

Received: 2019.03.05

Accepted: 2019.07.01

Published: 2019.08.27

# A Multicenter, Prospective, Observational Study of Conversion from Twice-Daily Immediate-Release to Once-Daily Prolonged-Release Tacrolimus in Liver Transplant Recipients in France: The COBALT Study

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABDE 1 **Jérôme Dumortier**  
ABDE 2 **Christophe Duvoux**  
ADE 3 **Laurence Dubel**  
ACE 4 **Fabienne Bazin**  
ABDE 5 **Pauline Housel-Debry**

1 Department of Hepatology, Edouard Herriot Hospital, Lyon, France  
2 Department of Hepatology, Henri Mondor Hospital APHP, Paris Est University UPEC, Créteil, France  
3 Astellas Pharma, Levallois-Perret, France  
4 ITEC Services, Bordeaux, France  
5 Department of Hepatology, Pontchaillou Hospital, Rennes, France

**Corresponding Author:** Laurence Dubel, e-mail: laurence.dubel@astellas.com

**Source of support:** This study was funded by Astellas Pharma Global Development Incorporated, Chertsey, UK, which also funded editorial support

**Background:** In adult liver transplant patients, the use of prolonged-release tacrolimus may have treatment adherence benefits over the immediate-release formulation. The aim of this study was to characterise real-world practice data on conversion of liver transplant recipients from immediate- to prolonged-release tacrolimus in France.

**Material/Methods:** A prospective, observational study (NCT02143479) was conducted in 18 transplant centers in France between June 2014 and March 2016. Liver transplant recipients (n=398) included patients who changed from immediate-release to prolonged-release tacrolimus within the first three months (early conversion group) (n=205) or between three and 12 months after transplantation (late conversion group) (n=184). Clinical data were collected at an initial baseline outpatient visit and six-month and 12-month follow-up visits. Endpoints included the dose conversion ratio from immediate-release to prolonged-release tacrolimus, number of and reasons for additional visits due to conversion, safety, and tolerability.

**Results:** Baseline clinical and demographic characteristics were similar between the two cohorts. The mean  $\pm$ SD ratio of conversion of tacrolimus dose was  $1.04 \pm 0.28$ ;  $1.01 \pm 0.28$  (early) and  $1.08 \pm 0.28$  (late) ( $p=0.0247$ ). The mean  $\pm$ SD time from conversion to the first tacrolimus trough blood concentration was  $30.8 \pm 42.8$  days;  $24.8 \pm 45.4$  days (early) and  $37.5 \pm 38.7$  days (late). Only one patient required an additional visit due to conversion. Reasons for conversion included the physician's preference (56.3%), center practice (38.6%), and the dosing frequency (36.0%). Conversion was associated with a low rate of graft rejection, and no new safety issues were reported.

**Conclusions:** Conversion of liver transplant recipients from immediate-release to prolonged-release tacrolimus within three to 12 months of transplantation was easy to manage and associated with favorable clinical outcomes and safety profiles.

**Clinical trial registration link:** <https://clinicaltrials.gov/ct2/show/NCT02143479?term=NCT02143479&rank=1>

**MeSH Keywords:** Liver Transplantation • Observational Study • Tacrolimus

**Full-text PDF:** <https://www.annalsoftransplantation.com/abstract/index/idArt/916041>

 4297

 3

 5

 28



## Background

In the past two decades, improvements in immunosuppressive regimens, and other advances in liver transplantation, have resulted in six-month graft survival rates of more than 90% [1]. Tacrolimus, a calcineurin inhibitor, is given to more than 90% of liver transplant recipients immediately following transplant surgery, as part of an immunosuppressive regimen in combination with corticosteroids and anti-proliferatives (e.g. mycophenolate mofetil or mycophenolic acid) [1,2]. Poor adherence to immunosuppressive therapy is a significant issue following transplantation and can contribute to graft failure [3]. Several studies have shown that reducing the frequency of dosing of immunosuppressive therapy has a positive impact on treatment adherence in transplant patients [4–6].

Once-daily, prolonged-release tacrolimus has been available since 2007, for the prevention of graft rejection in adults who have had kidney or liver transplants and for the treatment of allograft rejection in adult transplant recipients resistant to therapy with other immunosuppressive drugs. The primary benefit of the prolonged-release formulation is improved patient adherence with once-daily dosing [7–9], which has been shown in observational and randomized controlled trials [10–13]. Furthermore, the findings from several studies that have included hundreds of liver transplant recipients who have converted from immediate-release to prolonged-release tacrolimus have shown comparable safety and efficacy between the two formulations [9,13,14].

The safety and efficacy of both immediate-release and prolonged-release tacrolimus formulations are now well established. In clinical practice, immediate-release tacrolimus remains a popular therapeutic option in the immediate post-transplant phase, followed by conversion to the prolonged-release formulation. Currently, there is a lack of practical recommendations regarding the initiation of prolonged-release tacrolimus in liver transplant recipients [9], including the optimal timing of conversion from the immediate-release to the prolonged-release formulation. Furthermore, the basis for the clinical decision regarding the choice of formulation and when to convert remains poorly described in the literature. The use of both formulations of tacrolimus varies widely according to local preferences, and individual circumstances, and previously published studies have rarely described conversion earlier than six months following liver transplantation.

Therefore, the aim of this study was to characterise real-world practice data on conversion of liver transplant recipients from immediate- to prolonged-release tacrolimus in France.

## Material and Methods

### Patients and study design

A prospective, observational, cohort study (NCT02143479) was undertaken in 18 centers in France that included liver transplant recipients who converted from twice-daily immediate-release tacrolimus (Prograf®, Astellas Pharma Ltd., Chertsey, UK) to once-daily prolonged-release tacrolimus (Advagraf®, Astellas Pharma Europe BV, Netherlands). The study was conducted in accordance with the relevant ethical standards, approved by the local advisory committee (CCTIRS) and was authorized by the French National Commission for Data Processing and Privacy (CNIL) (authorization No. DR-2014-136). All study participants provided informed consent and were free to withdraw from the study at any stage.

Stable liver transplant recipients ( $\geq 18$  years) who had undergone transplantation in the preceding 12 months, were eligible for inclusion in the study if their physician had decided to convert them from immediate-release to prolonged-release tacrolimus according to the usual medical practice at a previously scheduled appointment. The only exclusion criterion was concomitant participation in any other international clinical study.

