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Once daily tacrolimus conversion in lung transplantation: A prospective study on safety and medication adherence

Laurent Godinas, MD, PhD,[a,c] Fabienne Dobbels, PhD,[b] Leni Hulst, MD,[a] Ive Verbeeck, MSN,[b] Ines De Coninck, MSN,[b] Pieter Berrevoets, MSN,[b] Veronique Schaevers, MSc,[a] Jonas Yserbyt, MD, PhD,[a,c] Lieven J. Dupont, MD, PhD,[a,c] Stijn E. Verleden, PhD,[c] Bart M. Vanaudenaerde, PhD,[c] Laurens J. Ceulemans, MD, PhD,[c,d] Dirk E. Van Raemdonck, MD, PhD,[c,d] Arne Neyrinck,[c,e] Geert M. Verleden, MD, PhD,[a,c] and Robin Vos, MD, PhD[a,c]

From the [a]Department of Respiratory Diseases, Lung Transplantation Group, UZ Leuven, Campus Gasthuisberg, Leuven, Belgium; [b]Academic Center for Nursing and Midwifery, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium; [c]Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department CHROMETA, KU Leuven, Leuven, Belgium; [d]Department of Thoracic Surgery, Lung transplantation group, UZ Leuven, Campus Gasthuisberg, Leuven, Belgium; and the [e]Department of Anesthesiology, Lung transplantation group, UZ Leuven, Campus Gasthuisberg, Leuven, Belgium.

KEYWORDS:
lung transplantation;
therapeutic adherence;
tacrolimus;
therapeutic drug monitoring;
kidney function

BACKGROUND: Lung transplantation (LTx) requires a calcineurin inhibitor-based immunosuppressive regimen. A once daily (QD) tacrolimus regimen was developed to increase medication adherence. However, data concerning its safety and efficacy in LTx are lacking.

METHODS: In this prospective study, stable LTx patients were consecutively converted from twice daily (BID) tacrolimus to QD tacrolimus on a 1 mg:1 mg basis. Trough level (C_{min}), renal function, cholesterol, fasting glucose, potassium and lung function were monitored six months before and up to one year after conversion. Adherence and its barriers were assessed by self-reported questionnaires (Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) and Identification of Medication Adherence Barriers questionnaire (IMAB)) and blood-based assays (mean C_{min} and coefficient of variation (CV)).

RESULTS: We included 372 patients, in whom we observed a decrease in tacrolimus C_{min} of 18.5% ($p < 0.0001$) post-conversion, requiring subsequent daily dose adaptations in both cystic fibrosis (CF) (n = 72) and non-CF patients (n = 300). We observed a small decrease in eGFR one year post-conversion ($p = 0.024$). No significant changes in blood creatinine, potassium, fasting glucose, cholesterol or rate of lung function decline were observed. In a subgroup of 166 patients, significantly fewer patients missed doses (8.4% vs. 19.3%, $p = 0.016$) or had irregular intake post-conversion (19.3% vs. 32.5%, $p = 0.019$). Mean C_{min} and CV, as well as the total number of barriers, also decreased significantly post-conversion.

Reprint requests: Laurent Godinas, MD, PhD, Department of Respiratory Diseases, Campus Gasthuisberg, UZ Leuven, Herestraat 49, Leuven 3000, Belgium. Telephone: +32 16 346 802. Fax: +32 16 346 803
E-mail address: Laurent.Godinas@uzleuven.be

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CONCLUSIONS: In LTx, conversion from BID to QD tacrolimus (1 mg:1 mg) requires close monitoring of tacrolimus C_{min}. QD tacrolimus after transplantation is safe with respect to renal function, metabolic parameters and allograft function and improves LTx recipient adherence.
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Lung transplantation (LTx) is an accepted treatment for selected patients suffering from end-stage lung disease. Overall long-term survival is limited by the development of chronic lung allograft dysfunction (CLAD), which remains the leading cause of mortality beyond the first year.[1,2] Rejection can be prevented using immunosuppressive medications, primarily calcineurin inhibitors, such as cyclosporine or tacrolimus.[3] The original tacrolimus compound was developed for twice-daily (BID) administration and is associated with several side effects, such as chronic kidney failure, diabetes mellitus, dyslipidemia and electrolyte disorders,[4] which may account for long-term complications after solid organ transplantation. Side effects are partially due to the pharmacokinetic profile of BID administration, resulting in high peak values (C_{max}), together with more or less steady state trough levels (C_{min}), which must be maintained within a narrow therapeutic window. Once-daily (QD) tacrolimus with extended release was obtained by adding ethylcellulose, slowing the tacrolimus diffusion rate and prolonging its release along the gastrointestinal tract.[5] QD dosing attains similar C_{min} and AUC_{24} values with less variability and lower C_{max} levels.[6,7] Twice daily intake may also result in suboptimal adherence, which may accelerate the development of CLAD.[8] Evidence in kidney and liver transplant patients showed favorable outcomes in terms of graft survival, acute rejection rate and safety profile, as well as improved medication adherence after conversion from BID tacrolimus to a QD prolonged-release tacrolimus regimen.[9−13] However, data are still lacking concerning safety and the impact on adherence after conversion from BID to QD tacrolimus after LTx.

The primary aim of this prospective cohort study was to evaluate the safety profile of QD tacrolimus with respect to lung function, rejection, renal function and metabolic profile in a large single-center cohort of LTx recipients. Second, medication adherence after the transition from BD to QD was also prospectively assessed in a subset of patients.

