ORIGINAL ARTICLE

Conversion From Prograf to Advagraf in Adolescents With Stable Liver Transplants: Comparative Pharmacokinetics and 1-Year Follow-Up

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The recommended dose of Advagraf for conversion from Prograf is considered to be 1:1 on a milligram basis. However, the long-term equivalence of Prograf and Advagraf has been questioned. The relative bioavailability of Advagraf and Prograf was evaluated in a single-center, open-label study of Prograf-to-Advagraf conversion in 20 patients, ranging in age from 12 to 18 years, who had a stable liver transplant and were receiving Prograf. After the supervised administration of Prograf for 7 days, the patients were converted to Advagraf. On days 7 and 14, serial blood samples were obtained for tacrolimus determinations. The pharmacokinetic parameters were calculated with a noncompartmental approach, and the relative bioavailability of both formulations was calculated according to standard statistical methods. Polymorphisms in cytochrome P450 3A5 (rs776746), adenosine triphosphate–binding cassette B1 (rs1045642), POR*28 (rs1057868), and POR (rs2868177) were determined with standard methods. The clinical and analytical data from a 1-year follow-up period were collected for all patients 30, 90, 180, and 360 days after conversion. The mean ratios for C_{max} and $AUC_{0\text{-}24}$ were 96.9 (90% confidence interval = 85.37-110.19) and 100.1 (90% confidence interval = 90.8-112.1), respectively. No relationship was found between the patients' genotypes and the pharmacokinetic tacrolimus values. During the follow-up, biochemical parameters (aspartate aminotransferase, alanine aminotransferase, bilirubin, cystatin C, and creatinine) did not change significantly; 3 patients presented with relevant clinical events, but no event was considered to be related to tacrolimus. A decrease in tacrolimus blood levels and an increase in dose/level ratios were observed 3 and 6 months after conversion, but they returned to basal levels by month 12. In conclusion, conversion from Prograf to Advagraf with a 1:1 dose equivalence is appropriate as an initial guideline. Our 1-year follow-up showed a transient decrease in tacrolimus levels, so closer monitoring of tacrolimus levels may be required after conversion. ***Liver Transpl 19:1151–1158, 2013***. © **2013 AASLD.**

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Nonadherence to treatment has been determined to be a significant factor that may contribute to adverse outcomes for various transplants.[1] In our experience, this nonadherence particularly affects afternoon and night doses, and it is most evident in the pediatric population: 50% of children receiving a solid organ

Abbreviations: ABCB1, adenosine triphosphate–binding cassette B1; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C_{max}, maximun concentration; C_{min}, minimun concentration; C_0, concentration at zero time; C_{12}, concentration at 12 hours; C_{24}, concentration at 24 hours; AUC, area under the curve; $AUC_{0\text{-}24}$, area under the curve from 0 to 24 hours.; Cl_{oral}, apparent oral clearance; $t_{1/2}$, half-life; CYP, cytochrome P450; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

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transplant consider a regimen of 2 daily doses inconvenient.[2] Sudan et al.[3] found that nonadherence to treatment may be the third most common cause of late mortality in pediatric liver transplant patients. In addition, Weng et al.[4] suggested that a single daily dose would improve treatment adherence and, consequently, graft persistence in all patients and particularly in the pediatric population.[4]

Advagraf is a once daily tacrolimus formulation, and the conversion from Prograf to Advagraf has been implemented widely in the clinical setting over the past few years with the objective of improving adherence. De novo treatment with Advagraf has been found to have efficacy similar to that of the twice daily formulation. According to the recommendations of the manufacturer and the information sheets from the Food and Drug Administration and the European Medicines Agency, the equivalent dosage for Prograf and Advagraf should be 1:1 on a milligram basis. However, recent conversion and de novo studies have found that the disposition of tacrolimus may be lower after the use of Advagraf than after Prograf,[5-7] and this puts the long-term bioequivalence of Prograf and Advagraf into question.[8]

The present study evaluated the relative bioavailability of Advagraf and Prograf formulations in liver transplant patients between 12 and 18 years of age, compared patients' genotypes with tacrolimus pharmacokinetics, and analyzed 1 year of follow-up after conversion.

