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Pharmacoepidemiology of tacrolimus in pediatric liver transplantation

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Abstract

AEs during immunosuppressive treatment with tacrolimus are very common. We retrospectively evaluated FK safety and efficacy in a large pediatric liver transplant cohort in Latin America. During 2-year follow-up, we analyzed data from patients who underwent liver transplantation over the period 2010-2012 and recorded FK exposure, AEs, and AR episodes. AEs were classified according causality and severity. Tacrolimus exposure before and during AE was compared using Wilcoxon matched-pairs test. Kaplan-Meier curves were used for survival analysis. In total, 46 patients (out of 72 patients) experienced 69 AEs, such as hypomagnesemia (49%), PTLD (6%), hypertension (6%), and/or nephrotoxicity (22%). 43% of AEs were classified as moderate or serious, and 89% were assigned as probable or definitive. Patients who had one or more AR episodes accounted for 65%. The 12-month acute rejection-free survival was 41% (95% CI, 30.1%-53.1%). A significant difference was observed in FK trough concentrations before and during hypomagnesemia and nephrotoxicity ($P<.05$). This study is the first report of FK safety in a large group of pediatric liver transplant patients in Latin America. Children experience AEs, even in protocols with low FK doses. Therapeutic monitoring is an important tool to manage immunosuppressive schemes containing tacrolimus in vulnerable populations.

KEYWORDS

liver transplantation, pediatrics, pharmacovigilance, tacrolimus, therapeutic drug monitoring

1 | INTRODUCTION

The management of immunosuppression in pediatric liver transplant is complex and usually includes use of calcineurin inhibitors.[1] Tacrolimus has become the cornerstone in immunosuppression of pediatric liver transplant patients. Tacrolimus therapeutic drug monitoring is performed in the post-transplant routine based on the narrow therapeutic window, high variability in tacrolimus pharmacokinetics, and the previously documented relationship between systemic exposure and AEs to this calcineurin inhibitor.[1,2]

Furthermore, it is challenging to find the balance between efficacy and toxicity in pediatric transplantation, as serious consequences exist if the FK target range is not maintained. Low FK blood concentrations may result in impairment of graft function or AR, while overimmunosuppression may increase the risk of AEs, including infections, malignancies, tremor, headache, hypertension, renal dysfunction, PTLD, encephalopathy, and post-transplant diabetes.[3–5] These complications cause significant patient morbidity and mortality.[3,6,7] Therefore, the analysis of AEs to FK can be used to improve and individualize the immunosuppressive treatment.

Currently, immunosuppression in pediatric liver transplantation consists of multidrug therapy including induction therapy, low-dose tacrolimus, steroids, sirolimus, and/or mycophenolate mofetil.[1,8] The

Abbreviations: AE, adverse event; AR, acute rejection; C0, tacrolimus trough blood concentration; EBV, Epstein-Barr virus; FK, tacrolimus; PTLD, post-transplant lymphoproliferative disease.

aim of the treatment is to avoid rejection but also to minimize renal dysfunction, PTLD, infection, hypertension, and hyperlipidemia.[3] As previously reported, tacrolimus trough concentrations in the range of 5-12 ng/mL were sufficient to achieve optimal efficacy with minimal toxicity.[9,10]

Nevertheless, data are limited with regard to the long-term results of tacrolimus in low-dose-therapeutic schemes which are characterized by minimal exposure to immunosuppressive drugs.[9,11–13]

There are very limited safety reports in pediatric patients, and less described is the outcome in Latin American patients. For all of the above-mentioned reasons, the objective of this study was to evaluate safety and efficacy of FK in liver transplant patients in a high-complexity pediatric hospital, where most pediatric liver transplantations in Argentina are performed.

2 | MATERIALS AND METHODS

We conducted a retrospective observational study. The present project was approved by the Institutional Review Board (Project # 670), while pharmacokinetic and laboratory parameters were evaluated as part of the routine monitoring (Form 1418F62).

2.1 | Inclusion criteria

Included patients received a first liver transplantation between 2010 and 2012 and survived at least 1 month after surgery. Furthermore, patients who did not demonstrate an acceptable adherence were excluded from the study. Adherence was defined according to (i) the criteria of the treating physician; (ii) clinical evaluation during the follow-up period; (iii) patient assistance to appointments with clinicians; and (iv) patient visits to the outpatient pharmacy. All of the subjects were transplanted in Hospital de Pediatría JP Garrahan and received a low-dose tacrolimus scheme as part of an immunosuppressive protocol implemented in 2010. The protocol consisted of calcineurin inhibitor minimization and induction therapy as described by others.[9,12,14–16] Induction therapy was provided depending on the availability of basiliximab at the clinical center.