Material and methods

Design, sample, and setting

This study was conducted at the LTx outpatient clinic of the University Hospitals Leuven (Belgium). All patients remained in long-term follow-up and returned to the outpatient clinic at least once every 3-4 months. Safety was determined based on a prospective cohort study, consecutively enrolling all stable LTx patients who were converted from a BID (Prograft, a twice-daily immediate-release tacrolimus capsule) to a QD tacrolimus (Advagraf, a once-daily extended-release tacrolimus capsule[5]) regimen from March 2016 until February 2017. Doses were equivalent (1 mg:1 mg), meaning that we determined the QD tacrolimus dose based on the total BID tacrolimus daily dose, but this could be adapted at the discretion of the treating physician based on tacrolimus C_{min} to avoid toxicity due to overdose or therapeutic inefficacy due to underdosing. In the first weeks following conversion, blood tests were systematically performed to ensure adequate tacrolimus C_{min} according to our immunosuppressive medication protocol (tacrolimus C_{min} range between 10 to 15 μg/L during the first year post-transplant, 8 to 10 μg/L between one and two years post-transplant and 6 to 8 μg/L after two years post-transplant). Patients were eligible for conversion if they were considered stable (no current infection, absence of new respiratory symptoms, absence of new onset of lung function decline). For logistical reasons, medication adherence was assessed in a limited subgroup of patients undergoing conversion from March to May 2016 (consecutive sampling). In these patients, per protocol adherence was reassessed after 1 year. A flowchart describing the study population is shown in **Figure 1**. The Ethics Committee of University Hospital Leuven approved this study (MP10411 and MP18442). Some of these data were presented at the Annual Meeting of ISHLT in 2018 (Nice, France).

Variables and measurements

Demographic and clinical characteristics

Age, sex and type of end-stage lung disease were retrieved from participant medical files. At each outpatient visit, clinical examination, weight, spirometry, chest X-ray, and blood and urine tests were performed. Blood tests included kidney function, fasting glucose, total, LDL and HDL cholesterol (in mg/dL) and tacrolimus C_{min}. Glycated hemoglobin (HbA1c) was also measured in patients with diabetes mellitus. Estimated glomerular filtration rate (eGFR) was routinely assessed using the CKD-EPI equation.[14] Classification of chronic kidney disease (CKD) was performed according to the KDIGO classification.[15] Dyslipidemia was defined as LDL cholesterol levels greater than 70 mg/dl.[16] CLAD was defined according to the ISHLT statement.[17] Bronchoscopy with transbronchial biopsies was performed according to clinical suspicion of rejection, and biopsy-proven acute rejection events were recorded during the study period. Data from 6 months and 3 months before conversion, at the time of conversion and at 3 months, 6 months and 12 months after conversion were recorded and compared. Overall patient and graft survival were assessed at the current follow-up (February 1, 2020).

Due to frequent pancreatic insufficiency and malabsorption in cystic fibrosis (CF) patients, we decided to perform a subgroup analysis to explore the potential variation in tacrolimus dose requirement after conversion in the CF population.

Adherence to the immunosuppressive regimen

Adherence refers to the process by which patients take a medication as prescribed. This study focused on the implementation phase of adherence,[18] measuring problems with immunosuppressive medication intake and regularity/timing of intake, by

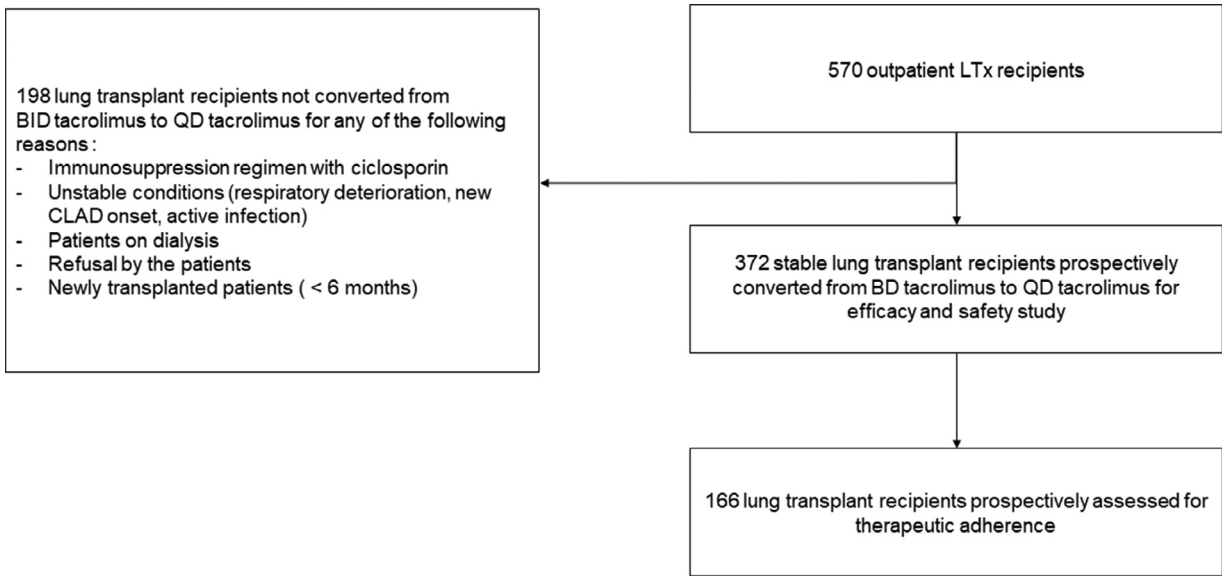

Figure 1 Flowchart of study. CLAD, chronic lung allograft dysfunction; LTx, lung transplant.

combining two methods, as per the state-of-the-art recommendations, to combine measurement methods to increase accuracy.[19]

The Basel Assessment of Immunosuppressive Medications Scale (BAASIS) is a validated self-reported questionnaire consisting of 4 Likert-type items asking for missed doses, missed consecutive doses (drug holidays), a deviation of medication intake of greater than 2 hours of prescribed timing of intake, and self-initiated dose reductions in the past month.[20] The questionnaire was administered immediately prior to conversion and 1 year post-conversion, comparing the proportion of patients missing a dose or exhibiting irregular intake in the month prior to the clinic visit.

We also calculated the following two metrics based on tacrolimus C_{min} trough level: 1) mean C_{min} level, using the past three tacrolimus BD values immediately prior to conversion and the three tacrolimus QD levels immediately preceding the one-year post-conversion time-point; 2) the pre- and post-conversion coefficient of variation (CV), expressed as the standard deviation (S) divided by the mean (M) of these three tacrolimus trough levels multiplied by 100: ($CV = \frac{S}{M} \times 100$).