PATIENTS AND METHODS

Study Design

This was a single-center, open-label study of the conversion of tacrolimus treatment from Prograf to Advagraf in patients who were 12 to 18 years old with a stable liver transplant. The main objective was to evaluate the relative bioavailability of the 2 formulations. After the completion of the study, data from a 1-year follow-up period were collected to evaluate the kinetic and clinical changes that occurred during this period.

The study was performed at La Paz University Hospital, a tertiary hospital of reference for pediatric liver transplantation. The study protocol was approved by the ethics committee of La Paz University Hospital and by the Spanish Drug Regulatory Agency, and the study was registered at European Union Drug Regulating Authorities Clinical Trials (2008-001440-39).

Patients

Liver transplant patients between 12 and 18 years of age who had normal graft function [aspartate aminotransferase (AST) level = 29 ± 7 U/L, alanine aminotransferase (ALT) level = 25 ± 10 U/L, total bilirubin level = 0.5 ± 0.2 mg/dL] and were on a stable treatment with tacrolimus were selected for this trial. The tacrolimus treatment was considered stable if the patient had received a stable dose of tacrolimus for the last 2 controls (<20% variation) and there had been no changes in concomitant drugs that could modify the tacrolimus kinetics for the last 15 days. Patients were required to be able to understand the study's objectives, procedures, and treatment indications. Parents and caretakers were required to have the ability to adequately control the administration of Prograf and Advagraf as established in the protocol. Patients who had experienced a rejection episode in the previous 90 days were excluded from the study.

Sample Size

The number of required subjects was calculated from a similar conversion study, the European public assessment report for Advagraf (code 02-0-131), which was performed with adults with heart and kidney transplantation.[9] The mean $AUC_{0\text{-}24}$ (Area under the curve of tacrolimus concentrations from 0 to 24 hours) values in the steady state for Advagraf and Prograf were 200.7 ± 57.5 and 206.6 ± 58.4 ng/mL·h, respectively. For a difference between formulations of 5%, a power of 80%, and a 90% confidence interval, the number of patients required was determined to be 18. According to data from Heffron et al.,[10] the number of patients needed was 15. Considering these 2 references and taking into account possible withdrawals, we established the study size at 20 patients.

Study Development

The patients were included after they met the selection criteria, were informed about the study design and procedures, and gave written informed consent. They were administered Prograf with monitoring for 1 week in accordance with the manufacturer's recommendations and under parental supervision; a treatment card was used on which the drug dose and the timing of its administration were noted during these 7 days. The total daily dose of Prograf was administered in 2 equal doses. After this week of treatment, each patient was admitted to the hospital to begin the kinetic study. On the first day, venous access was canalized for blood extractions, and a blood sample was obtained for the basal measurement of tacrolimus. Subsequently, the patients received a Prograf dose between 8:00 and 9:00 AM with 200 mL of water. The blood sampling then followed a scheduled timetable (see the following section). Breakfast was scheduled at 10:00 AM, a standard lunch was served at 1:00 PM, and dinner was served at 7:00 PM. Twelve hours after the morning administration, the second dose of Prograf was administered, and blood extractions continued until the next morning. On the second morning, the patients received a new administration control card and a new treatment protocol, and they started Advagraf once a day at the same dose (a 1:1 conversion ratio). After 7 days of the supervised

TABLE 1. Demographic and Clinical Characteristics of the Patients (n = 20)

Sex: male/female (n/n)	9/11
Race (n)	
White	17
Black	1
Hispanic	2
Age (years)*	13.9 ± 1.66 (12-17)
Weight (Kg)*	47.9 ± 8.8 (29.4–67.5)
Height (cm)*	155.1 ± 8.28 (139–169)
Pretransplant liver disease (n)	
Biliary atresia	9
Alpha-1-antitrypsin deficiency	3
Budd-Chiari syndrome	1
Acute liver failure	3
Cystic fibrosis	1
Alagille syndrome	1
Bile salt export pump deficiency	1
Maple syrup urine disease	1
Graft type (n)	
Whole liver	10
Split liver	1
Reduced size	8
Living donor	1
Biliary reconstruction (n)	
Roux-en-Y loop	17
End to end	3
Total daily dose of Prograf at baseline (mg)	
Mean ± standard deviation	4.8 ± 1.70
Median (range)	4.50 (3–10)
Time from transplantation (years)	
Median	11.70
Range	1.4–15.5

