; Fig. 2b). The maximum trough values were lower during the QD phase (10.4–13.9 ng/ml) than the BID phase (14.0–16.3 ng/ml); low minimum levels (<2.5 ng/ml) occurred with both formulations.

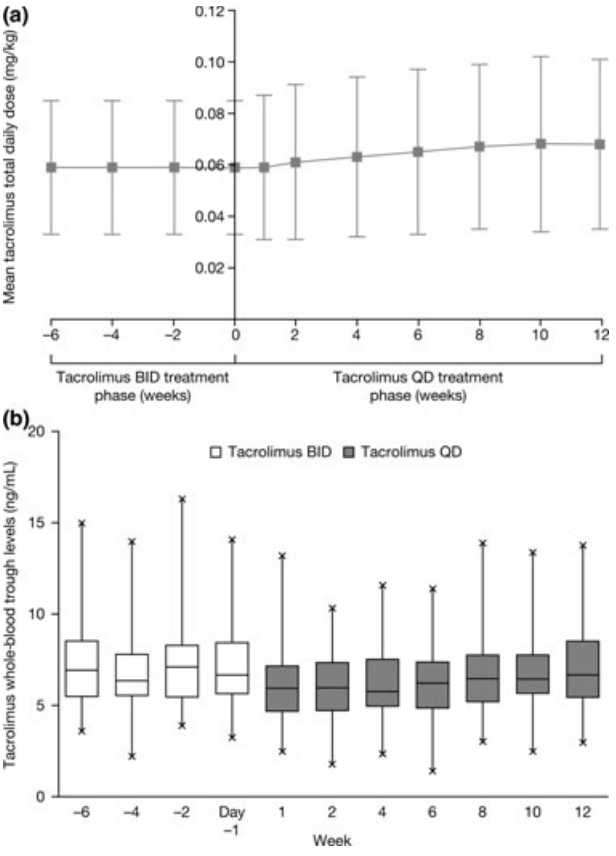

Figure 2 Tacrolimus (a) mean (± SD) total daily dose (mg/kg) (FAS) and (b) median whole-blood tacrolimus trough levels (ng/ml) during both treatment phases (FAS). Box represents 25% quartile, median value and 75% quartile of range. Highest and lowest values designated by crosses. SD, standard deviation; FAS, full analysis set.

Following conversion to tacrolimus QD, 40.9% of patients (FAS) required no dose adjustments to maintain tacrolimus trough levels within the recommended range. Of the 59.1% of subjects who did require a dose adjustment, one change was sufficient to achieve recommended trough levels in most cases (57.4%) (FAS; Fig. 3a). The mean change in daily dose was relatively small (0.6–0.7 mg/day) and this was similar regardless of the patients pre-conversion daily dose.

The majority of dose adjustments (64.2%) were dose increases during the first 6 weeks after conversion (FAS; Fig. 3b), although both increases and decreases were seen. Dose increases were more commonly required in patients receiving the lowest doses of tacrolimus at baseline, and those with underlying diabetes or high Body Mass Index (BMI), although the effects of each factor were small. Factors that may be associated with dose decreases could not be identified. No patient required more than three dose changes to reach the recommended tacrolimus trough level.

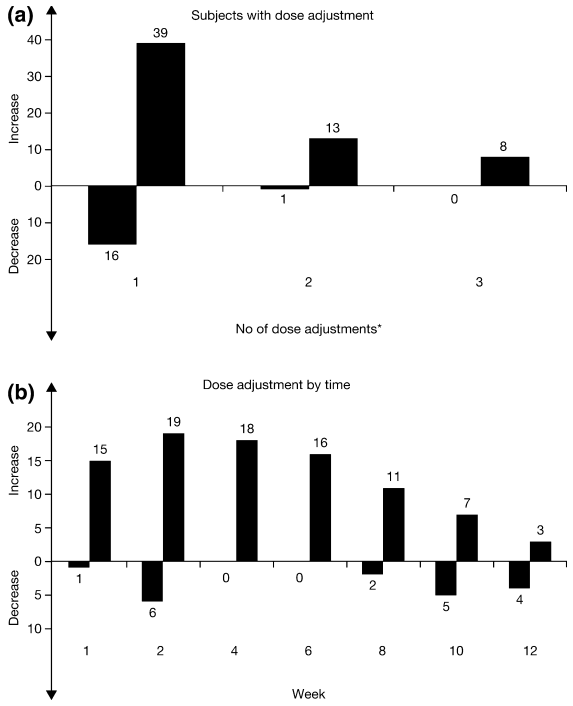

Figure 3 Number of subjects with tacrolimus dose adjustments by (a) number of dose adjustments and (b) dose adjustments by time (FAS; $n = 115$). *Some patients may have had both increase and decrease of dose. FAS, full analysis set.

