ORIGINAL ARTICLE

Conversion from twice-daily to once-daily tacrolimus formulation in pediatric liver transplant recipients – a long-term prospective study

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SUMMARY

To assess the safety and efficacy of conversion from twice-daily tacrolimus to once-daily tacrolimus in pediatric liver transplant recipients. Conversion from twice-daily to once-daily tacrolimus was made in stable pediatric liver transplant recipients. Doses and serum levels of tacrolimus, liver, and renal function were recorded on the day before the conversion and at days 5, 30, 90, and 180 postconversion. Patients were controlled every 2–3 months thereafter. Fifty-five patients were enrolled in the study. The mean age at conversion was 10.2 ± 3.6 years. The mean tacrolimus trough level was 4.7 ± 1.9 ng/dl preconversion, followed by a significant decline to 4.2 ± 1.7 30 days after the switch ($P < 0.004$). Mean daily tacrolimus dose was 0.09 ± 0.046 mg/Kg preconversion with a significant increase to 0.11 ± 0.060 3 months postconversion ($P < 0.001$). Fifteen patients with calculated glomerular filtration rate between 60 to 80 ml/min/m^2 preconversion showed a significant improvement one and 3 years after the switch (73 ± 4.1, 83 ± 4.3 and 90.3 ± 7.3 ml/min/m^2, respectively ($P < 0.001$). The mean follow-up was 5.2 ± 2.4 years. Conversion to once-daily tacrolimus is safe and effective in a cohort of stable pediatric liver transplant patients.

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Introduction

A significant factor that contributes to the incidence of transplant rejection is patient nonadherence with immunosuppressive therapies.[1,2] Drug adherence declines over time in patients after organ transplantation and depends on the type of medication, the number of drugs to be taken and the number of daily

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doses.[3,4] Moreover, compliance issues are particularly concerning in children and adolescents.[5,6]

Tacrolimus (TAC) is one of the most commonly used immunosuppressive therapies in pediatric liver transplantation (LT). A prolonged-release once-daily tacrolimus (TAC-OD) formulation (Advagraf®, Astellas Pharma, Tokyo, Japan) has been developed to improve adherence to immunosuppressive treatment and thereby may result in a better long-term allograft survival.[7] Big data have been obtained on pharmacokinetics, safety, and efficacy of TAC-OD in adult population, and nowadays, it is regularly used by adult liver transplant teams.[8]

Unfortunately, in pediatric patients, scarce data are available. Preliminary studies have shown equivalence in pharmacokinetic parameters from twice-daily tacrolimus (TAC-BD) to TAC-OD both in pediatric kidney and liver transplantations.[6–9] Accordingly, a 1:1 mg conversion from TAC-BD to TAC-OD was recommended by the European Medicine Agency. Nevertheless, results from recent clinical studies performed in pediatric kidney transplant patients showed high variable changes in pharmacokinetics parameters,[10] contradicting the impression that the switch from TAC-BD to TAC-OD could be done without any concerns neither in efficacy nor in safety.[11]

The aim of this study was to determine the efficacy, safety, and immunosuppressant adherence of TAC-BD to TAC-OD conversion in stable pediatric LT recipients.

Materials and methods

Study design

This is a prospective observational unicentric study of conversion from TAC-BD to TAC-OD conducted in pediatric LT patients. Informed consent was obtained from each patient included in the study. The study was reviewed and approved by the ethics committee of our center.

Inclusion criteria

Pediatric LT recipients were eligible for the switch from TAC-BD to TAC-OD when they fulfilled the following criteria: (i) Patients were younger than 18 years of age and able to swallow intact capsules with a previous TAC-BD based immunosuppressive treatment; (ii) they had received the liver graft at least 1 year prior to the switch; (iii) TAC whole blood trough concentrations was stable (variation <20%) measured at least three times during the last 12 months before the conversion; (iv) they did not present any episode of biopsy-proven acute cellular rejection at least 1 year before the recruitment; (v) they presented a calculated glomerular filtration rate (cGFR) >60 ml/min/m^2 using the Schwartz modified formula at least 6 months before the conversion; and (vi) their hepatic function, defined as liver enzymes (alanine aminotransferase, aspartate transaminase and gamma-glutamyl transpeptidase), was normal, bilirubin plasma levels were lower than two times the upper limit of normal rage, and synthetic function (INR and albumin serum levels) was normal.

Exclusion criteria

Patients were excluded from the study when they used sirolimus or other drugs that can interfere with the whole blood levels of TAC or if they had presented more than two rejections throughout their evolution after LT.