The total number of barriers to taking immunosuppressive medication immediately before and at 1 year after conversion was compared using the 'Immunosuppressive Medication Adherence Barrier' (IMAB) 27-item self-reported scale. A barrier is defined as a personal or environmental constraint making it difficult to act upon one's intentions (e.g., I find it difficult to take my immunosuppressive medications because I forget, when I am busy with other things, because I experience side effects, because there are too many pills to take (see also **Table 3** for an overview). Each barrier was scored by the patients as present or absent.

Statistical analyses

All analyses were performed using GraphPad Prism 8 software (San Diego, CA, USA) or IBM SPSS Statistics version 25 (Armonk, NY, USA). Results are expressed as proportions, mean ± standard deviation (SD) or median (interquartile range) (IQ), wherever appropriate. Proportions were compared using Chi-square testing. Two-group means were compared using unpaired t-tests or Mann-Whitney tests, depending on the distribution of the data. Paired t-tests or Wilcoxon matched-pairs signed rank tests were used for repeated measures. Multiple comparisons were performed using repeated measures ANOVA with Tukey's multiple comparisons test, Friedman test with Dunn's multiple comparisons test or mixed-effects model analysis with Tukey's multiple comparisons test, depending on normality distribution and missing data. Each p-value for multiple comparisons was adjusted to account for a total of 15 comparisons. The Chi-square test was used to compare proportions. All p-values are two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Patients

During the study period, 372 stable outpatients (CF = 72, non CF = 300; subgroup for adherence study = 166) were converted from BID tacrolimus to QD tacrolimus. The main demographic characteristics for the entire pooled population, the CF population, the non-CF population and the subgroup of adherence study population are summarized in **Table 1**. The median (IQ) time between LTx and conversion was 64 (6-301) months. Pre-transplant diseases included chronic obstructive pulmonary disease (51%), pulmonary fibrosis (16%), CF (18%), pulmonary hypertension (6%) or other (9%), including redo-LTx, bronchiolitis obliterans, sarcoidosis, histiocytosis X, and lymphangioleiomyomatosis. At baseline (6 months before conversion), most patients suffered from CKD, with 58% of patients being KDIGO stage 3 or higher. The prevalence of diabetes and dyslipidemia at baseline was 23% and 62%, respectively. Patients had preserved lung function with a mean FEV_1 of 85 ± 28% predicted, and 115 patients (31%) had stable CLAD at baseline. At the time of conversion, 369 (99%) patients were receiving glucocorticoids, 169 (46%) were receiving mycophenolic acid, 142 (38%) were receiving azathioprine, and 61 (16%) were receiving no antimetabolite drug. At the current follow-up, 35 patients (9%) died, and 8 patients (2%) were retransplanted (11% graft loss) (**Supplementary Material**).

Table 1 Demographic and Baseline Characteristics of the Subjects

	Overall population N = 372	Subgroup study, medication adherence N = 166	Patients not included in adherence study N = 206	p^a	Non-CF population N = 302	CF population N = 70	p^b
Age, y	50 ± 14	50 ± 13	49 ± 14	0.312	54 ± 11	32 ± 14	<0.0001
Sex, % M/F	51/49	48/52	55/45	0.140	53/47	46/54	0.353
Previous disease before transplantation, n (%)				0.381			<0.0001
COPD	188 (51)	85 (51)	103 (50)		188 (62)	-	
PF	61 (16)	31 (19)	30 (15)		61 (20)	-	
CF	68 (18)	26 (16)	42 (20)		-	70 (100)	
PH	22 (6)	7 (4)	15 (7)		22 (7)	-	
Other	33 (9)	17 (10)	16 (8)		33 (11)	-	
Type of transplantation, n (%)				0.817			0.078
Double LTx	346 (93)	154 (93)	192 (93)		278 (92)	68 (98)	
Single LTx	11 (3)	5 (3)	6 (3)		10 (3)	1 (1)	
Heart + LTx	12 (3)	5 (3)	7 (3)		12 (4)	0 (0)	
Liver + LTx	2 (0.5)	1 (0.5)	1 (0.5)		2 (1)	0 (0)	
Kidney + LTx	1 (0.5)	1 (0.5)	0 (0)		0 (0)	1 (1)	
Time since transplantation, m	65 (6-301)	61 (7-291)	70 (6-301)	0.130	60 (6-301)	70 (8-259)	0.292

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; LTx, lung transplantation; PF, pulmonary fibrosis; PH, pulmonary hypertension.

Age between groups was compared using t test. Comparison of proportion of patients according to gender was evaluated using exact Fisher's exact test. Comparisons of proportions of patients according to type of disease and type of transplantation were assessed using chi-square test. Comparison of time to transplantation was assessed using Mann-Whitney test.

[a] p value corresponding to the comparison of the populations included in the adherence study and the patients not included.

[b] p value corresponds to the comparison of the CF population with the non-CF population.

Evolution of tacrolimus daily dose and C_{min}

Tacrolimus BID to tacrolimus QD conversion was performed at a ratio of 1 mg per 1 mg (according to the BID total daily dose) in 325 patients (88%). In the entire population, we observed a slight mean increase of 1.3% between tacrolimus BID daily dose and tacrolimus QD daily dose (**Table 2**). In the 45 patients (12%) for whom conversion was not performed at a ratio of 1 mg:1 mg, 16 patients received a decreased dose of QD tacrolimus after conversion, ranging between 8% and 50%, and 29 patients received an increased dose of QD tacrolimus, ranging from 3% to 100%, corresponding to an average 11% increase in the tacrolimus daily dose.