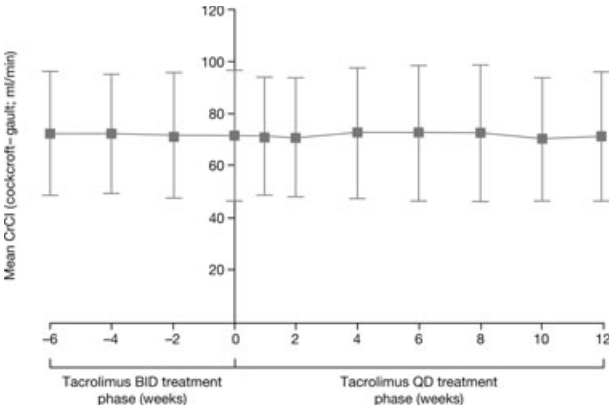

Figure 4 Mean (± SD) creatinine clearance over time using Cockcroft–Gault) (SAF). SD, standard deviation; SAF, safety analysis set; CrCl, creatinine clearance.

Concomitant medication

Concomitant immunosuppressive therapies and doses remained unchanged for all patients (FAS) during both treatment phases. All patients who entered the study on tacrolimus BID monotherapy (16.5%) were maintained on monotherapy throughout the study period. In the 48 (52.7%) patients treated with corticosteroids, mean (± SD) dose was 4.7 (± 1.3) mg (based on prednisolone equivalent); 43 (47.3%) patients were receiving a steroid-free regimen. Forty-eight patients (52.7%) received mycophenolate mofetil, 11 (12.1%) received mycophenolic acid, 3 (3.3%) received azathioprine, and 4 (4.4%) received sirolimus as adjunctive treatment throughout the study. No association was observed between corticosteroid administration and dose adjustments [data not shown].

Use of non-immunosuppressive medications in the FAS during either treatment phase included antihypertensive medications (84.3%), lipid-lowering medications (47.8%), antidiabetic medications (20.0%), and diuretics (19.1%).

Efficacy

There were no incidences of BPAR or AR diagnosed by clinical signs and symptoms during the tacrolimus BID or QD treatment phases. Both patient and graft survival were 100%.

Safety

The mean steady-state CrCl was 72.5 ml/min during the tacrolimus BID treatment phase and 72.1 ml/min after conversion to tacrolimus QD. For the primary endpoint, renal function as measured by change in steady-state CrCl, non-inferiority of tacrolimus QD against tacrolimus BID was demonstrated, the relative difference in mean (± SD) calculated CrCl was −0.7% (± 5.33) in the PPS; the 95% confidence interval (CI) (−1.8, 0.5) falling well within the predefined 10% non-inferiority margin. Fig. 4 shows the CrCl over time in the SAF population. Similar results were found using the MDRD formula: the relative difference in mean (± SD) treatment difference calculated CrCl was −0.8% (± 5.94; 95% CI −2.1, 0.4). The robustness of these results was substantiated by the secondary analyses using the FAS (relative difference in mean [± SD] calculated CrCl of −0.5% [± 5.88]; 95% CI −1.5, 0.6 [$P < 0.0001$]).

In total, 22.2% and 25.0% of patients in the tacrolimus BID and tacrolimus QD treatment phases, respectively, experienced an AE during the study (SAF). None of the AEs led to dose modifications or discontinuation. Overall, reported AEs were similar during the 6-week BID and 12-week QD phases. The most frequent AEs (MedDRA) regardless of relationship to study drug were 'infections', reported in 5.6% and 12.1% of patients during the tacrolimus BID (6 weeks) and QD phases (12 weeks), respectively. All other reported AEs occurred in <6% of patients (Fig. 5).