2.2 | Immunosuppressive treatment

Tacrolimus (0.1 mg/kg/d) was administered in association with steroids and/or antimetabolites. In case of induction therapy, basiliximab was administered at days 0 and 4 after transplantation. Subsequently, FK doses were adjusted according to blood levels, liver and kidney function, and EBV/cytomegalovirus (CMV) viral load. FK trough concentration (C0) target levels in the first 6 months were 7-8 ng/mL, during the next 6 months 5-7 ng/mL, and after the first year post-transplantation 5 ng/mL. Concomitant drugs during maintenance treatment (after 30 days post-transplantation) were sulfamethoxazole-trimethoprim, magnesium supplements, omeprazole (in all patients), acyclovir, and antibiotics, as needed. Mycophenolate sodium was added in those cases in which tacrolimus reduction was necessary, at a dose of 20-40 mg/kg/d.[15,17] Cases of biopsy-proven AR were treated with steroid pulse therapy consisting of methylprednisolone at a dose scheme of 10 mg/kg/d intravenous for 3 days and 30%-50% increased dose of tacrolimus followed by weekly controls.[14]

2.3 | Clinical end-points: AEs and AR episodes

AEs related to FK were evaluated retrospectively through the review of medical records and physician consultations to confirm the event. The definitions of AEs were described as follows[18]:

1. Hypertension was defined as average systolic blood pressure and/or diastolic blood pressure greater than or equal to the 95th percentile for sex, age, and height on three or more occasions, followed by the administration of antihypertensive drugs including angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers in patients without previous history of hypertension.[19] Concomitant administration of alpha-/beta-adrenergic agonists was excluded from the registry.
2. Hypomagnesemia was considered an AE if magnesium serum concentration was lower than 1.6 mg/dL and magnesium supplement was provided to the patient.[20,21]
3. Nephrotoxicity identification was based on a serum creatinine increase of at least 30% relative to the baseline value for each patient, oliguria, or anuria. Also, nephrotoxicity was considered if it was secondary to tacrolimus, and other causes were discarded, such as sepsis, dehydration, or co-administration of nephrotoxic drugs such as vancomycin or aminoglycosides.[22,23]
4. Hepatotoxicity was defined as cholestasis with bilirubin elevation (>10 mg/dL), excluding biliary, vascular, infectious, inflammatory, and immunological causes, after stabilization of liver function post-transplantation.[24]
5. PTLD was diagnosed by histopathological evidence of lymphoproliferation, commonly with the presence of DNA, RNA, or EBV protein detected in tissue.[25]
6. Post-transplant hyperglycemia was defined by Crutchlow et al. on patients at risk after transplantation. Patients with fasting plasma glucose (FPG) of ≥126 mg/dL were considered patients with diabetes, while those with values between 100 and 125 mg/dL were considered patients with altered fasting glycemia (IFG). Insulin administration was also considered in patients with no previous history of diabetes.[26]

In this report, drug-drug interactions with azoles, macrolides, and calcium channel blockers (nifedipine) or anticonvulsants (phenobarbital and phenytoin) were not present concurrently with episodes of AEs.

For detected AEs, the causal relationship between the AE and FK levels was established through the application of the Naranjo algorithm[27] in definitive, probable, possible, or doubtful. Moreover, AEs were classified according to severity as mild, moderate, serious,

and lethal.[28] A serious AE was considered as any untoward medical occurrence that at any dose a) resulted in death; b) was life-threatening; c) required inpatient hospitalization or prolongation of existing hospitalization; or d) resulted in persistent or significant disability/incapacity.[29]

Once confirmed, the AE was reported to the local health authority, ANMAT (National Administration of Medicines, Food and Medical Technology, Argentina). Finally, acute rejection-free survival rate, based on biopsy-proven AR episodes, as a surrogate of efficacy of FK was analyzed using Kaplan-Meier curves (GraphPad Prism v.5).