There was a statistically significant change in C_{min} before vs. after conversion ($p < 0.0001$), with a significant decrease one week after conversion ($p < 0.0001$) and a subsequent increase due to deliberate dose correction (up-titration) ($p < 0.0001$) (**Table 2** and **Figure 2A**). Tacrolimus C_{min} before conversion and 1 week afterwards was 7.6 μg/L (6.3-9.4) and 5.8 μg/L (4.6-7.5), respectively ($p < 0.0001$), representing a significant mean decrease of 18.5%. This was correlated with a statistically significant variation in the daily dose during the study period, with an observed 13.7% increase in daily dose (up-titration) after the first C_{min} control 1 week after conversion ($p < 0.0001$) (**Table 2** and **Figure 2B**). Subgroup analysis of the CF and non-CF transplant recipients revealed that tacrolimus C_{min} was equally decreased by 19.6% and 18.4%, respectively, between the time before conversion and 1 week afterwards ($p = 0.773$). However, the CF population needed a 50% higher daily dose of tacrolimus to obtain the same target C_{min} compared to patients without CF 3 months after conversion (4.5 (3.5-7.0) mg vs. 3.0 (2.0-4.0); $p < 0.0001$).

There was no difference in the percentage of variation in C_{min} post-conversion according to time since transplantation ($p = 0.550$) (**Supplement**).

Effect of conversion on renal function and potassium levels

There was no significant variation in CKD KDIGO stages during the study period ($p = 0.998$) (**Figure 3A**). Six months before and twelve months after conversion, blood creatinine levels were not significantly different (1.27 (1.02-1.61) mg/dL vs. 1.30 (1.04-1.63) mg/dL; $p = 0.2765$) (**Figure 3B**), although eGFR was slightly, but significantly, lower at twelve months (55 (41-76) mL/min/1.73 m^2 vs. 52 (39-71) mL/min/1.73 m^2; $p = 0.024$) (**Figure 3C**). Blood

Table 2 Evolution of Tacrolimus Daily Dose and Tacrolimus C_{min} for the Entire Population, the CF Population and the non-CF Population, at Conversion, at First Controle After 1-2 Weeks and Second Controle After 3 Months

		Conversion		First control after conversion	3 months after conversion
		BID	QD		
Entire population N = 372	Tacrolimus daily dose, mg	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.5)[a]	3.0 (2.0-4.5)[a]
	Mean daily dose variation compared with the previous daily dose, %		+1.3%	+13.7%[c]	+1.1%
	Tacrolimus C_{min}, μg/L	7.6 (6.3-9.4)[d]	5.8 (4.6-7.5)[d]	6.9 (5.8-8.1)[d]	
	Mean C_{min} variation compared with the previous C_{min}, %			-18.5%[e]	+29.7%[e]
CF population N = 70	Tacrolimus daily dose, mg	4.0 (3.0-6.0)	4.0 (3.0-6.0)	5.0 (3.5-7.0)[b]	4.5 (3.5-7.0)[b]
	Mean daily dose variation compared with the previous daily dose, %		+3.4%[f]	+11.4%	-2.9%[g]
	Tacrolimus C_{min}, μg/L	7.2 (6.1-9.6)	5.8 (4.7-7.0)[h]	7.0 (5.7-8.5)[i]	
	Mean C_{min} variation compared with the previous C_{min}, %			-19.6%[e]	+35.2%[e]
Non-CF population N = 302	Tacrolimus daily dose, mg	2.5 (2.0-3.5)	2.5 (2.0-3.5)	3.0 (2.0-4.0)[a]	3.0 (2.0-4.0)[a]
	Mean daily dose variation compared with the previous daily dose, %		+0.8%	+14.9%[c]	+5.3%
	Tacrolimus C_{min}, μg/L	7.8 (6.3-9.4)[d]	5.8 (4.6-7.5)[d]	6.8 (5.8-8.0)[d]	
	Mean C_{min} variation compared with the previous C_{min}, %			-18.4%[e]	+28.4%[e]

CF, cystic fibrosis; C_{min}, trough level.

Results are expressed with median (IQ). Daily dose, C_{min} and percentage of variation of daily dose comparisons at different time points were assessed using Friedman test with Dunn's multiple comparisons test. Percentage of variation of C_{min} at the two different time points were assessed using Wilcoxon matched-pairs signed rank test. Differences of daily dose and C_{min} variation at the same time point between non-CF and CF were assessed using Mann-Whitney test and found not significant.

[a] $p < 0.0001$ with tacrolimus daily dose QD and BID.
[b] $p < 0.05$ with tacrolimus daily dose QD and BID.
[c] $p < 0.0001$ with mean daily dose variation at conversion and three months after.
[d] $p < 0.0001$ with other tacrolimus C_{min}.
[e] $p < 0.0001$ with mean C_{min} variation.
[f] $p < 0.05$ with mean aily dose variation at first control.
[g] $p < 0.001$ with mean daily dose variation at 3 months.
[h] $p < 0.0001$ with tacrolimus C_{min} at conversion.
[i] $p < 0.05$ with tacrolimus C_{min} at first control after conversion.

potassium levels exhibited statistically significant variation during the study with a significant decrease in the value between 3 months before conversion and 1-2 weeks after conversion (4.2 (3.9-4.5) vs. 4.1 (3.9-4.4), respectively; $p = 0.006$), although the clinical relevance of this change remains unclear (**Supplement**).

Effect of conversion on metabolic parameters

There was no statistically significant difference in fasting glucose between 6 months before conversion and 12 months after conversion (95 (86-108) mg/dL vs. 95 (87-110) mg/dL, respectively; $p = 0.312$)). In the subgroup of diabetic patients, there was no increase in HbA1c (6.3 (5.7-7.4) % vs. 6.6 (5.8-7.4) %; $p = 0.643$). Weight significantly increased during the observed period (66 (57-78) kg vs. 68 (56-77) kg; $p < 0.0001$). Total cholesterol (173 (151-195) mg/dL vs. 175 (154-195) mg/dL; $p = 0.294$), LDL cholesterol (78 (60-101) mg/dL vs. 79 (62-95) mg/dL; $p = 0.318$) and HDL cholesterol (63 (51-80) mg/dL vs. 65 (51-83) mg/dL; $p = 0.528$) were not different. Figures representing variations in fasting glucose, HbA1c, weight and cholesterol are presented in the Supplemental Materials.