Sample size

In our population, up to 30% of patients can present a biopsy-proven acute cellular rejection during the first 5 years after the LT. For a noninferiority one-sided analysis using a difference in the rate of rejections between formulations of 10%, a power of 80%, and a 95% confidence interval, the number of patients required was determined to be 46. Considering the possible withdrawals, the study size was set to 50 patients.

Conversion from TAC-BD to TAC-OD

The switch from TAC-BD (Prograf®, Astellas Pharma, Tokyo, Japan) to TAC-OD (Advagraf®, Astellas Pharma, Tokyo, Japan) was made on a 1:1 mg proportion basis for their total daily dose. We instructed our patients to use the TAC-OD following the product information provided by the company. After the conversion, TAC doses were adjusted to maintain target trough levels with a variation lower than 20% of the baseline TAC concentrations.

No diagnostic or monitoring procedures other than those required in the course of current clinical practice were applied to the patients before the switch to TAC-OD. Doses and serum levels of TAC and liver and renal function were recorded on the day before the conversion (day 0) and at days 5, 30, 90, and 180 postconversion. Patients were controlled every 2–3 months thereafter. Additionally, rejection episodes,

adherence, and adverse events were assessed during the follow-up.

Adjustment of doses of other immunosuppressive medications (corticosteroids or mycophenolic acid), used in combination with TAC, was performed following clinical practice.

Liver rejection

Patient and graft survival and biopsy-proven acute rejection episodes were assessed throughout the study. A liver biopsy was carried out if clinical signs or laboratory parameters were suspicious of the occurrence of an episode of rejection. Histological evaluation was performed according the Banff criteria.[12] Graft loss was defined as retransplantation or death.

Renal function

Renal function was evaluated by serum creatinine and calculated GFR using the Schwartz modified formula. Suboptimal renal function was defined as cGFR between 60 and 80 ml/min/m^2.

Safety and side effects

Safety was determined at each visit based on physical examination, vital signs measurements, occurrence of adverse events and results of laboratory tests.

Adherence

Self-reported adherence with immunosuppressive treatment was assessed using the Visual Analogue Scale at baseline and 1 year after the conversion.[13] The person responsible for the administration of medication (always the same person in all visits) scored the medication adherence during the last 4 weeks from 0 (immunosuppression medication never taken as prescribed) to 100 (immunosuppressive medication always taken as prescribed).[13] Causes of nonadherence were collected every visit by asking the responsible of the medication administration.

Patients' preference for the treatment regimen was also assessed by a self-report at the end of the first year after the switch.

Statistic analysis

Continuous variables are presented as mean and SD (unless indicated) and categorical variables as number with percentage. The mean comparisons were performed using the Student's *t*-test. The median comparison for paired data was performed using the Wilcoxon test. In order to calculate the intra-individual variability of TAC trough levels, the last three levels before the switch were used to calculate the preswitch individual coefficient of variation (CV = standard deviation/mean). The last three TAC trough levels before the end of the first year after conversion were used to calculate the postswitch individual CV. Values between different assessments of the same patient were calculated using paired t-test and those between patients with unpaired *t*-test. The statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 18.0 was used for the analysis. The significance level was set at 0.05.

Results

A total of 55 patients were enrolled in the study between August 2008 and September 2015. No patients were lost during the follow-up; therefore, all of them were included in the final analysis. Fifty-six per cent of the patients were male with a mean age at switch of 10.2 $\pm$ 3.6 years. The conversion was made at a mean of 6.4 $\pm$ 2.5 years after the LT. The most usual indication for LT was biliary atresia (56.4%), as usual in pediatrics. The mean follow-up was 5.2 $\pm$ 2.4 years with a minimum follow-up of 13 months. Data regarding patient characteristics are summarized in Table 1.

Tacrolimus levels

At the study entry, the mean TAC trough level was 4.7 $\pm$ 1.9 ng/dl, followed by a significant decline to 4.2 $\pm$ 1.6 and 4.2 $\pm$ 1.7 at 5 and 30 days after the switch ($P < 0.001$ and $P < 0.004$, respectively). The TAC levels remained stable afterward. No statistical significance was observed between the TAC levels at the different time-points of the follow-up after the conversion (Fig. 1). At day 5, TAC concentrations were lower in 56% and higher in 42% of patients compared to baseline. In 29.0% (16/55) and 12.7 (7/55) of patients, TAC concentrations were >25% lower and >25% higher than preswitch, respectively.

The mean coefficient of variation of TAC trough levels was 0.42 $\pm$ 0.1 before the switch and 0.42 $\pm$ 0.04 1 year after the switch, without any statistical significance.