### Treatment

Conversion from twice-daily immediate-release to once-daily prolonged-release tacrolimus was undertaken either within the first three months post-transplantation (the early conversion group) or between three and 12 months (the late conversion group). The individual tacrolimus dosing regimen and care of the patient during the conversion were left to the discretion of the treating physician.

Conversion from immediate-release to prolonged-release tacrolimus took place at the initial baseline clinic visit, and the study data were gathered during routine follow-up visits at six months and 12 months post-conversion. Detailed dosing and treatment information was collected, as well as the time to the first measurement of tacrolimus trough blood concentration ( $C_0$ ) and the number of additional visits due to conversion. Reasons for conversion, complications, biopsy-confirmed acute rejection (BCAR), graft and patient survival rates, and emerging comorbidities were also recorded.

### Endpoints

The primary endpoint was an evaluation of the modalities of conversion, using the following: the dose ratio of conversion from immediate-release to prolonged-release tacrolimus, expressed as  $=1$ ,  $<1$ , or  $>1$ ; the time to first determination of the tacrolimus trough blood concentration ( $C_0$ ) after conversion;

and the number of additional visits due to conversion (if any). The secondary endpoints included reasons for conversion, quality of life, patient adherence to treatment, complication rate, concomitant comorbidities and treatment, and drug safety and tolerability.

For patients in the late group only, quality of life was recorded at baseline and one-year post-conversion using the EQ-5D-5L questionnaire, which has been previously validated in patients with chronic hepatic disorders [15]. Adherence to treatment in the late group was measured using the 8-item Morisky Medication Adherence Scale (MMAS-8) [16], where scores of 8, 6–7, and <6 indicated full, moderate, and low adherence, respectively.

Details of adverse events (AEs) and severe adverse events (SAEs) that occurred at any time during treatment with prolonged-release tacrolimus were recorded, and the treating physician assigned their relationship to treatment.

### Statistical analysis

The target enrollment was 400 liver transplant recipients, based on the number of participating sites and the annual rate of liver transplantation in France at the time of initiation of the study [17]. This sample size was determined to allow data description at a precision of 5% and a confidence interval (CI) of 95%. The baseline data and all safety analyses were based on the full population. All other analyses were based on the per-protocol population (PPS), which included all enrolled patients who complied with the inclusion and exclusion criteria, with no significant deviations. Qualitative data were compared using Pearson's chi-squared test or Fisher's exact test. Quantitative data were compared using Student's t-test or Wilcoxon test. Statistical analysis was performed using SAS™ software, version 9.3 or above (SAS Institute, NC, Cary, USA). There was no input for missing data.

## Results

### Patient characteristics

Overall, 398 liver transplant recipients were screened by 30 physicians in 18 centers between June 2014 and March 2016. Nine recipients were ineligible for enrollment (due to unmet inclusion criteria or missing data). The per-protocol population (PPS) comprised 389 patients, of whom 205 underwent early conversion and 184 late conversion, between three months and 12 months (Figure 1). During follow-up, 23 liver transplant recipients (12 early conversions, and 11 late conversions) withdrew from the study. The mean  $\pm$ SD time between inclusion and withdrawal was  $4.81\pm 3.48$  months.

Baseline characteristics were similar between early and late conversion groups (Table 1). The mean  $\pm$ SD age of all liver transplant recipients at conversion was  $54.88\pm 11.0$  years. The majority of liver transplant patients were Caucasian (90.4%) and male (76.9%). The most common indications for liver transplant were alcoholic cirrhosis (58.4%) and hepatocellular carcinoma (HCC) (42.9%) (Table 1).

The mean  $\pm$ SD time between liver transplant and conversion was  $40.27\pm 24.48$  days in the early conversion group, and  $188.92\pm 75.88$  days in the late conversion group. Additional baseline demographics and clinical characteristics are shown in Table 1. The mean  $\pm$ SD total follow-up duration was  $11.81\pm 2.34$  months.

### Conversion from twice-daily immediate-release to once-daily prolonged-release tacrolimus

The overall mean  $\pm$ SD ratio of conversion of the tacrolimus dose was  $1.04\pm 0.28$ ;  $1.01\pm 0.28$  in the early conversion group and  $1.08\pm 0.28$  in the late conversion group ( $p=0.0247$ ) (Table 2). In the early conversion group, 39.7% of liver transplant patients had a dose conversion ratio of 1, with a rate of 58.5% in the late conversion group.