NOTE: The main diagnoses that motivated liver transplantation were biliary atresia, alpha-1-antitrypsin deficiency, Budd-Chiari syndrome, acute liver failure, cystic fibrosis, Alagille syndrome, bile salt export pump deficiency, and maple syrup urine disease.
*The data are presented as means and standard deviations (with ranges in parentheses).

administration of Advagraf, patients were again admitted to the hospital, and the procedure that had been followed on the first day after the week of Prograf treatment was repeated. Patients were discharged with a prescription for Advagraf, and regular follow-up visits were scheduled.

Concomitant drugs that patients were taking were not modified during the pharmacokinetic study.

Timing of Blood Extractions for Pharmacokinetic Analysis

Blood samples were extracted for pharmacokinetic analysis just before the administration of the morning dose and at the following times: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20, and 24 hours after the administration of Prograf (at 0 and 12 hours) and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, and 24 hours after the administration of Advagraf.

Tacrolimus Blood Measurements

Samples were collected in duplicate tubes with ethylene diamine tetraacetic acid and were frozen at −20°C until the analysis. A homogeneous enzyme immunoassay (an antibody-conjugated magnetic immunoassay) on a Dimension platform (Siemens Health Care Diagnostic, Ltd., Frimley, United Kingdom) was used. The lower limit of quantification was 2 ng/mL, and the upper limit of quantification was 30 ng/mL. Results greater than 30 ng/mL were diluted to obtain concentrations between 2 and 30 ng/mL.

Pharmacokinetic and Statistical Analysis

The kinetic data analysis was performed according to a noncompartmental model. $AUC_{0\text{-}24}$ was calculated with the trapezoidal rule, and the apparent oral clearance (Cl_{oral}) was calculated as the dose divided by $AUC_{0\text{-}24}$. C_{max} (maximun concentration), C_0 (concentration at zero time), C_{12} (concentration at 12 hours), and T_{max} (time to maximun concentration) were obtained directly from raw data. The fluctuation was calculated as follows: $(C_{max} - C_{24})/C_{24} \times 100$, being C_{24} the concentration at 24 hours after dosing.

To compare kinetic parameters [the area under the curve (AUC) and C_{max}] and to evaluate the relative bioavailability of the 2 formulations over a 24-hour period, we used an analysis of variance and calculated the standard 90% confidence interval. Calculations were made after logarithmic transformation. The pharmacokinetic and bioequivalence statistical analysis was performed with WinNonlin 2.0 (Pharsight Corp., Cary, NC). Differences in the tacrolimus concentrations at various time points and during fluctuations were determined with a t test. To calculate the fluctuation in Prograf, the 24-hour period was divided into 2 parts (with 12 hours between each dose), and it was calculated between C_{max} of each period and the tacrolimus concentrations at 12 or 24 hours as appropriate. The Advagraf fluctuation was calculated between C_{max} and the tacrolimus concentration at 24 hours.

Genotyping Assays

Genomic DNA was isolated from peripheral blood with a commercial extraction kit (QuickGene DNA Whole Blood Kit S, Fujifilm Life Science, Singapore), and it was amplified by polymerase chain reaction with the Applied Biosystems 7900HT fast real-time polymerase chain reaction system (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. The assay numbers for the genotyping assays from Applied Biosystems were as follows: C__26201809_30 for rs776746, C___7586657_20 for