Effect of conversion on lung function and acute rejection

During the course of the study, there was a slight, but significant, decrease in lung function in terms of $FEV_{1\%}$ predicted between values 6 months before conversion and one year after conversion (86 ± 27% predicted vs. 85 ± 28% predicted, respectively; $p = 0.0206$) and FEV_1 in absolute values (2476 ± 923 mL vs. 2420 ± 949 mL, respectively; $p < 0.0001$) (**Figure 4A and B**). Neither FVC % predicted (96 ± 23% predicted vs. 98 ± 24% predicted; $p = 0.992$) nor FVC absolute value (3387 ± 1015 mL vs. 3371 ± 1040

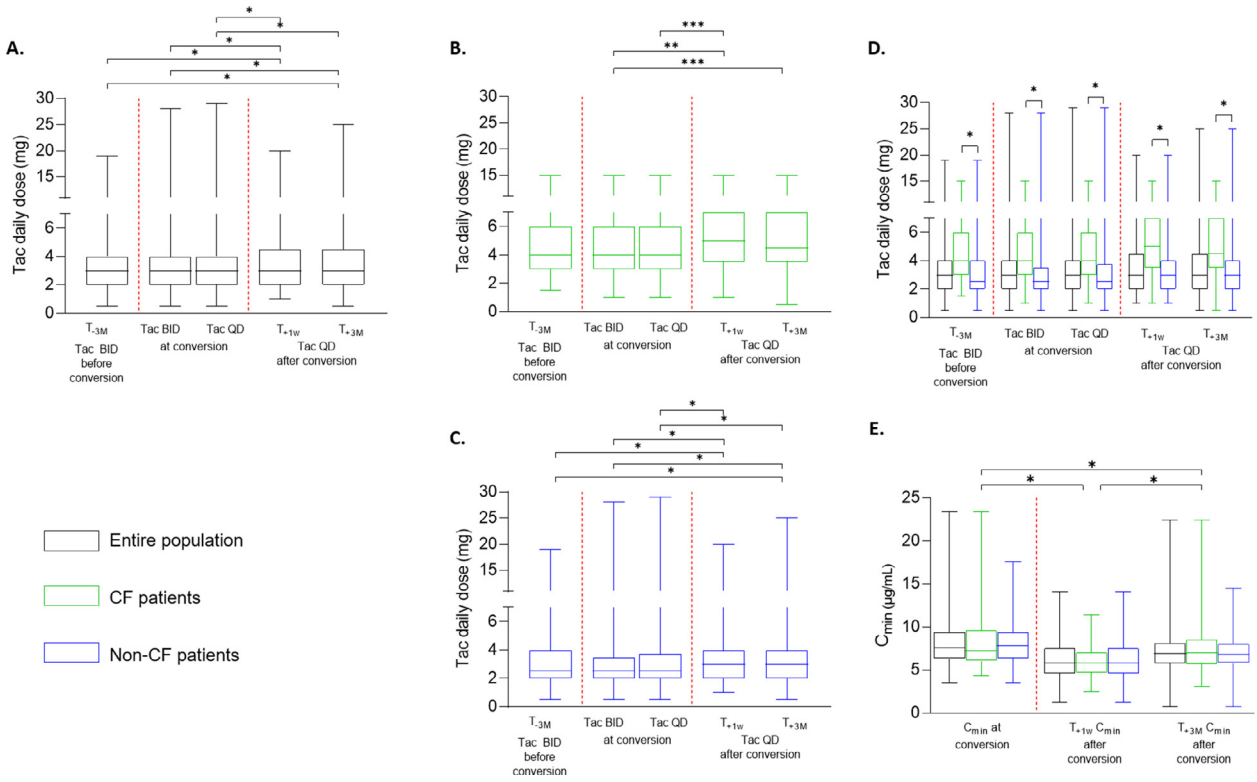

Figure 2 Evolution of tacrolimus C_{min} and tacrolimus daily dose intake before and after conversion in the entire population, in the CF subpopulation and in the non-CF subpopulation. Colors represent different patients population: the black box-and-whisker plots represent the entire population, the green box-and-whisker plots represent the CF population and the blue box-and-whisker plot represent the non-CF population. The red dotted line represents the tacrolimus conversion from BID to QD. A. Evolution of tacrolimus daily doses before and after conversion from tacrolimus BID to tacrolimus QD in the entire population. $*p < 0.0001$. B. Evolution of tacrolimus daily doses before and after conversion from tacrolimus BID to tacrolimus QD in the CF subpopulation. $**p < 0.001$, $***p < 0.05$ C. Evolution of tacrolimus daily doses before and after conversion from tacrolimus BID to tacrolimus QD in the non-CF subpopulation. $*p < 0.0001$. D. Evolution of tacrolimus daily doses before and after conversion from tacrolimus BID to tacrolimus QD. $*p < 0.0001$. E. Evolution of tacrolimus C_{min} after conversion from tacrolimus BID to tacrolimus QD. $*p < 0.0001$ and for comparison of the corresponding C_{min} in the same patients population at different time point (for convenience, only one bracket per time point representing simultaneously the three patients population) P n.s. for the comparison of C_{min} between each patients population at a same time point. $T_{-3M} = 3$ month before conversion, $T_{+1w} = 1$-2 weeks after conversion, $T_{+3M} = 3$ months after conversion, C_{min} = trough level, Tac = tacrolimus. Daily dose and C_{min} comparisons at different time points were assessed using Friedman test with Dunn's multiple comparisons test. Daily dose and C_{min} between CF and non-CF population at a same time point were assessed using Mann-Whitney test. The comparison between C_{min} between the different population (whole, CF, non-CF) was performed using a Kruskal-Wallis test followed by a Dunn's multiple comparisons test.