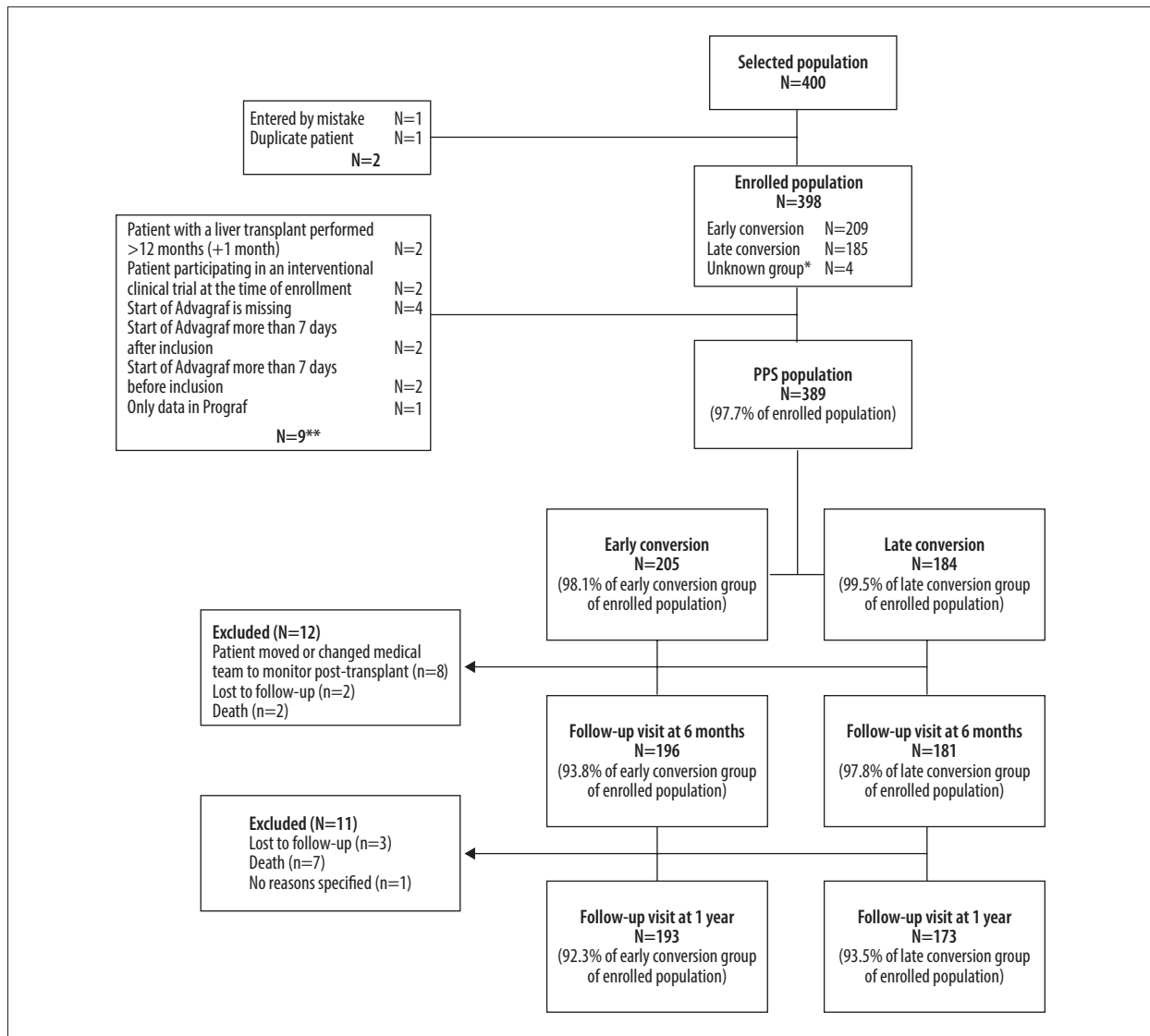
Overall, the mean  $\pm$ SD tacrolimus dose at conversion was  $6.07\pm 3.3$  mg/day, with significantly higher doses recorded in the early conversion group ( $6.93\pm 3.4$  mg/day) compared with the late conversion group ( $5.11\pm 3.0$  mg/day) ( $p<0.0001$ ). The mean  $\pm$ SD time from conversion to the first tacrolimus trough blood concentration measurement was  $30.8\pm 42.8$  days;  $24.8\pm 45.4$  days in the early conversion group and  $37.5\pm 38.7$  days in the late conversion group. Only one patient required an additional visit as a result of conversion, which occurred in a patient in the late conversion group at 17 days post-conversion.

### Reasons for conversion

The main reasons for conversion from immediate-release to prolonged-release tacrolimus included the physician's decision in 56.3% of all cases; 44.9% in the early conversion group and 69.0% in the late conversion group. The next reason for conversion was according to the standard clinical practice of the center in 38.6%; 45.9% in the early conversion group and 30.4% in the late conversion group. The final reason was the number of treatment doses required in 36.0%; 27.3% in the early conversion group and 47.5% in the late conversion group (Figure 2).

### Quality of life and adherence to treatment

Compared with baseline, the quality of life in the late conversion group improved at one-year post-conversion for all five EQ-5D-5L dimensions, particularly mobility and usual activities, from 41.4% to 25.2%, and from 42.6% to 28.6%, respectively.



**Figure 1.** Flowchart of the study population.

\* Patients without recorded dates of transplantation and conversion. \*\* Several possible modalities. PPS – per-protocol population.

Health status, defined as the proportion of recipients experiencing problems with at least one of the five EQ-5D-5L dimensions, decreased from 74.6% to 62.0% during the year following conversion in the late conversion group (Figure 3).

The mean  $\pm$ SD adherence score in the late conversion group was  $7.48 \pm 0.78$  at conversion with immediate-release tacrolimus and  $7.51 \pm 0.91$  at one year following conversion (Figure 4). More liver transplant recipients recorded full adherence (score=8) with prolonged-release tacrolimus at one year than at baseline (70% compared with 61%, respectively). However, the proportion of liver transplant recipients with moderate adherence (score 6–8) decreased from conversion to one-year follow-up (34% compared with 25%, respectively).

### Patient survival, complications, and comorbidities

Overall, at one-year post-conversion, 4.7% of patients had renal failure (Table 3); 4.2% in the early conversion group and 5.4% in the late conversion group. Seven (1.9%) new cases of diabetes were recorded, and dyslipidemia occurred in six patients (1.7%). Non-hepatocellular carcinoma (HCC) occurred in six patients (1.7%), and six patients (1.7%) experienced recurrence of their initial disease. Eleven patients (3.1%) developed arterial hypertension as an emergent comorbidity, which was higher in the late conversion group (5.4%) compared with the early conversion group (1%) (Table 3), indicating that the incidence of arterial hypertension increases with time.