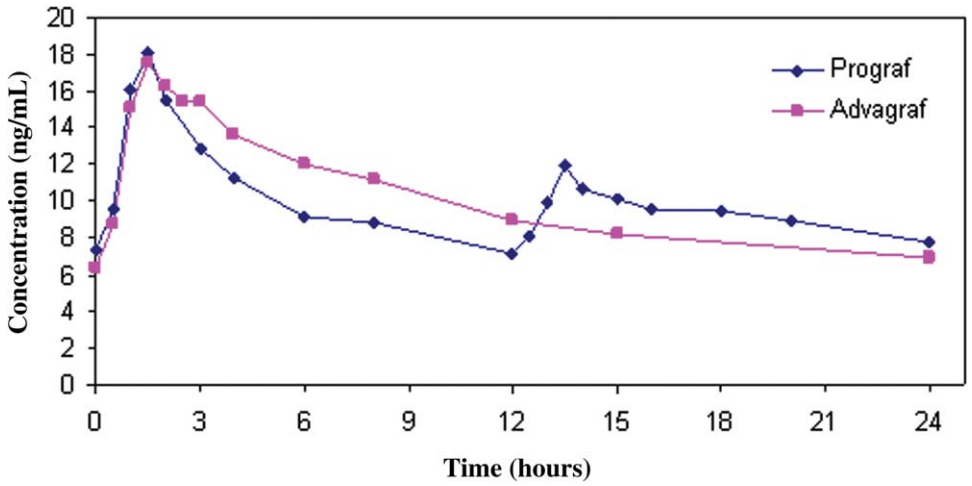

Figure 1. Mean concentrations for each formulation.

rs1045642, C___8890131_30 for rs1057868, and C__11213971_10 for rs2868177. Amplifications were performed in a 384-well format.

One-Year Follow-Up

After the completion of the pharmacokinetic study, patients were followed at the clinic as usual. Analytical data nearest to follow-up days 30, 90, 180, and 360 were recovered from the computerized laboratory system available at our hospital. Clinical records were also reviewed, and all relevant clinical events, including rejection episodes, graft dysfunction, and hospitalizations, were noted. Three patients presented with clinical events that required hospitalization but were not considered related to the treatment (see the Results section). To prevent interference, the analytical values of these concurrent episodes were disregarded because in all cases these values returned to previous figures once they were resolved. The tacrolimus doses, tacrolimus concentrations, and analytical values (creatinine, cystatin C, ALT, AST, bilirubin, and hemoglobin) at the time of inclusion in the study were compared with values at each predefined time (30, 90, 180, and 360 days) with the Wilcoxon test; the correction of the alpha error for multiple comparisons was performed with the Bonferroni method (the final alpha error was set at 0.0125).

RESULTS

Twenty patients were recruited as established in the protocol. Their demographic and clinical characteristics are detailed in Table 1.

All patients completed the pharmacokinetic study as determined by the protocol. There were no analytical alterations considered to be clinically relevant. Two patients (one for each formulation) reported self-limited diarrhea during the inter-admission period. All patients had data available for the 1-year follow-up.

Concomitant Treatment During the Pharmacokinetic Study

All patients had tacrolimus as their main immunosuppressive agent. Nineteen patients were taking prednisolone at an average dose of 4 mg every other day. Four patients also received mycophenolate mofetil with a dose range of 11.5 to 25 mg/kg/day. Other drugs included clotrimazole (18 patients), tediprima (1 patient), magnesium (10 patients), ursodeoxycholic acid (3 patients), valganciclovir (2 patients), and omeprazole (2 patients). No changes in concomitant drugs or their doses were made during the pharmacokinetic study.

Pharmacokinetic Results and Relative Bioavailability of Both Formulations

Figure 1 displays the mean concentrations of tacrolimus after Prograf and Advagraf administration. Primary pharmacokinetic parameters reflecting the drug disposition (C_{max} and $AUC_{0\text{-}24}$) were similar for the 2 formulations (see Table 2).

In Figure 1, we can also observe that the mean C_{max} value for the first dose of Prograf was higher than the value for the second dose. In all but 2 patients, C_{max} for Prograf was obtained from the morning dose. It should also be noted that C_0, C_{12}, and C_{24} were all quite similar, although C_{12} was somewhat lower for Prograf, as was expected. The fluctuation of tacrolimus concentrations between doses was larger for Prograf versus Advagraf (see Table 2).