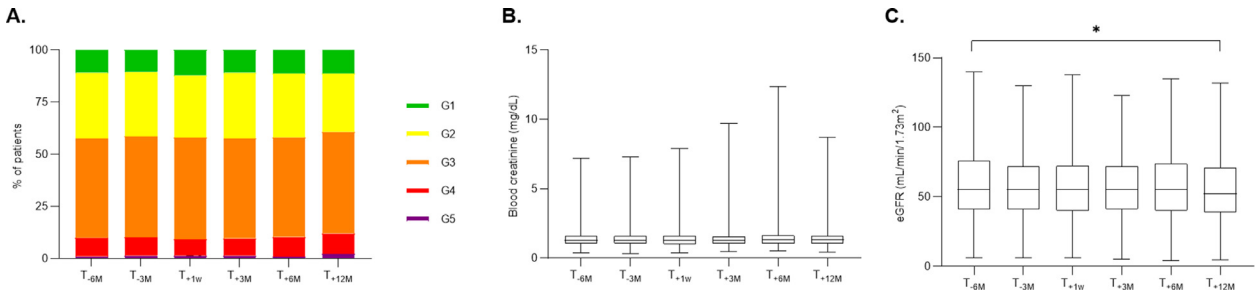

Figure 3 Evolution of renal function before and after conversion. A. Evolution of chronic renal failure proportion of patients according to KDIGO criteria during the periods before and after tacrolimus conversion from BID to QD. B. Evolution of serum creatinine levels during the periods before and after tacrolimus conversion from BID to QD. C. Evolution of estimated glomerular filtration rate levels during the periods before and after tacrolimus conversion from BID to QD. $*p < 0.05$. $*p < 0.001$. $T_{-6M} = 6$ months before conversion. $T_{-3M} = 3$ months before conversion. $T_{+1w} = 1$-2 weeks after conversion. $T_{+3M} = 3$ months after conversion. $T_{+6M} = 6$ months after conversion. $T_{+12M} = 12$ months after conversion. G = KDIGO glomerular filtration rate stage 1 to 5.KDIGO classifications were compared using chi-square test, blood creatinine and eGFR were assessed using Friedman test with Dunn's multiple comparisons test.

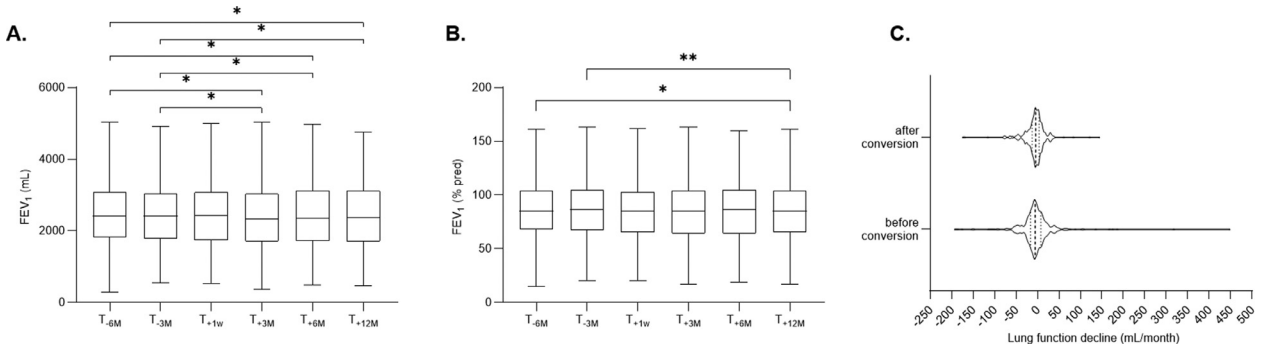

Figure 4 Evolution of lung function before and after parameters before and after conversion. A. Evolution of FEV_1 in absolute value during the periods before and after tacrolimus conversion from BID to QD. *$p < 0.0001$. B. Evolution of FEV_1 in % pred value during the periods before and after tacrolimus conversion from BID to QD. *$p < 0.01$. **$p < 0.001$. C. Evolution of the monthly lung function decline 6 months before and one year after tacrolimus conversion from BID to QD. T_{-6M} = 6 months before conversion. T_{-3M} = 3 months before conversion. T_{+1w} = 1-2 weeks after conversion. T_{+3M} = 3 months after conversion. T_{+6M} = 6 months after conversion. T_{+12M} = 12 months after conversion. FEV_1 = Forced expiratory volume in 1 second. % pred = percentage of predicted value. FEV_1 values (% and mL) were assessed using repeated measure ANOVA with Tukey's multiple comparisons test. FEV_1 decline was measured using Wilcoxon matched-pairs signed rank test.

mL; $p = 0.199$) was significantly changed. The monthly rate of FEV_1 decrease over the 6 months before vs. after conversion was not significantly different (-5 (-16 to +8) mL/month vs. -4 (-12 to +4) ml/month, respectively; p= 0.755) (**Figure 4C**). There were 12 biopsy-proven episodes of acute rejection during the 6-month period before conversion (4B1, 4 B2, 2B3, 2 A2B1) and 23 during the 12 months after conversion (9 B1, 7 B2, 1 B3, 3 A1, 2 A2, 1 A1B2) (p= 0.684). There was no statistically significant difference in C_{min} between patients who experienced AR and patients who did not (7.1 μg/L vs 6.2 μg/L, respectively, $p = 0.064$). During the 6-month period before conversion, 14 new patients met the definition of CLAD, and 6 met the definition during the 6-month period after conversion (p= 0.940).

Effect of conversion on medication adherence

Adherence data were available for 166 patients (44.6%). Age (57 ± 13 y; $p = 0.143$), sex (47.6% male; $p = 0.140$), time since LTx (81 ± 56 months; $p = 0.130$), and etiology of end-organ disease (51% chronic obstructive pulmonary disease, 19% pulmonary fibrosis, 16% CF, 4% pulmonary hypertension, and 10% other; $p = 0.690$) were similar to the characteristics of the original cohort (**Table 1**).