**Table 1.** Demographic characteristics of liver transplant recipients at baseline.

	Early conversion (N=205)	Late conversion (N=184)	Total (N=389)
Age, years (SD)	54.2 (11.3)	55.6 (10.6)	54.9 (11.0)
Gender, n male (%)	154 (75.1)	145 (78.8)	299 (76.9)
Ethnic origin, n (%)			
Caucasian	174 (85.7)	175 (95.6)	349 (90.4)
African	18 (8.9)	5 (2.7)	23 (6.0)
Asian	1 (0.5)	1 (0.5)	2 (0.5)
Other	10 (4.9)	2 (1.1)	12 (3.1)
BMI, kg/m <sup>2</sup> (SD)	24.9 (4.9)	24.7 (4.5)	24.8 (4.7)
Indications for liver transplant, n (%)			
Cancer (HCC)	88 (42.9)	79 (42.9)	167 (42.9)
Viral cirrhosis (HCV)	47 (22.9)	38 (20.7)	85 (21.9)
Viral cirrhosis (HBV)	21 (10.2)	17 (9.2)	38 (9.8)
Alcoholic cirrhosis	110 (53.7)	117 (63.6)	227 (58.4)
Repeat transplantation	9 (4.4)	7 (3.8)	16 (4.1)
Cholestatic disease	19 (9.3)	15 (8.2)	34 (8.7)
Fulminating hepatitis	7 (3.4)	5 (2.7)	12 (3.1)
Dysmetabolic cirrhosis	29 (14.1)	34 (18.5)	63 (16.2)
Other	22 (10.7)	18 (9.8)	40 (10.3)
Comorbidities, n (%)			
Diabetes	80 (39.0)	66 (35.9)	146 (37.5)
Dyslipidemia	15 (7.3)	19 (10.3)	34 (8.7)
Arterial hypertension	106 (51.7)	81 (44.0)	187 (48.1)
Cancer (other than HCC)	1 (0.5)	2 (1.1)	3 (0.8)
Other	28 (13.7)	40 (21.7)	68 (17.5)
Time since liver transplant (days)	40.3 (24.5)	188.9 (75.9)	110.6 (92.5)
Graft complications between liver transplant and conversion, n (%)			
Acute graft rejection	9 (4.4)	10 (5.4)	19 (4.9)
BCAR	8 (3.9)	8 (4.3)	16 (4.1)

BP – blood pressure; BCAR – biopsy proven acute rejection; BMI – body mass index; HBV – hepatitis B virus; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; SD – standard deviation.

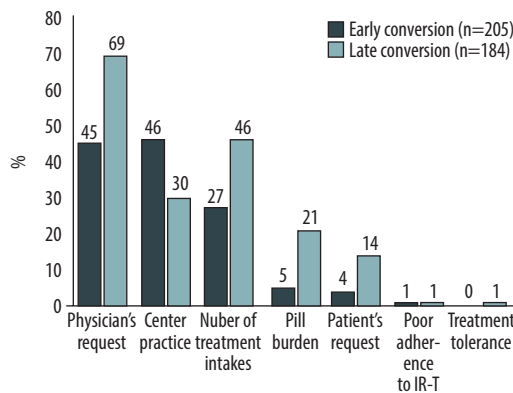
At six months post-conversion, there were six (1.6%) biopsy-confirmed acute rejection (BCAR) episodes in patients treated with prolonged-release tacrolimus, including 2/196 (1.0%) in the early conversion group and 4/181 (2.2%) in the late conversion group. The mean  $\pm$ SD time from conversion to first BCAR was

93.0 $\pm$ 57.1 days; 90.0 $\pm$ 19.8 days in the early conversion group and 94.5 $\pm$ 72.8 days in the late conversion group. Between six months and 12 months post-conversion, eight BCAR episodes (2.2%) occurred under treatment with prolonged-release tacrolimus; 7/193 (3.6%) in the early conversion group and 1/173 (0.6%) in

**Table 2.** Dose conversion ratio and conversion-related additional visits between pre-conversion immediate-release tacrolimus and post-conversion prolonged-release tacrolimus dose in liver transplant recipients.

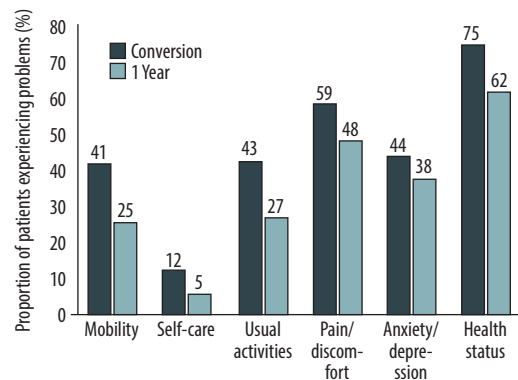
	Early conversion (N=205)	Late conversion (N=184)	Total (N=389)	P value
Conversion ratio, mean ( $\pm$ SD)	1.01 (0.28)	1.08 (0.28)	1.04 (0.28)	0.0247*
Proportion of subjects, n (%)				
Ratio <1	66 (32.4)	23 (12.6)	89 (23.0)	
Ratio =1	81 (39.7)	107 (58.5)	188 (48.6)	<.0001**
Ratio >1	57 (27.9)	53 (29.0)	110 (28.4)	
Conversion ratio, mean ( $\pm$ SD)				
Ratio <1	0.76 (0.13)	0.76 (0.13)	0.76 (0.13)	0.8696*
Ratio >1	1.32 (0.31)	1.37 (0.35)	1.35 (0.33)	0.4780*
Tacrolimus dose at conversion, mg/day, mean ( $\pm$ SD)	6.9 (3.0)	5.11 (3.0)	6.1 (3.3)	<0.0001#
Additional visits due to conversion, n (%)	0 (0.0)	1 (0.5%)	1 (0.3%)	

Conversion ratios of the tacrolimus dose are shown. \* Student t-test; \*\* chi-square test, # Wilcoxon test. SD – standard deviation.



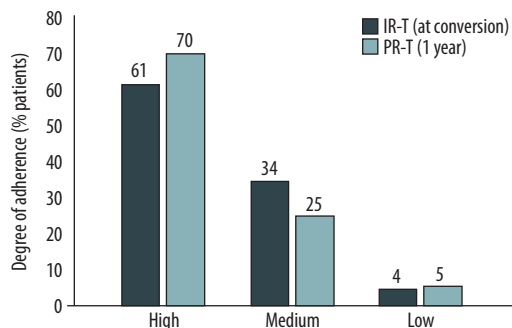
**Figure 2.** Reasons for conversion from immediate-release to prolonged-release tacrolimus in liver transplant recipients. Individual liver transplant recipients may have been converted from immediate-release to prolonged-release tacrolimus for multiple reasons. IR-T – immediate-release tacrolimus.

the late conversion group. The mean  $\pm$ SD time from conversion to late-onset BCAR (between six and 12 months) was 287.1 $\pm$ 70.9 days; 302.4 $\pm$ 60.6 days in the early conversion group and 180 days for one patient in the late conversion group. At one-year post-conversion, 12/389 (3.1%) of all liver transplant recipients had BCAR; 8/205 (3.9%) in the early conversion group and 4/184 (2.2%) in the late conversion group. The mean  $\pm$ SD time between conversion and the first BCAR was 6.54 $\pm$ 4.12 months, with no difference between the two groups (p=0.3307).