2.4 | Tacrolimus exposure according to time post-transplantation

Dose-normalized tacrolimus trough concentration (C0/Dose) was assessed in different periods after transplantation: 0-1, 1-3, 3-6, 6-12, and 12-24 months. Tacrolimus C0 values in all patients during each period were grouped for analysis, and those trough levels lower than the limit of quantification (2 ng/mL) were considered half of the limit of quantification for statistical analysis. Kruskal-Wallis test with Dunn's multiple comparisons test was used to compare dose-normalized tacrolimus C0 between the different post-transplant intervals (GraphPad Prism v.5). The coefficient of variation of C0/Dose (CV %), defined as the percentage ratio of the standard deviation to the mean, was calculated for each period post-transplantation.[30]

2.5 | C0-adverse event relationship

Most frequent AEs, nephrotoxicity and hypomagnesemia, were recorded. Blood samples that would most probably correspond to the occurrence of nephrotoxicity and hypomagnesemia were chosen according to the following criteria: all samples taken during the first week to 10 days prior to the AE. These were compared with samples taken 10-60 days before the AEs. Mean tacrolimus C0 recorded during each AE was calculated, and Wilcoxon matched-pairs test was used for statistical analysis (GraphPad Prism v.5).

Furthermore, the mean FK C0 during each AE was classified in one the following FK C0 ranges: low exposure: 4.0-9.0 ng/mL; moderate exposure: 9.1-14.0 ng/mL; and high exposure: 14.1-17.0 ng/mL.

3 | RESULTS

In total, 89 patients were analyzed. Patients were excluded secondary to a survival shorter than 1 month (n=5), unavailable medical records (n=4), retransplantation during the first month post-surgery (n=2), and non-adherence as previously defined (n=6). Finally, 72 patients were included in this evaluation. No patient was non-compliant and no patient was lost during the follow-up period. Specifically, 13 patients had a shorter follow-up for different reasons: official transfer to an adult liver transplantation center, referral to another health center, or relocation to another district. The median (range) follow-up time was 23.8 months (1.1-31.5). The median (range) age and weight were 2.1 years (0.5-17.6) and 12.0 kg (6.0-88.5), respectively. Demographic characteristics are presented in Table 1.

TABLE 1 Demographics and relevant medical history (n=72)

Characteristic/Parameters	Results
Total subjects	72
Age (years)[a]	2.1 (0.5-17.6)
Gender (females/males)	45/27
Weight (kg)[a]	12.0 (6.0-88.5)
Donor (deceased/living donor)	53/19
Follow-up time (months)[a]	23.8 (1.1-31.5)
Graft (complete/technical variant)	26/46
Diagnosis	
Biliary atresia	29 (40.3%)
Fulminant liver failure	14 (19.4%)
Cholestatic cirrhosis[b]	7 (9.7%)
Hepatic cirrhosis: autoimmune and cryptogenic	12 (16.6%)
Malignancies[c]	7 (9.7%)
Metabolic diseases: metabolic liver failure	3 (4.2%)
Immunosuppressive therapy (total number of patients, 72)	
Basiliximab	52/72
Tacrolimus	72/72
Prednisone (1.25-3.75 mg/kg/d)	39/72
Mycophenolate sodium (20-40 mg/kg/d)	34/72
Azathioprine	6/72
Sirolimus	5/72
Nationality	
Argentina	63
Paraguay	8
Bolivia	1
Distribution of clinical end-points	
Acute rejection (total events)	92
Mild	39 (42.4%)
Moderate	36 (39.1%)
Severe	10 (10.9%)
Chronic rejection	3 (3.3%)
Steroid-resistant	4 (4.3%)
Adverse events (total events)	69
Hypomagnesemia	35 (49%)
Nephrotoxicity	16 (22%)
Hypertension	4 (6%)
Tremor	4 (6%)
PTLD	4 (6%)
Others (alopecia, hyperglycemia, anemia, hepatotoxicity)	6 (8%)
Death	5 (7%)

[a]Data are expressed as median (range).
[b]Including Alagille syndrome, congenital hepatic fibrosis, sclerosing cholangitis.
[c]Including hepatoblastoma and hepatocellular carcinoma.

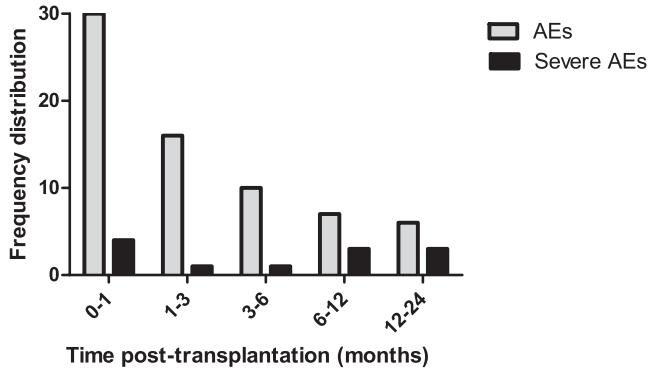

FIGURE 1 Frequency distribution of tacrolimus adverse events after liver transplantation in pediatric patients. AE, adverse event