Based on self-reporting, the proportion of patients who missed a dose of their immunosuppressive medication in the previous month was significantly reduced 1 year after conversion compared to before conversion (8.4% vs. 19.3%, respectively; p = 0.016). The proportion of patients exhibited, irregular medication intake was also significantly reduced after conversion (19.3% vs. 32.5%, respectively; p = 0.019). The mean C_{min} and CV were higher before conversion than at 1 year post-conversion (mean C_{min} 8.7 μg/L ± 2.3 vs. 7.4 μg/L ± 2.0, respectively; $p < 0.001$; mean CV 24.4 ± 13.0 vs. 17.3 ± 13.2; $p < 0.001$). The total number of barriers also decreased significantly from before to 1 year after conversion (3 (0-10) vs. 0.5 (0-7), respectively, $p < 0.0001$) (see **Table 3** for an overview of the proportion of patients experiencing a specific barrier).

Discussion

In this study, we demonstrated that conversion from BID tacrolimus (total daily dose) to QD tacrolimus in stable LTx recipients was safe with respect to renal function, metabolic parameters, lung function and acute rejection, with no clinically relevant change in renal function, cholesterol, glycemia, FEV_1 rate of decline or acute rejection 12 months after conversion from BID to QD tacrolimus. We also showed that adherence significantly improved 1 year after conversion in a large subgroup of LTx recipients representative of the general transplant population. To our knowledge, this study is the first to broadly assess the effects of conversion from BID to QD tacrolimus in a large cohort of stable LTx recipients with respect to safety, efficacy and adherence.

Pharmacokinetic studies in healthy subjects comparing BID to QD tacrolimus have shown similar drug exposure using a conversion rate of 1 mg:1 mg, with no significant difference in AUC or C_{min} but with a decrease in C_{max}.[21] Bioequivalence ranged between 80% and 125%.[21] The same observations were also observed in stable kidney[22] and liver transplant recipients.[23] In our study of stable LTx recipients, we demonstrated that a 1 mg:1 mg tacrolimus conversion resulted in a slight but significant decrease in C_{min}, requiring subsequent up-titration of the daily dose to maintain a similar level of pharmacological immunosuppression. This observed decrease in C_{min} is in contrast to a previous study in which a 1:1 mg conversion in a non-CF LTx recipient population provided similar tacrolimus exposure 2 to 4 weeks after conversion from BID to QD tacrolimus.[24] However, a decreased C_{min} after 1:1 mg conversion has also been observed in renal,[6,25,26] liver,[27,28] and heart[29,30] transplant recipients and was correlated with time since transplantation, higher blood creatinine, lower

Table 3 Proportion of Patients Experiencing Barriers Immediately Before and 1 Year After Conversion (IMAB Self-Report Questionnaire) (n = 166)

	Barrier: having difficulties to take the immunosuppressive medications for following reasons	% experiencing barriers before conversion	% experiencing barrier at 1 year after conversion
1	Forgetfulness	39 (23.5%)	5 (3%)
2	Not renewing a prescription on time	7 (4.2%)	7 (4.2%)
3	Taking them several times a day	8 (4.8%)	0
4	Not knowing how to take them	0	2 (1.2%)
5	Difficulties to remove them from the packaging	19 (11.4%)	4 (2.4%)
6	Too many pills at the time	18 (10.8%)	14 (8.4%)
7	Bad taste	98 (59%)	4 (2.4%)
8	Difficulties to swallow them	11 (6.6%)	5 (3%)
9	When others are watching	19 (11.4%)	6 (3.6%)
10	Being busy with other things	70 (42.2%)	10 (6%)
11	Falling asleep or overslept	36 (21.7%)	19 (11.4%)
12	Feeling ill	24 (14.5%)	26 (15.7%)
13	Forgetting to take them with them when going away	23 [13.9%)	7 (4.2%)
14	When nobody reminds them to take them	18 (10.8%)	5 (2.4%)
15	Questioning whether they are effective	0	1 (0.6%)
16	Not having sufficient money	9 (5.4%)	2 (1.2%)
17	Difficulties understanding the instructions on how to take them	0	20 (12%)
18	Side effects	84 (50.6%)	18 (10.8%)
19	Being unsure whether the medications were taken already	27 (16.3%)	2 (1.2%)
20	Not understanding why they need to be taken	0	2 (1.2%)
21	Inconvenient timing of intake	11 (6.6%)	0
22	Weekends or holidays	13 (7.8%)	1 (0.6%)
23	Interruptions in daily routines	44 (26.5%)	5 (3%)
24	Having difficulties sticking to a routine	4 (2.4%)	2 (1.2%)
25	Feeling sad or down	6 (3.6%)	2 (1.2%)
26	Not knowing when to take them	0	0
27	Not needing them because they feeling fine	0	0
	Total number of barriers	3.0 (0-10)	0.5 (0-7)[a]

In gray and in bold, the 5 most frequent answers.
[a] $p < 0.0001$.

hemoglobin and CYP3A5 polymorphisms.[26] The observed decrease in C_{min} also tends to diminish over time.[25] In our study, the transiently lower C_{min} had no clinically apparent effects, with similar rates of lung function decline and number of acute rejection events before and after conversion, likely due to deliberate subsequent dose up-titration to maintain stable long-term C_{min} levels. Furthermore, we performed a specific analysis of the CF patient population, where similar findings were demonstrated compared to the non-CF population. However, CF patients needed a higher dose of tacrolimus to achieve the same target C_{min}, as previously shown, probably due to CF-related malabsorption and decreased tacrolimus bioavailability.[31] A previous pharmacokinetic study showed that exposure to tacrolimus was reduced in CF LTx recipients after conversion from BID to QD tacrolimus and that CF patients systematically needed a mean dose increase of 28%.[32] No pharmacokinetic evaluation was performed in our study, precluding conclusions regarding the tacrolimus AUC in our cohort.