**Figure 3.** Quality of life in liver transplant recipients following conversion from immediate-release to prolonged-release tacrolimus. Data represent the proportion of liver transplant recipients experiencing any problem with each of the five dimensions of the EQ-5D-5L; late conversion group only. Health status indicates the proportion of liver transplant recipients with problems relating to at least one of the five dimensions of the EQ-5D-5L. N=184. EQ-5D-5L – EuroQol, 5 dimensions and 5 levels.

No graft loss occurred in the late conversion group. Two individuals in the early conversion group suffered graft loss, at 8.5 months and 8.3 months following liver transplantation, respectively, which was 8.2 and 6.0 months, respectively since conversion to prolonged-release tacrolimus. Reasons for graft loss were bile duct stenosis and chronic hepatic rejection (Table 3),



**Figure 4. Adherence of liver transplant recipients to immediate-release and prolonged-release tacrolimus.** Adherence to immediate-release tacrolimus at conversion and to prolonged-release tacrolimus at one-year follow-up; late conversion group only. Adherence was measured using MMAS-8; the maximum score of 8 indicated high adherence, scores of 6–8 indicated moderate adherence, and <6 indicated low adherence. N=184. IR-T – immediate-release tacrolimus; MMAS-8 – 8-item Morisky medication adherence scale PR-T – prolonged-release tacrolimus.

but neither were considered related to tacrolimus. Overall one-year survival in liver transplant recipients following conversion was 97.7% (Table 3). Nine liver transplant recipients (2.3%) died during the study, two (1.0%) in the early conversion group, and seven (3.8%) in the late conversion group (Table 3). Contributing factors included, but were not limited to, acute kidney injury, veno-occlusive disease, lymphoproliferative disorder, endocarditis, cerebrovascular accident (CVA), hemorrhagic shock, multiple organ dysfunction, and sepsis. The overall mean  $\pm$ SD time between liver transplant and death was  $9.78 \pm 2.90$  months;  $11.32 \pm 1.42$  months in the early conversion group and  $9.34 \pm 3.14$  months in the late conversion group;  $p=0.3055$ ). The overall mean  $\pm$ SD time between conversion and death was  $5.73 \pm 3.44$  months;  $10.43 \pm 0.86$  months in the early conversion group and  $4.38 \pm 2.49$  months in the late conversion group ( $p=0.0570$ ). One death, due to sepsis, was considered to be related to tacrolimus. Overall, infections and infestations was the class of AE most commonly associated with death and was recorded in 4/9 cases (44%).

### Immunosuppressive treatment regimens

At baseline, the combination of prolonged-release tacrolimus with mycophenolic acid (with or without corticosteroids) was the most commonly initiated immunosuppressive regimen for the liver transplant recipients who underwent conversion. This immunosuppression regimen was used in 86.7% of patients; 94.1% in the early conversion group and 78.6% in the late conversion group (Figure 5). Overall, this treatment regimen was the most commonly used at six months, in 77.5% of

recipients; 80.4% in the early conversion group and 74.4% in the late conversion group. Also, this treatment regimen was the most commonly used at one-year, in 78.7% of recipients; 82.4% in the early conversion group and 74.7% in the late conversion group. The proportion of liver transplant recipients receiving prolonged-release tacrolimus as a monotherapy increased over time from 3.1% at conversion to 7.6% at one-year post-conversion and was less common in the early compared with the late conversion group (3.2% compared with 12.4%). The mammalian target of rapamycin (mTOR) inhibitors, sirolimus, and everolimus, were used by 0.8% patients at baseline, which increased to 4.5% at one-year post-conversion.

During the first six months following conversion, 64.7% of patients had no change to their prolonged-release tacrolimus therapy; 66.8% in the early conversion group and 62.4% in the late conversion group. Between six months and one year, 87.9% of patients had no modification of their prolonged-release tacrolimus dosing; 91.7% in the early conversion group and 83.7% in the late conversion group. The most common change was dose modification, which was required in 32.6% of patients from conversion to six months; 30.6% in the early conversion group and 34.8% in the late conversion group. Dose modification was required in 11.3% of patients from six months to one year; 7.8% in the early conversion group and 15.1% in the late conversion group. In total, 42.9% of patients required dose modification of prolonged-release tacrolimus one year after conversion, and 54.1% had no modification. Ten patients during the first six months post-conversion and three patients during the following six months discontinued prolonged-release tacrolimus. Six of these patients returned to immediate-release tacrolimus, mainly due to tolerance issues and  $C_0$  adjustment.

The two add-on therapies for which doses were modified most frequently during the first 6 months were mycophenolate mofetil and corticosteroids. Mycophenolate mofetil was modified in 14.9% of patients; 20.4% in the early conversion group and 8.8% in the late conversion group. Corticosteroids were modified in 21.0% of patients; 31.1% in the early conversion group and 9.9% in the late conversion group. Discontinuation of treatment occurred most commonly with corticosteroids during the first six months in 28.9% of patients; 36.2% in the early conversion group and 21.0% in the late conversion group. In the following six months, 2.7% of patients discontinued corticosteroid treatment; 4.2% in the early conversion group and 1.2% in the late conversion group.

### Safety and tolerability

Between baseline and one-year post-conversion, 65.6% of patients reported at least one adverse event (AE), and 28.1% reported at least one serious adverse event (SAE). A total of 739 AEs were recorded, which were similarly distributed between

**Table 3.** Outcomes in liver transplant recipients including newly presenting complications and comorbidities at 1-year post-conversion.