The terminal half-life $t_{1/2}$ values were also similar for the 2 formulations: 19.46 hours (13.63 hours) for Prograf and 22.87 hours (10.54 hours) for Advagraf. The median for T_{max} was the same for the 2 formulations (1.5 hours).

TABLE 2. Main Pharmacokinetic Parameters for Tacrolimus After Prograf and Advagraf Administration

Parameter	Prograf	Advagraf	Ratio (90% Confidence Interval)
C_{max} (ng/mL)	19.52 ± 5.50	18.96 ± 5.52	96.9 (85.37-110.19)
$AUC_{0–24}$ (ng/mL·h)	234.86 ± 66.99	238.50 ± 68.76	100.1 (90.8-112.1)
T_{max} (hours)	1.5 (1–13.5)	1.5 (1–4)	
Cl_{oral} (L·hour)	21.4 ± 8.46	20.77 ± 7.02	
C_0 (ng/mL)	7.09 ± 3.97	7.09 ± 3.89	
C_{12} (ng/mL)	7.08 ± 2.38	8.88 ± 2.72*	
C_{24} (ng/mL)	7.82 ± 2.96	6.81 ± 2.49	
Fluctuation (%)			
0–12 hours	175.96 ± 84.90†		
12–24 hours	88.09 ± 96.20		
0–24 hours	173.72 ± 99.69	201.48 ± 124.79	

NOTE: The data are presented as means and standard deviations for all parameters except T_{max} (whose values are presented as medians and ranges).
*P = 0.03 for Prograf versus Advagraf.
†P = 0.004 for 0 to 12 hours versus 12 to 24 hours.

TABLE 3. Patients' Genotype Frequencies for CYP3A5, ABCB1, and 2 Analyzed PORs

Variant	Genotype	n (Frequency)	95% Confidence Interval
CYP3A5 rs776746	*1/*1	0 (0)	0-0.2005
	*1/*3	4 (0.2)	0.0661-0.4427
	*3/*3	16 (0.8)	0.5573-0.9339
ABCB1 rs1045642	CC	9 (0.45)	0.2383-0.6795
	CT	7 (0.35)	0.1631-0.5905
	TT	4 (0.2)	0.0661-0.4427
POR*28 rs1057868	CC	9 (0.45)	0.2383-0.6795
	CT	8 (0.4)	0.1998-0.6359
	TT	3 (0.15)	0.0396-0.3886
POR rs2868177	AA	7 (0.35)	0.1631-0.5905
	AG	11 (0.55)	0.3205-0.7617
	GG	2 (0.1)	0.0175-0.3313

The interindividual coefficients of variation for the primary disposition parameters were also similar for the 2 formulations: 28.20% and 28.50% for C_{max} and AUC_{0-24}, respectively, for Prograf and 29.10% and 28.80% for C_{max} and AUC_{0-24}, respectively, for Advagraf. We found no differences between males and females in AUC_{0-24} or C_{max} when adjustments were made by the administered dose per kilogram.

A finding worth highlighting is the difference in the concentration profiles of Prograf between the morning and evening doses, which reflects the circadian rhythm in the disposition of tacrolimus. C_{max} was 18.87 ± 5.96 ng/mL after the morning dose and 13.19 ± 3.89 ng/mL after the evening dose. We found no differences in the tacrolimus half-life with the morning dose of Prograf versus the evening dose.

When the statistical analysis of bioequivalence was performed for AUC_{0-24} and C_{max}, the 90% confidence intervals for the Advagraf/Prograf ratio were 90.8 to 112.1 and 85.37 to 110.19, respectively. This finding means that the formulations can be considered bioequivalent according to the requirements established by international regulatory agencies.[11,12]

Genetic Results

The frequency of patients with each genotype was typical for a white population (Table 3). The more frequent genotypes were cytochrome P450 CYP3A5 *3/*3 (0.80), adenosine triphosphate–binding cassette B1 (ABCB1) CC (0.45), POR rs2868177 AG (0.55), and POR*28 CC (0.45). In our population, we found no patients with CYP *1/*1 expression. Our population followed the Hardy-Weinberg principle. No relationship was found between patients' genotypes and the pharmacokinetic values.