Nephrotoxicity of calcineurin inhibitors remains a major issue in LTx, with a high rate of impaired renal function and a doubling of blood creatinine in 42.2% of LTx patients 4 years after transplantation.[33] Calcineurin inhibitors may damage the kidney at different levels, glomeruli, arterioles and tubule interstitium, in acute or chronic settings with reversible or irreversible damage.[30] Local vasoconstrictive arteriolopathy and direct toxic effects on tubular epithelial cells are hypothesized to play a major role in these issues.[34] QD tacrolimus could potentially have reduced nephrotoxic effects due to a decreased C_{max} with a similar exposure. Improvement of renal function with QD tacrolimus in renal transplant recipients has been reported.[35] However, it is difficult to distinguish this improvement from a decreased toxicity or an immunological effect on the graft. Studies in liver and heart transplantation showed no deleterious effect on renal function.[28,29] Due to the need for higher levels of tacrolimus to obtain adequate immunosuppression in LTx, we speculate on the potentially reduced nephrotoxicity of QD tacrolimus. However, we did not observe a significant improvement in renal function in our cohort but a slight decrease in eGFR compatible with the natural history of kidney function of patients treated with calcineurin inhibitors. However, the number of patients with CKD assessed with KDIGO stages was not significantly increased. These results suggest a safe profile of QD tacrolimus regarding renal function. Importantly, our study included stable transplanted patients. An eventual nephrotoxicity-sparing effect of QD tacrolimus in newly transplanted patients who are

exposed to the highest dose of tacrolimus cannot be ruled out. Evidence in renal transplantation has already shown a possibility for early conversion after transplantation (i.e., 11 days)[36] or direct treatment with QD tacrolimus.[37] Further studies are required to assess the efficacy and safety of early conversion or de novo QD tacrolimus use in lung transplantation, especially taking into account the potential problem of gastroparesis.

Tacrolimus also has deleterious metabolic effects. It increases blood cholesterol levels, increases the risk of developing diabetes mellitus and induces hyperkalemia. Some studies have shown a decrease in fasting glucose in stable kidney transplant recipients using QD tacrolimus.[38] Moreover, long-term studies have demonstrated the absence of adverse outcomes or abnormal laboratory findings after conversion from BID to QD tacrolimus in stable kidney transplant recipients.[39] Cardiovascular risk factors remained stable in patients who converted to QD tacrolimus after liver transplantation.[28] In our study, we likewise did not observe an increase in harmful effects of QD tacrolimus on the cardiovascular risk profile compared to tacrolimus BID.

We observed a slight but significant decrease in lung function (FEV_1) after conversion. However, this is not surprising, taking into account the natural history of lung function after transplantation and the possible development of CLAD in a subset of patients. Interestingly, conversion from BID to QD tacrolimus had no significant negative impact on the rate of lung function decline or on the number of patients with new onset of CLAD. Moreover, we did not observe an increased rate of biopsy-confirmed acute rejection after conversion. This is in line with data from other studies demonstrating that QD tacrolimus was safe regarding allograft function and acute rejection in kidney[40] and liver transplantation.[28,41] Taken together, these data suggest an acceptable safety profile for QD tacrolimus in LTx recipients, and additional clinical studies with control arms are required to confirm these findings.

Moreover, reducing the number of daily doses seems to have a beneficial impact on patient adherence, both in view of missed doses and the timing of intake.[42] Previous studies in other solid organ transplant populations have already demonstrated improved adherence after conversion from a BID to a QD regimen,[12,28,43] which may have a beneficial impact on long-term graft survival.[44] Given that nonadherence is a risk factor for rejection and mortality, strategies to tackle nonadherence in immunosuppressive regimens are urgently needed. Assessing barriers to medication intake might be an important first step, as we did in this study, allowing us to discuss tailored solutions for the remaining barriers present. Although nonadherence cannot be ruled out completely by reducing the number of daily doses, it is a relatively simple way to reduce the number of missed doses and facilitate timely intake. Due to the lack of a control group, the impact of improved adherence on graft function, CLAD development and clinical outcomes cannot be directly assessed in this study. However, optimal therapeutic adherence has been linked to improved outcomes in LTx. A previous study in a very small number of patients showed that QD intake decreased the variation in tacrolimus C_{min}, resulting in stabilization of lung function in a subset of CLAD patients.[45] However, this study had no direct control group, and it is difficult to link lung function stabilization to tacrolimus conversion and better adherence, rather than natural evolution of CLAD, which sometimes exhibits periods of stabilization. Our results may suggest an improvement of long-term outcomes in response to QD tacrolimus in LTx, although this will need further evaluation.

The present study has several limitations. First, as a consequence of the study design, we had no control group, precluding a direct comparison of the effects observed with both tacrolimus formulations. Second, we had no pharmacokinetic data and no assessment of AUC before and after conversion for either tacrolimus formulation. However, previous studies assessing the pharmacokinetics of tacrolimus suggest that there is no significant difference in tacrolimus exposure between groups[21] or at least an acceptable bioequivalence after daily dose adjustment.[24,32] Moreover, our study was performed in stable LTx patients, and whether our results could be extrapolated to newly transplanted recipients starting immediately with QD tacrolimus should be further evaluated. We have, however, included stable patients in the first year after transplantation, precluding analysis of data further than 6 months before the conversion and precluding a comparison of the same frame of time, which may potentially bias some results. This was addressed by using monthly normalization. In conclusion, BID to QD tacrolimus conversion with a 1 mg per 1 mg conversion rate requires close monitoring of the post-conversion C_{min}, with minor dose adjustments to obtain a similar exposure of immunosuppression in stable LTx recipients. Conversion is safe with respect to renal function, metabolic parameters, allograft function and acute rejection. Further clinical studies with control arms are required to validate our findings. The use of QD tacrolimus rather than BID tacrolimus improves therapeutic adherence in LTx recipients.

Author contribution

All the authors listed in the manuscript have substantially participated to the research. LG, RV, FD, GV, LH were involved in the conception of the work. LG, LH, RV, IV, ID, PB, VS, JY, LD were involved in the conductance of the research and the acquisition of the data. The analysis and the interpretation of the data was conducted by LG, RV, FD, LH, IV, GV. The drafting of the work and it is critically revision was performed by LG, RV, FD, GV, JY, SV, LD, BV, LC, DV, AN. All the co-authors have read and accepted the manuscript in its present form.

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Supplementary materials

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Supplementary data

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