	Early conversion (N=205)	Late conversion (N=184)	Total (N=389)	P value
Survival at 1-year, n (%)	203 (99.0)	177 (96.2)	380 (99.7)	0.0909*
Death at 1-year, n (%)	2 (1.0)	7 (3.8)	9 (2.3)	0.0909*
Time between transplantation and death, months (SD)	11.3 (1.4)	9.34 (3.1)	9.78 (2.9)	0.3055**
Time between conversion and death, months (SD)	10.43 (0.9)	4.38 (2.5)	5.73 (3.4)	0.0570**
Graft complications, n (%)	205	184	389	
Graft loss	2 (1.0)	0 (0)	2 (0.5)	0.3249#
BCAR	8 (3.9)	4 (2.2)	12 (3.1)	0.0508**
Time between conversion and first BCAR, months (SD)	8.26 (3.76)	3.10 (2.39)	6.54 (4.12)	
Complications, n (%)				
n	192	172	364	
Renal failure	8 (4.2)	9 (5.2)	17 (4.7)	
Diabetes	2 (1.0)	5 (2.9)	7 (1.9)	
Dyslipidemia	3 (1.6)	3 (1.7)	6 (1.6)	
Arterial hypertension	2 (1.0)	9 (5.2)	11 (3.0)	
Cancer (other than HCC)	1 (0.5)	5 (2.9)	6 (1.6)	
Initial disease recurrence	3 (1.6)	3 (1.7)	6 (1.6)	
Other	47 (24.5)	45 (26.2)	92 (25.3)	
Laboratory data, mean (±SD)				
n	183	165	348	
Blood creatinine (µmol/l)	96.8 (56.9)	106.0 (34.4)	101.3 (47.5)	
Alkaline phosphatase (UI/l)	119.2 (78.3)	113.3 (120.0)	116.2 (101.3)	
AST (UI/l)	98.8 (933.5)	26.2 (32.2)	63.8 (672.1)	
ALT (UI/l)	56.9 (331.6)	30.9 (50.2)	44.3 (241.2)	
GammaGT (UI/l)	95.7 (206.1)	83.0 (189.0)	89.5 (197.8)	
Total bilirubin (µmol/l)	12.0 (13.9)	11.0 (6.1)	11.5 (10.8)	
Fasting blood glucose (mmol/l)	6.3 (1.9)	7.1 (5.8)	6.7 (4.3)	

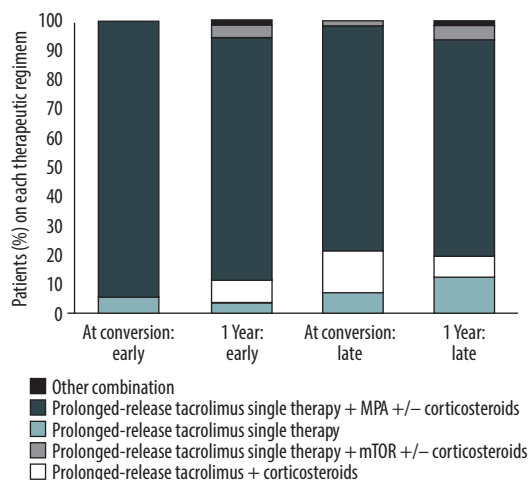
Data represents new cases of complications and comorbidities since conversion. N numbers vary due to occasional missing data.

\* Fisher's exact test; \*\* Wilcoxon test; # Chi-Square. ALT – alanine aminotransferase; AST – aspartate aminotransferase; BCAR – biopsy-confirmed acute rejection; GT – glutamyl transferase; HCC – Hepatocellular carcinoma; SD – standard deviation.

the early conversion group, with 390 AEs, and the late conversion group, with 349 AEs. The most common AEs were infections and infestations (16.3%), together with urinary and renal disorders (14.6%).

AEs and SAEs considered to be associated with tacrolimus therapy, were reported in 15.6% and 3.0% of patients, respectively. The proportion of AEs associated with tacrolimus therapy was lower in the early conversion group (12.4%) compared with the late conversion group (19.5%). Twelve patients (3.0%) recorded 19 tacrolimus-related SAEs, including one death due to sepsis.





**Figure 5.** Change in immunosuppressive regimens in liver transplant recipients. Therapy combinations in liver transplant recipients in early and late conversion groups at conversion and at one-year follow up. MPA – mycophenolic acid; mTOR – mammalian target of rapamycin.

## Discussion

Despite excellent clinical outcomes in the majority of liver transplant recipients, a minority experience graft rejection during the first year post-transplantation [1]. Liver transplant rejection may be due to an insufficient or variable dose of immunosuppressant drugs or from non-adherence to therapy [18–20]. This real-world clinical study investigated data from 18 liver transplant centers in France on early and late conversion from immediate-release to prolonged-release tacrolimus. Demographic data analysis showed that the mean age of the patients studied was 54.9 years and that more than 90% of the patients were Caucasian, which was representative of the liver transplant patient population in France [17].

Previous studies have reported good clinical outcomes following the use of prolonged-release tacrolimus when treatment begins both immediately post-transplantation and following conversion from immediate-release formulations [14,21,22]. Stable hepatic and renal function has been reported in a previous study conducted in France, in which 394 liver transplant recipients were converted to prolonged-release tacrolimus six years after transplantation [23]. There was no change in the incidence of hypertension or dyslipidemia and only a slight increase in the incidence of diabetes [23]. Also, a two-year follow-up study of patients who converted to prolonged-release tacrolimus at least six months after liver transplantation reported high rates of patient survival and graft survival [14]. Analysis of the European Liver Transplant Registry showed

reduced graft rejection and reduced patient mortality when liver transplant recipients were treated with prolonged-release compared with immediate-release tacrolimus [21].

The timing of treatment conversion in previous studies typically ranged from six months to several years post-transplantation [23], but there have been few studies on outcomes following conversion in the medium term, between three and 12 months [9]. This observational, real-world study was undertaken on a population of liver transplant recipients in France, who converted from immediate-release to prolonged-release tacrolimus, primarily as a result of routine clinical practice, either early, up to three months, or late, between three months and 12 months, after liver transplantation. Following conversion, adherence tended to be higher at 1 year when patients were receiving prolonged-release tacrolimus, compared with baseline when patients were taking immediate-release tacrolimus.

The overall dose conversion ratio was 1.04, which is consistent with the recommended 1:1 ratio in the manufacturer's guidelines for tacrolimus [24]. The dose conversion ratio in this study was slightly different from that recommended, as the real-world observational nature of the study meant that physicians were free to adjust tacrolimus doses according to the needs of the patient. Only one patient in the late conversion group required an additional visit as a result of the conversion, which indicated the ease with which conversion was achieved. Tacrolimus has a narrow therapeutic window, and careful dosing is required to achieve a maximal immunosuppressive effect with minimal drug-related adverse events (AEs) [12]. A previous study reported a significant dip in the mean tacrolimus trough concentrations ( $C_0$ ) in the first two weeks following conversion from twice-daily to once-daily formulations, requiring stabilization by dose adjustment [10].