One-Year Follow-Up

By the end of the follow-up, all patients who had participated in the study were still living. During the follow-up, no adherence problems and no episodes of rejection were detected. At month 9 of the follow-up, 1 patient presented with graft dysfunction due to hepatic artery thrombosis that had occurred during an episode of severe diarrhea with dehydration. This patient recovered completely after thrombectomy with

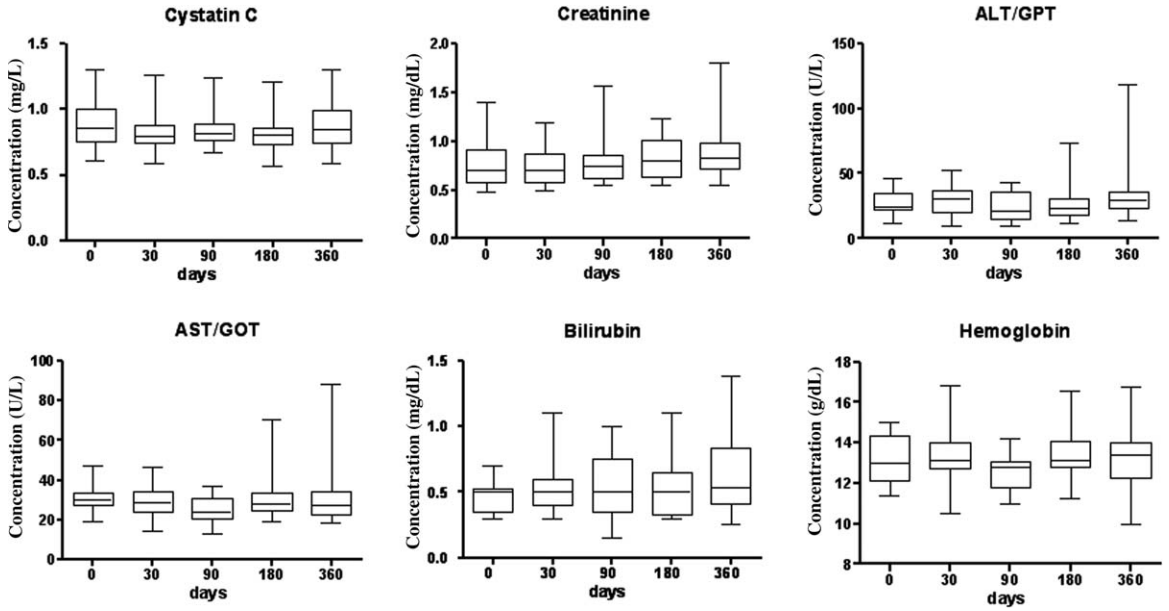

Figure 2. Evolution of the main analytical parameters. The data are presented as 95% box plots. The lines in the boxes represent the median values, the boxes represent the 25th and 75th percentiles, and the outer lines represent the 5th and 95th percentiles. No significant differences ($P < 0.05$) in comparison with time 0 were found for any parameter at any time of follow-up.