The incidence of AEs considered to be causally related to study medication was low in both the tacrolimus BID (6.3%) and QD (6.0%) treatment phases. The most

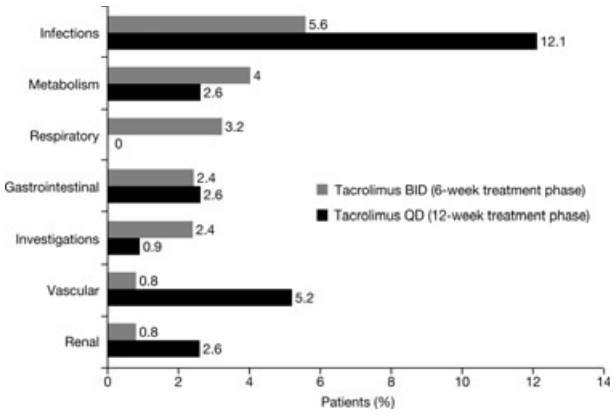

Figure 5 Most frequently reported adverse events (Medical Dictionary for Regulatory Activities system organ class) regardless of relationship to study drug (SAF). Investigations: abnormal laboratory values. SAF, safety analysis set.

frequently reported causally related AEs were metabolism and nutrition disorders (2.4% vs. 0.9%), and infections (2.4% vs. 0.9%) for tacrolimus BID and tacrolimus QD, respectively.

Infection was the only reported SAE in either treatment phase, occurring with an overall incidence of 0.8% during the tacrolimus BID phase (one case of acute bronchitis) and 1.7% in the tacrolimus QD treatment phase (one case each of bacterial pyelonephritis and a tooth abscess). None of these were considered to be causally related to study medication.

No clinically relevant differences were found in mean BP measurements between day −1 and week 12 (FAS; mean [SD] differences: arterial BP −0.3 [5.9] mmHg; systolic BP −0.2 [8.2] mmHg; diastolic BP −0.4 [5.4] mmHg). A change in antihypertensive medication was initiated in three patients during the tacrolimus BID treatment phase and in six patients during the tacrolimus QD treatment phase. There were no clinically relevant changes in HbA_{1c} between day −1 and week 12 (5.2% vs. 5.3%; mean difference 0.04%) in subjects without pre-existing diabetes mellitus. Furthermore, no clinically meaningful changes in hematology or biochemistry laboratory values, or vital signs (including weight and pulse) were observed.

Discussion

This is the first study specifically designed to investigate the safety and efficacy of tacrolimus QD in stable renal transplant patients converted from a tacrolimus BID-based immunosuppressive regimen. Renal function was stable throughout the study; tacrolimus QD was non-inferior to tacrolimus BID following a 1 : 1 (mg : mg) total daily dose conversion. This finding was observed in the primary analysis of CrCl calculated using the Cockcroft–Gault formula, and confirmed when CrCl was calculated using the MDRD formula, in both the PPS and the FAS.

These findings are consistent with previous pharmacokinetic studies in renal transplant recipients converted from tacrolimus BID to tacrolimus QD in which renal function remained stable [7,10]. Four-year follow-up data in renal transplant recipients have shown long-term maintenance of renal function with tacrolimus QD [11].

The study also provides evidence of the short-term safety of tacrolimus QD. There were no patient deaths, graft losses, or episodes of BPAR following conversion from tacrolimus BID to tacrolimus QD, consistent with previous US and European studies in stable kidney transplant recipients converted from tacrolimus BID to tacrolimus QD [7,10]. Follow-up data from the US study have shown that the efficacy and safety of tacrolimus QD is maintained for 2 years following conversion [12]. Similar findings have been described in stable liver transplant recipients converted from tacrolimus BID to tacrolimus QD [13].

In the present study, patients remained on stable immunosuppressive regimens after conversion from tacrolimus BID to tacrolimus QD on a 1 : 1 (mg : mg) basis. The majority of patients (79%) required either no or only a single dose change of tacrolimus QD post-conversion, and most dose adjustments occurred in the first few weeks following conversion. Concomitant immunosuppression remained unchanged throughout the study. Moreover, those patients who started on tacrolimus BID monotherapy were successfully maintained on tacrolimus QD monotherapy during the QD treatment phase.