Furthermore, in a randomized trial that compared the pharmacokinetics of tacrolimus in *de novo* liver transplant patients, the mean area under the curve (AUC) between 0 to 24 hours for tacrolimus on treatment Day 1 was approximately 50% lower for prolonged-release versus immediate-release tacrolimus, but was comparable by Day 14 [25]. Therefore, the prolonged time to the first determination of the tacrolimus trough blood level ( $C_0$ ) was relatively unexpected, at  $24.8 \pm 45.4$  days after early conversion, and  $37.5 \pm 38.7$  days after late conversion ( $p=0.041$ ). It is important to note that a low number of  $C_0$  measurements were reported in the present study, resulting in insufficient data to accurately describe the degree of exposure of patients to prolonged-release tacrolimus. The data relating to the first determination of the  $C_0$  were considered unreliable, especially for inpatient variability and steady-state assessments. Therefore, these data were not presented.

However, consistent with previously published reports, more than half (57.1%) of patients in this study did not require dose adjustment of their prolonged-release tacrolimus dose over the course of the study [10,14]. Other studies have suggested that higher doses are needed to achieve target tacrolimus concentrations after early conversion, within less than one month following liver transplant, compared with late conversion following liver transplant [22]. Similarly, in the present study, the mean dose was significantly higher in the early conversion group ( $6.93 \pm 3.36$  mg/day) compared with the late conversion group ( $5.11 \pm 3.00$  mg/day) ( $p < 0.0001$ ).

Only minor changes to immunosuppressive regimens were needed during the one-year post-conversion period, indicating that emerging treatment-related complications and AEs were manageable and did not require a change of therapy. Ideally, due to potential AEs, corticosteroid therapy should be rapidly tapered and maintained in the immunosuppression regimen for at least the first three to six months following liver transplantation [2]. In this study in real-world clinical practice, a significant proportion of liver transplant recipients remained on corticosteroids up to a year following liver transplantation. This finding was consistent with data from the USA in which 58% of liver transplant recipients remained on corticosteroids as part of their immunosuppressive regimen at one-year post-transplant [1].

Adherence to immunosuppressive therapy is essential following liver transplantation to reduce the risk of acute episodes of rejection [19]. Non-adherence with anti-rejection medication has been associated with the increased complexity of dosing regimens [26], including dosing frequency [27]. In the present study, there was a trend towards improved adherence following the conversion from twice-daily immediate-release to once-daily prolonged-release tacrolimus. Using the MMAS-8 [16], 69.7% of patients achieved full adherence, with an MMAS-8 score of 8/8, at one-year after conversion, compared with 61.0% at conversion. This finding was consistent with previous studies that reported statistically significant improvements in adherence following conversion from twice-daily to once-daily tacrolimus formulations [11]. However, it is important to note that high levels of adherence at baseline may have explained the lack of a more substantial improvement in the present study. Also, while improvement in patient's quality of life was also observed, the high quality of life at baseline may have explained the lack of a more significant improvement.

The efficacy and safety of tacrolimus following conversion from immediate-release to prolonged-release formulations were confirmed up to 12 months post-transplantation. Clinical outcomes were good, with overall patient survival of 97.7% and graft survival of 99.5%. These values are similar to those described by Beckebaum et al., who reported 96% patient and

graft survival at one year after the conversion to prolonged-release tacrolimus [10]. In the present study, neither of the reported graft losses were considered to be related to tacrolimus. Of the nine deaths reported, just one was considered to be related to tacrolimus, which was a case of sepsis. At one-year post-conversion, biopsy-confirmed acute rejection (BCAR) was recorded in only 3.1% of patients, including 3.9% in the early conversion group and 2.2% in the late conversion group. There were no new safety signals, and the most commonly recorded drug-related AEs were consistent with previous studies [9].

This observational study had several limitations. The limited available data on the tacrolimus trough concentration ( $C_0$ ), prevented the reliable analysis of this outcome. The time between conversion and the first determination of  $C_0$  was around 30 days for the whole population, which meant that the analysis of tacrolimus blood trough levels in the early post-conversion phase was not possible. Rather than giving an accurate representation of when  $C_0$  measurement was performed, we speculate that this may be due to incomplete recording of earlier  $C_0$  measurements. For patients in the early conversion group, within three months of transplantation, it is unrealistic that the first attempt to measure  $C_0$  would have occurred as late as suggested by the study records. Incomplete recording of  $C_0$  also affected the ability to investigate inpatient variability, which could not be analyzed. However, the aim of this study was to investigate the conversion of patients from immediate-release to prolonged-release tacrolimus in a real-world clinical setting. Early post-conversion trough levels of tacrolimus have been reported in previous studies [10,28], therefore, despite its observational nature, the real-world findings of the study complement the results obtained from previous randomized controlled trials.

## Conclusions

This study describes the real-world practicalities of converting liver transplant recipients from immediate- to prolonged-release tacrolimus within 3–12 months of transplantation in France. Favourable clinical outcomes and safety profiles were observed, suggesting that medium-term conversion to once-daily tacrolimus is an appropriate option for liver transplant recipients in preventing transplant rejection. Conversion from immediate-release to prolonged-release tacrolimus was performed with a dose ratio of 1. In most cases, the initial decision to convert was taken by the physician or according to the local clinical practice of the transplant center. Most importantly, tacrolimus conversion was associated with a very low number of additional clinical visits and a low rate of graft rejection. No new safety signals were detected with the switch to prolonged-release tacrolimus.

## Acknowledgments

Jenny Smith, PhD, and Julia Donnelly, PhD, from Cello Health MedErgy assisted in drafting the manuscript under the direction of the authors. Editorial support was provided by Cello Health MedErgy throughout the development process. The authors would like to acknowledge the 18 liver transplant centers, 30 doctors and 400 patients who participated in this study.