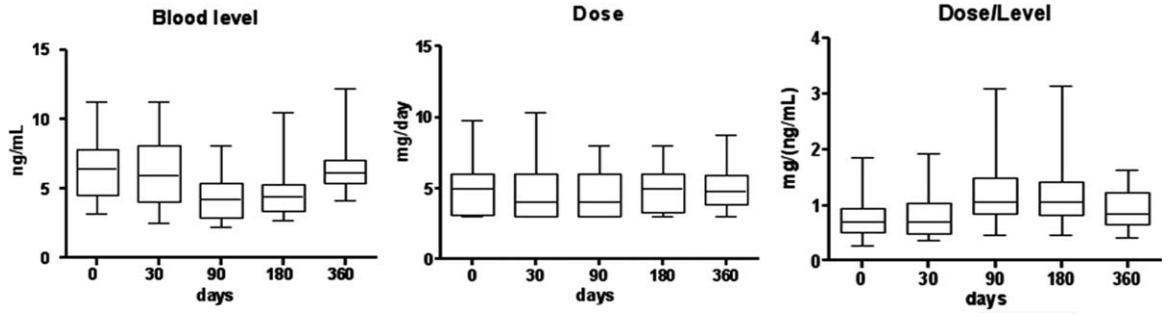

Figure 3. Tacrolimus blood levels, doses, and dose/level ratios during the first year after the conversion from Prograf to Advagraf. The lines in the boxes represent the median values, the boxes represent the 25th and 75th percentiles, and the outer lines represent the 5th and 95th percentiles. Significant differences were found for tacrolimus level between 0 and 90 days ($P < 0.002$) and 180 days ($P = 0.01$) and for dose/level ratio between 0 and 90 days ($P = 0.02$) and 180 days ($P = 0.008$).

intra-arterial urokinase and subsequent angioplasty. Two cases suffered uncomplicated influenza A, 1 patient developed warts, and 1 patient with cystic fibrosis needed hospital admission because of a lung infection. Routine Epstein-Barr virus DNA quantitation detected just 1 case with values greater than 2×10^4 copies/mL. No posttransplant lymphoproliferative disorders occurred.

Figure 2 shows the relevant analytical parameters at the start of the study and during the 1-year follow-up. There were no significant changes in the mean hepatic enzyme levels during this period; 2 patients had transient levels of ALT above the upper limit of normality (the patient suffering hepatic artery thrombosis and the patient with cystic fibrosis). Cystatin C and creatinine levels in plasma revealed no significant changes in renal function (Fig. 2). Changes in the administered tacrolimus dose and the concentration levels are displayed in Fig. 3. The tacrolimus level decreased significantly from 6.43 ng/mL before the conversion to 4.25 ng/mL (range = 2.2-8.2 ng/mL) at 90 days and 4.4 ng/mL (range = 2.7-10.6 ng/mL) at 180 days, whereas the dose/level ratio for tacrolimus (and the dose/level ratio adjusted by weight) showed an increase at the same time points. These parameters tended to return to basal levels by month 12. The dose/level/weight ratio was also evaluated, but its values were similar to those for the dose/level ratio, and the distribution was also similar.

DISCUSSION

Among adult liver transplant patients, the rate of nonadherence to immunosuppressive drugs ranges from 15% to 40%, and the rate is nearly 4 times higher among pediatric and adolescent patients.[13] A once daily tacrolimus formulation, Advagraf, is being adopted in clinical practice and was developed with the aim of improving patient adherence because nonadherence to immunosuppressant treatment has been cited as a major cause of acute and chronic rejection, preventable graft loss, and mortality in patients undergoing solid organ transplantation.[14]

On the basis of our results and as previously reported for adult and pediatric patients, Advagraf can be considered truly bioequivalent to Prograf with a very close ratio, a narrow confidence interval, and adequate strength (81% for C_{max} and 96% for $AUC_{0\text{-}24}$); therefore, the formulations are interchangeable from a pharmacokinetic perspective.

The pharmacokinetic properties of tacrolimus did not reveal differences with respect to sex, CYP3A4, CYP3A5, or P-glycoprotein polymorphisms. The relatively small patient population of this study may have limited our ability to detect a biologically meaningful difference. The donor genotype may be more relevant for tacrolimus metabolism,[15-17] and our genotyping was more likely to be a reflection of the recipient genotype. The known effects of circadian rhythm on tacrolimus metabolism[18] may explain higher C_{max} and AUC values in the morning versus the evening.

From a purely pharmacokinetic point of view, the appropriateness of the conversion from Prograf to Advagraf with a dose ratio of 1:1 is consistent with our data and practically all data published to date.[19] However, the long-term equivalence of the dose after the conversion to Advagraf and the previous Prograf dose has been questioned.[19] In adult liver transplant patients, several reports have described the need to modify the dose after the conversion from Prograf to Advagraf.[20-22] The decrease in tacrolimus levels is usually between 0.5 and 1 ng/mL and is observed 15 to 30 days after the conversion.