Tacrolimus doses

Mean daily TAC dose was 0.09 $\pm$ 0.046 mg/Kg preconversion with a significant increase to 0.11 $\pm$ 0.060 at 3 months after conversion ($P < 0.001$).

Transplant International 2018; 31: 38–44

Table 1. Summary of patient's baseline characteristics.

Gender (Male/Female)	31 (56.4%)/24 (43.6%)
Weight (Kg)	32.3 ± 10.6
Age at transplantation (months)	45.6 (2.1-158.0)
Age at conversion (years)	10.2 ± 3.6
Time from transplantation to conversion (years)	6.4 ± 2.5
Underlying liver disease	
Biliary Atresia	31 (56.4%)
Acute Liver Failure	8 (14.6%)
Alagille Syndrome	4 (7.3%)
Progressive Familial Cholestasis Type 1	2 (3.6%)
Polycystic Hepatic-Kidney Disease type 1	2 (3.6%)
Retransplantation	2 (3.6%)
Cryptogenic cirrhosis	2 (3.6%)
Crigler Najjar	1 (1.8%)
Cystic Fibrosis	1 (1.8%)
Hepatoblastoma	1 (1.8%)
Alfa-1 Deficiency	1 (1.8%)
Immunosuppressive therapy	
Tacrolimus	32 (57.7%)
Tacrolimus + Methylprednisolone	16 (29.8%)
Tacrolimus + Mycophenolic Acid	7 (12.7%)
Type of graft	
Whole graft	43 (78.2%)
Partial graft	12
Split	7 (12.7%)
Reduced	2 (3.6%)
Living donor	3 (5.5%)

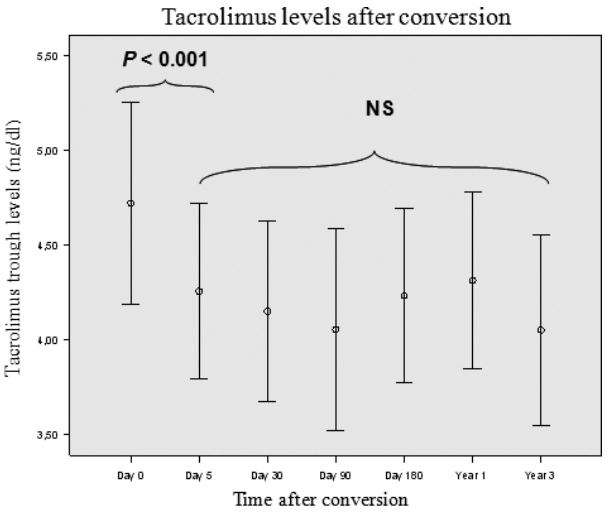

Figure 1 During the first month after the conversion, a significant decrease in tacrolimus trough levels was observed. After the first month, there is a stability of the tacrolimus concentration in the other time-points of the follow-up.

Subsequently, patients presented progressive decline in TAC dose to 0.10 ± 0.046 mg/Kg at 1 year and 0.07 ± 0.02 mg/Kg 3 years after the switch ($P = 0.42$). Thirty-five of 55 patients (63.6%) needed modification of their original TAC dose to maintain their plasma trough levels during the first year after the switch. Thirty-two of them (58.2%) increased their TAC total daily dose. The mean increase in the TAC dose was 0.013 mg/Kg, which represents an increase of 14.8% of their preconversion dose. All but one patient required a maximum of two dose changes during the first year of follow-up. All dose changes were performed during the first 6 months after the switch. All patients presented a stable dose of TAC 1 year after the conversion. Twenty patients (36.4%) did not need any dose adjustment.

Liver function and graft rejection

Liver function remained stable in all but one patient after the conversion. A 17-year-old patient presented raised liver enzymes 3 years after the switch. The patient presented a suboptimal TAC trough level of 1.2 mg/dl and reported not having taken properly the TAC-OD. A biopsy was performed observing a moderate acute cellular graft rejection (Banff scale 1-2-2), which was solved with methylprednisolone pulses. No other episodes of graft rejection were documented.

Renal function

The overall group of patients (55) presented a non-significant improvement of the kidney function as compared to baseline at one and 3 year (108.0 ± 30.7, 111.0 ± 25.1, 111.43 ± 26.3 ml/min/m^2). In contrast, the 15 patients with suboptimal glomerular filtration rate prior the conversion (cGFR between 60 to 80 ml/min/m^2) showed a statistically significant improvement in cGFR at one and 3 years after the switch (73 ± 4.1, 83 ± 4.3 and 90.3 ± 7.3 ml/min/m^2, $P < 0.001$ in both cases) (Fig. 2).