Following conversion to tacrolimus QD, dose increases were required more often than dose decreases, the daily change was however, small. Dose increases were most frequent in patients who received low tacrolimus daily doses at baseline (<2 mg/day), had underlying diabetes or a high BMI. A separate phase III study has shown that on average, slightly higher doses of tacrolimus QD were required to achieve recommended trough levels [4].

This and other recent studies provide clinicians with useful information which may be of practical assistance in the management of kidney transplant patients around the time of conversion. The finding that low daily doses of tacrolimus BID were associated with an increased probability of requirement for dose increases post-conversion is in line with the results of another study in which stable renal transplant recipients receiving low daily doses (less than 0.025 mg/kg) had the largest reductions in tacrolimus blood concentrations following conversion from tacrolimus BID to QD [14]. The minority of patients who are maintained on low blood levels of tacrolimus (<5 ng/ml)

may also require dose increases to ensure that levels remain within the therapeutic range post-conversion [15]. In one recent large study, the small minority (4%) of patients with levels <6 ng/ml were successfully converted on a 1 to 1 : 1 total daily dose basis for this reason [16].

Although increases in dose were required more frequently than dose decreases after conversion to tacrolimus QD in this study, both increases and decreases were observed, as has been seen previously [17]. In view of the possibility of overexposure, and the potential for toxicity, pre-emptive dose increases for all patients converted to the QD formulation would not appear necessary. Instead conversion on a 1 : 1 (mg : mg) total daily dose basis, with appropriate monitoring and adjustment of dose based on patients' blood levels and clinical condition is justified on the basis of these study findings and is recommended.

Previous conversion studies in stable kidney transplant recipients have shown comparable systemic steady-state tacrolimus exposure following conversion from tacrolimus BID to QD [7,10]. In this study, whole-blood trough levels of tacrolimus in both treatment phases were at the low end of the recommended range (5–15 ng/ml); however, both tacrolimus BID and QD provided effective immunosuppression, as there were no cases of AR during either treatment phase. Conversion to tacrolimus QD provided consistent and predictable tacrolimus exposure within the recommended target trough-level range. There were patients in both treatment phases who received adequate immunosuppression despite 'low' exposure to tacrolimus; no cases of AR were reported even in individuals with minimum trough levels <2.5 ng/ml at isolated time-points.

Tacrolimus QD was well-tolerated, with a low incidence of AEs and SAEs, none of which led to dose modification or study withdrawal. The AEs reported here are consistent with the established safety profile of tacrolimus BID [18] and similar to those in previous studies with both formulations [4,7,10]. There were no clinically meaningful changes in BP, biochemistry or hematology values following conversion to tacrolimus QD, and no new incidences of hypertension, hyperlipidemia, or diabetes in either treatment phase.

While a limitation of this study was the lack of a comparator arm, all patients had stable renal function on enrollment, and renal function and other parameters were compared before and after conversion. The results of this study, therefore, reflect real clinical practice outside a controlled clinical-trial setting. However, the patient population was almost completely Caucasian, which although typical of the European transplant population, may prevent extrapolation of the findings to other patient groups, while the majority were also male.

Compared with twice-daily dosing, once-daily prolonged-release tacrolimus offers greater convenience for patients and may be preferable to them.

Nonadherence with immunosuppressive medication, a considerable problem among transplant recipients, leads to variable or suboptimal immunosuppression and has been identified as a leading cause of preventable graft loss [19,20]. Using the once-daily formulation of tacrolimus could improve adherence and consequently long-term renal allograft survival [3,19]. A recent multicenter study in Spain found that tacrolimus QD was preferred over tacrolimus BID by more than 99% of 1,800 patients converted to the QD formulation because of the less frequent dosing and a perception that their adherence was improved [16].

In conclusion, conversion from tacrolimus BID to a simplified tacrolimus QD regimen was straightforward, did not lead to any AR episodes or compromise renal function, may lead to more consistent exposure to tacrolimus within the target range, and was well tolerated in stable kidney transplant recipients. Once-daily dosing with tacrolimus QD might be of value in helping to optimize adherence to mainstay immunosuppression, and the potential to enhance long-term outcomes following renal transplantation should be investigated further in long-term outcome studies.

Authorship

JM, RL, and JvH: contributed to the recruitment of patients, data collection and drafting of this manuscript.

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