Parallel studies comparing treatment with Prograf and Advagraf in adult de novo liver transplant recipients suggest that patients treated with Advagraf need a somewhat higher dose to maintain the same tacrolimus concentrations.[23]

As far as we know, apart from a study by Heffron et al.,[10] no conversion studies on pediatric and adolescent patients with liver transplants have been published; Heffron et al. also reported 1 year of follow-up for this population. The patients included in their study were younger than the patients in our study (the mean difference in age for the 2 samples was 6 years), but their results for the relative bioavailability of the 2 formulations were comparable to our results. These authors reported that during the first year after conversion, no cases of rejection, Advagraf discontinuation, graft loss, or death were recorded, but detailed follow-up data for tacrolimus doses and concentrations and for clinical laboratory values were not provided. Tacrolimus levels were reported at the 1-year follow-up without noticeable differences [there was a small difference in the means (4.90 ± 2.44 ng/mL at 1 year versus 5.55 ± 2.61 ng/mL at the baseline), but there was no difference in the median tacrolimus levels (5.2 versus 5.1 ng/mL)]. Our raw data, in accordance with some studies in adults (both renal transplant patients and liver transplant patients), show that conversion brings a significant decrease in tacrolimus trough levels at 3 and 6 months, but the levels tend to return to basal concentrations during the 1-year follow-up. In addition to looking at tacrolimus levels and doses, we calculated the dose/level ratios, which reflected the disposition of tacrolimus, and we observed that the changes were concordant with the changes in the tacrolimus level, which were not significant at the 1-year follow-up. This tendency toward normalization during follow-up has been observed by others,[20,22] although the timing can differ from one study to another. The reasons for these changes are unclear because of the uncontrolled and longitudinal nature of the design of these studies, but they are probably related to several factors. The first could be a regression to the mean phenomenon usually seen in this kind of study. Also, we must consider that experience tells us that the intra-individual variability of C_{min} minimum concentration in clinical practice is quite high and that minor dose modifications are frequent. Finally, the abnormal nature of the parameter may influence the result, as we can see in the study performed by Heffron et al., in which the mean and median at 1 year were somewhat different (something not observed in our study). For the purpose of therapeutic drug monitoring, the trough levels of tacrolimus after Advagraf administration should be interpreted in the same way in which they are after Prograf use; the C_{min} minimum concentration and AUC values are very similar for the 2 formulations. The data from the literature on trough tacrolimus levels after Advagraf administration and total exposure (AUC) are scarce but suggest that they would be similar to those after Prograf administration.[24] Therefore, we must take into account the transient decrease in tacrolimus levels that we observed and closely monitor these levels after conversion, particularly when the target concentrations are in the lower range. In any case, the studies published to date have not reported a deterioration in the clinical status of patients after conversion because of the low relevance of this change or because therapeutic drug monitoring allows dose adjustments that can correct the minor changes in tacrolimus levels associated with conversion. In our study, during the year of follow-up, biochemical parameters (mainly associated with hepatic and renal function) did not change significantly; 3 patients presented with relevant clinical events, but none were considered to be related to tacrolimus.

In conclusion, the confidence intervals for the $AUC_{0\text{-}24}$ and C_{max} ratios for the 2 tacrolimus formulations are well within the interval of 80 to 125 and,

therefore, satisfy the criteria required by health authorities for bioequivalence. We conclude that Prograf conversion to Advagraf with a 1:1 dose equivalence is appropriate as an initial guideline. Follow-up at 1 year after the formulation conversion shows a decrease in the concentration without significant changes in the dose; although these changes are transient, they suggest the need for closer drug monitoring. This is the first study to present relevant laboratory results regarding hepatic and kidney biochemical parameters. Clinical control of the patient's condition during this period is not adversely affected by the change in the tacrolimus formulation.

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