Patients with a suboptimal cGFR did not present statistically significant differences in TAC trough levels compared to patients with normal GFR preconversion, and at 1 and 3 years after the switch. However, in patients with suboptimal cGFR, the TAC levels presented a significant decline from preconversion to 1 and 3 years postconversion (5.2 ± 2.0, 3.8 ± 1.7 and 4.3 ± 0.59 ng/dl. $P < 0.06$ and $P < 0.08$, respectively).

Seven of 15 patients with suboptimal cGFR were using concomitant immunosuppression at conversion (3 TAC+ methylprednisolone and 4 TAC+ mycophenolic

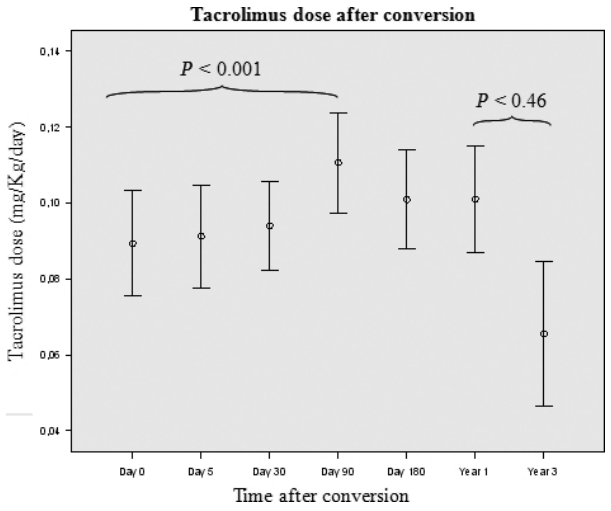

Figure 2 Patients with a glomerular filtration rate between 60 and 80 ml/min/m^2 present a significant improvement of the renal function at one and 3 years after the conversion.

acid). These concomitant medications were not increased after the switch in any of the patients.

Adherence

Up to 58.2% (32/55) of patients reported changes in drug administration before the conversion to TAC-OD. The most common alterations were changes in the time of administration (patients taking their dose with a delay of >2 h; 36.4%) and omission of the administration of one dose (18.2%). The percentage of drug administration changes decreased up to 38.2% (21/55) after the switch to TAC-OD ($P < 0.001$) (Table 2).

The visual analogue scale punctuation presents a significant improvement between preswitch and 1 year postconversion assessments (82.9 ± 11.3 vs. 91.8 ± 6,9; $P < 0.01$).

Adverse events

There were no cases of graft loss or death during the follow-up. No new cases of diabetes mellitus or glucose metabolism disorders were observed. The fasting glucose level was slightly lower from 92 ± 6.5 mg/dl preconversion to 90.7 ± 7.5 mg/dl 1 year after the switch ($P < 0.41$). There were no malignancies reported postconversion. No other adverse events were reported, and no patients needed to discontinue TAC-OD during the follow-up.

Discussion

This is the biggest cohort of pediatric liver transplant recipients converted from TAC-BD to TAC-OD in our knowledge. Taking into account the limitations of this unicenter study, following our results, the conversion from TAC-BD to TAC-OD could be safe and effective in a selected cohort of stable pediatric LT patients. Nonetheless, nearly a 64% of the patients needed a dose change during the first year after the switch. Most of them required a 15% increase in the dose compared to the preswitch dose, as it has also been described in adult population.[7] All these facts highlight the fact that the 1:1 conversion proposed is possibly insufficient to maintain the TAC trough levels stable after the conversion in a non-negligible proportion of patients. A close monitoring should be carried out after the conversion to TAC-OD in all patients to ensure its effectiveness. Nevertheless, the dose adjustments were performed during the first 6 months after the conversion showing that, after an initial relative instability in the drug plasma concentration, patients reached stable levels of TAC. In our study, all patients were taking a stable dose of TAC 1 year after the conversion. The preconversion CV was compared with the 1 year postswitch CV to assess the intra-individual variability of the two different formulations of TAC. High intrapatient TAC variability has been associated with worse clinical outcomes post-transplantation. Theoretically, TAC levels consistently outside the target therapeutic window may result in allograft dysfunction as subtherapeutic tacrolimus levels predispose to episodes of

Table 2. Adherence and adverse events.