## Participating centers

Hôpital Paul Brousse, Villejuif; Hôpital Trousseau, Tours; Hôpital Beaujon, Clichy; Hôpital Saint-Eloi, Montpellier; Hôpital de la Croix Rousse, Lyon; Hôpital Henri Mondor, Créteil; Hôpital Haut-Lévêque, Bordeaux; Hôpital Claude Huriez, Lille; Hôpital de la

Pitié-Salpêtrière, Paris 13; Hôpital de la Conception, Marseille; Hôpital Jean Minjoz, Besançon; Hôpital Pontchaillou, Rennes; Hôpital Côte de Nacre, Caen; Hôpital de Grenoble; Hôpital Edouard Herriot, Lyon; Hôpital de Rangueil, Toulouse; Hôpital Dupuytren, Limoges; Hôpital L'archet II, Nice.

## Disclosures

Jérôme Dumortier, Christophe Duvoux, and Pauline Houssel-Debry received fees from Astellas Pharma as members of the scientific committee for this COBALT study and have no other conflicts of interest. Laurence Dubel is an employee within the Medical Department of Astellas Pharma, France. Fabienne Bazin is an employee at ITEC Services SAS, CRO provider involved in the study.

## References:

- Kim WR, Lake JR, Smith JM et al: OPTN/SRTR 2016 annual data report: Liver. *Am J Transplant*, 2018; 18: 172–253
- Moini M, Schilsky ML, Tichy EM: Review on immunosuppression in liver transplantation. *World J Hepatol*, 2015; 7: 1355–68
- Laederach-Hofmann K, Bunzel B: Noncompliance in organ transplant recipients: A literature review. *Gen Hosp Psychiatry*, 2000; 22: 412–24
- 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
- Prendergast MB, Gaston RS: Optimizing medication adherence: An ongoing opportunity to improve outcomes after kidney transplantation. *Clin J Am Soc Nephrol*, 2010; 5: 1305–11
- Srivastava K, Arora A, Kataria A et al: Impact of reducing dosing frequency on adherence to oral therapies: A literature review and meta-analysis. *Patient Prefer Adherence*, 2013; 7: 419–34
- Guirado L, Cantarell C, Franco A et al: Efficacy and safety of conversion from twice-daily to once-daily tacrolimus in a large cohort of stable kidney transplant recipients. *Am J Transplant*, 2011; 11: 1965–71
- Muduma G, Odeyemi I, Smith-Palmer J, Pollock RF: Budget impact of switching from an immediate-release to a prolonged-release formulation of tacrolimus in renal transplant recipients in the UK based on differences in adherence. *Patient Prefer Adherence*, 2014; 8: 391–99
- Coilly A, Calmus Y, Chermak F et al: Once-daily prolonged release tacrolimus in liver transplantation: Experts' literature review and recommendations. *Liver Transpl*, 2015; 21: 1312–21
- Beckebaum S, Iacob S, Sweid D et al: Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. *Transpl Int*, 2011; 24: 666–75
- Eberlin M, Otto G, Krämer I: Increased medication compliance of liver transplant patients switched from a twice-daily to a once-daily tacrolimus-based immunosuppressive regimen. *Transplant Proc*, 2013; 45: 2314–20
- Cassuto E, Pageaux GP, Cantarovich D et al: Adherence to and acceptance of once-daily tacrolimus after kidney and liver transplant. *Transplantation*, 2016; 100: 2099–106
- Salas MAP, Srinivas TR: Update on the clinical utility of once-daily tacrolimus in the management of transplantation. *Drug Des Devel Ther*, 2014; 8: 1183–94
- Florman S, Alloway R, Kalayoglu M et al: Once-daily tacrolimus extended release formulation: experience at 2 years postconversion from a Prograf-based regimen in stable liver transplant recipients. *Transplantation*, 2007; 83: 1639–42
- Scalone L, Ciampichini R, Fagioli S et al: Comparing the performance of the standard EQ-5D 3L with the new version EQ-5D 5L in patients with chronic hepatic diseases. *Qual Life Res*, 2013; 22: 1707–16
- Albekairy A, Alkatheri A, Jarab A et al: Adherence and treatment satisfaction in liver transplant recipients. *Saudi J Gastroenterol*, 2015; 22: 127–32
- Agence de la biomédecine. Le rapport médical et scientifique du prélèvement et de la greffe en France. 2013. Available at: [URL]: <https://www.agence-biomedecine.fr/annexes/bilan2013/donnees/sommaire-organes.html> [in French]
- Lieber SR, Volk ML: Non-adherence and graft failure in adult liver transplant recipients. *Dig Dis Sci*, 2013; 58: 824–34
- Burra P, Germani G, Gnoato F et al: Adherence in liver transplant recipients. *Liver Transplant*, 2011; 17: 760–70
- Berlakovich GA, Langer F, Freundorfer E et al: General compliance after liver transplantation for alcoholic cirrhosis. *Transpl Int*, 2000; 13: 129–35
- Adam R, Karam V, Delvar V et al: Improved survival in liver transplant recipients receiving prolonged-release tacrolimus in the European Liver Transplant Registry. *Am J Transplant*, 2015; 15: 1267–82
- Considine A, Tredger JM, Heneghan M et al: Performance of modified-release tacrolimus after conversion in liver transplant patients indicates potentially favorable outcomes in selected cohorts. *Liver Transplant*, 2015; 21: 29–37
- Dumortier J, Guillaud O, Boillot O: Conversion from twice daily tacrolimus to once daily tacrolimus in long-term stable liver transplant recipients: A single-center experience with 394 patients. *Liver Transplant*, 2013; 19: 529–33
- Astellas Pharma Europe Ltd. Advagraf 0.5 mg, 1 mg, 3 mg, and 5 mg prolonged-release hard capsules. Summary of product characteristics. 2019. Available at: [URL]: <https://www.medicines.org.uk/emc/product/345/smpc>
- Fischer L, Trunečka P, Gridelli B et al: Pharmacokinetics for once-daily versus twice-daily tacrolimus formulations in *de novo* liver transplantation: A randomized, open-label trial. *Liver Transplant*, 2011; 17: 167–77
- Fine RN, Becker Y, De Geest S et al: Nonadherence consensus conference summary report. *Am J Transplant*, 2009; 9: 35–41
- Coleman CI, Limone B, Sobieraj DM et al: Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm*, 2012; 18: 527–39
- Guirado L, Cantarell C, Franco A et al: Efficacy and safety of conversion from twice-daily to once-daily tacrolimus in a large cohort of stable kidney transplant recipients. *Am J Transplant*, 2011; 11: 1965–71