	TAC-BD	TAC-OD	Significance
Modifications in tacrolimus administration			
Nonadherence	58.2% (32/55)	38.2% (21/55)	<0.001
Changes in the time	36.4% (20/55)	32.7% (18/55)	
Omission	18.2% (10/55)	5.5% (3/55)	
Both of them	3.6% (2/55)	0% (0/55)	
Visual analogue scale (mean)	82.9 ± 11.3	91.8 ± 6,9	<0.01

TAC-BD, Twice-daily tacrolimus. TAC-OD, Once-daily tacrolimus.

acute rejection, whereas supratherapeutic levels may cause nephrotoxicity.[14] The CV with TAC-OD was calculated 1 year after the conversion to avoid the initial instability of doses and plasma trough levels. There are not statistical significant differences between the intra-individual variability of TAC levels preswitch and 1 year after conversion. This could be interpreted as meaning that once the TAC-OD dose to maintain the plasma trough levels was reached, the intra-individual TAC levels were as stable as TAC-BD.

The only case of acute graft rejection in our study was observed 3 years after the conversion in a nonadherent diabetic adolescent patient with cystic fibrosis who was taking 34 pills per day. He reported not to have taken the TAC-OD prescribed because of psychosocial problems, and the TAC trough levels were of 1.2 ng/ml. After three pulses of 10 mg/Kg/day of corticoids and optimization of the TAC doses, the patient presented a good evolution. However, he was encouraged to be included in a program of psychological support, and at the end of the follow-up, he was in a very good condition and taking all his medication properly.

One of the most common side effects related to TAC administration in LT is renal dysfunction.[15] In our series, the overall population presented a stable renal function one and 3 years after the TAC-OD introduction. Moreover, a statistical significant improvement at 1 and 3 years postconversion has been observed in patients with suboptimal cGFR preswitch (73 ± 4.1, 83 ± 4.3 and 90.3 ± 7.3 ml/min/m^2, $P < 0.01$, respectively). This can be explained considering that these patients have significant lower concentrations of TAC 1 year after the switch compared to baseline (3.8 ± 1.7 ng/dl and 5.2 ± 2.0 and, respectively). If we take into account that these results were obtained in clinical practice, it is natural to consider that physicians try to preserve renal function in these patients by decreasing the levels of tacrolimus regardless of the formulation administered. Moreover, seven of 15 patients with suboptimal cGFR at conversion were treated with methylprednisolone or mycophenolic acid. Although doses of concomitant immunosuppressive treatment were not increased during the follow-up, it is reasonable to think that these medications allowed the physicians to keep TAC levels at lower ranges.

Although renal dysfunction associated with TAC is probably related to the peak TAC concentration,[16] and TAC-OD is reported to present a lower peak level than TAC-BD,[10] in our study, kidney function upturn should not be considered to be caused by a better tacrolimus once a day formulation pharmacokinetics but related to tacrolimus lower levels during the follow-up.

Nonadherence to prescribed immunosuppressive treatment is the leading cause of preventable graft loss in pediatric solid organ transplantation.[10] Up to 55% of renal transplant recipients have been reported to be nonadherent to immunosuppressive regimes, and pediatric patients are those with higher risk.[5] As a significant relationship between higher doses frequencies and decreased adherence has been described,[4] once-daily administration of TAC should improve the adherence and thereby might improve the graft outcome after LT.[7–17] Taking in care that the person responsible of the drug administration in our population is heterogeneous, we asked the families to choose one person who would administer the TAC during the study (parents, siblings, or the patient himself or herself). In our study, a significant improvement in adherence was reported by the person responsible of drug administration. This improvement could not only be explained by the easier administration of the TAC-OD, but also by the fact that patients may feel more inclined to take the medication while being observed in a study. Obviously, there was a selection bias of adherent patients in the study, because only patients without acute rejection during the year prior were able to be converted. This preconversion "good adherence" may influence achieving statistically significant improvement in adherence after the switch. Nevertheless, this improvement did not change the graft function in our patients.

Finally, it has been reported in adult populations that TAC-OD may be related to an increase of glucose metabolism alteration or new onset diabetes.[18,19] In our study, no cases of glucose metabolism disturbance have been observed. In fact, the fasting glucose levels decreased in a nonsignificant manner 1 year after the conversion. No malignancies or other adverse events were observed during the follow-up.

As a conclusion, conversion from TAC-BD to TAC-OD is safe and effective in a cohort of stable pediatric LT patients. During the first months after the switch, a non-negligible proportion of patients needs dose modifications to maintain the TAC trough levels so a close monitoring should be performed after the conversion.

Authorship

JQ: conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. JJ and JO: carried out the initial analyses, critically reviewed the manuscript, and approved the final manuscript as submitted. JAM, LC, IB, CR, and RC critically reviewed the manuscript and approved the final manuscript as submitted.

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Conflicts of interest

The authors have declared no conflict of interest.

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