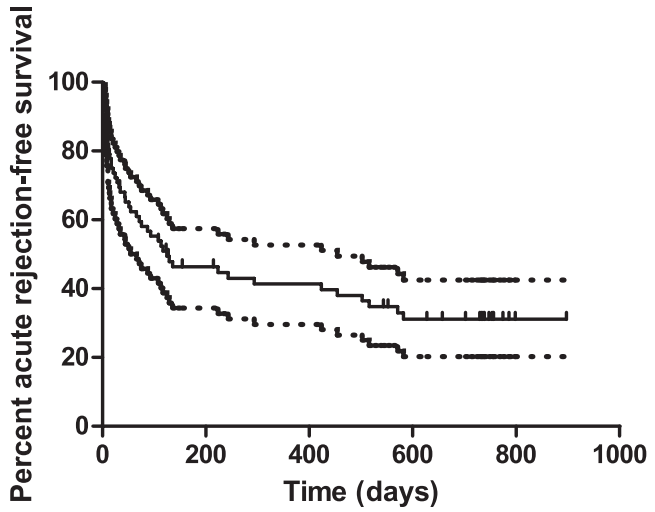

FIGURE 2 Acute rejection-free survival in pediatric liver transplant recipients (n=72). Probability of acute rejection-free survival at 1 y post-transplantation was 41.4% (95% CI, 30.1%-53.1%)

The incidence of AEs was 96% (69 cases in 72 patients). According to causality classification, 89% of them were definitive or probable, while according to severity, 43% of AEs were classified as moderate or serious. Noteworthily, 64% (46/72) of the analyzed patients experienced at least one AE during the follow-up period.

Furthermore, in the distribution analysis of AEs, we observed a decreasing frequency as postoperative time increased (Figure 1). In the first month, 13% (n=4) of AEs were serious including nephrotoxicity (n=2), hypomagnesemia (n=1), and tremor (n=1). Besides, 17% (n=5) of AEs were moderate and 70% (n=21) were mild in this time period. In the later period of 1-3 and 3-6 months post-transplantation, 16 and 10 AEs were observed, respectively. Interestingly, in these periods the incidence of serious AEs decreased with respect to the first month post-transplantation. Serious (n=1), moderate (n=5), and mild (n=10) AEs were recorded during the period 1-3 months. Besides, in the period 3-6 months post-transplantation, one serious, four moderate, and five mild AEs were observed. During the periods 6-12 and 12-24 months post-transplantation, seven and six AEs occurred and about 50% of them (three AEs in each period) were serious including (number of cases) PTLD (n=3), hypomagnesemia (n=2), and cholestasis (n=1). In the period 6-12 months post-transplantation, 29% (n=2) of AEs were moderate and 29% (n=2) were mild. In the second year post-transplantation (12-24 months), 33% (n=2) of AEs were moderate and 17% (n=1) were mild.

Regarding efficacy as indicated by biopsy-proven AR rate, 92 events occurred in 47 patients during the follow-up time period. According to histopathology, 42.4%, 39.1%, and 10.9% of the rejection episodes were mild, moderate, and serious, respectively. Four AR episodes (4%) were resistant to steroid treatment. The 12-month acute rejection-free survival in the study group was 41.4% (95% CI, 30.1%-53.1%) (Figure 2).

Tacrolimus dose-normalized concentrations (C0/Dose) and trough levels together with frequency of AR and serious AEs are presented in Table 2. The means of each period vary significantly when comparing C0/Dose in the five groups of time post-transplantation ($P<.05$). Specifically, the mean C0/Dose values in the periods 0-1 and 1-3 months post-transplantation were significantly different to the other periods ($P<.05$). The mean C0/Dose showed no significant difference among 3-6, 6-12, and 12-24 months post-transplantation ($P>.05$). Tacrolimus exposure variability was described in each period through the percent variation coefficient (CV %) of dose-normalized tacrolimus concentrations (Table 2). Noteworthily, a high number of serious AEs and severe AR episodes were registered during the first month post-transplantation. A significant difference was found in FK C0/D between

TABLE 2 Tacrolimus dose-normalized and trough concentrations, frequency of acute rejection, and serious adverse events in the study period (n=72)

Post-transplant period (months)	C0/D (mean, SD)	C0 (mean, SD)	CV%	Frequency of AR (number of cases)	Frequency of serious AEs
0-1*	246.6* (571.0)	7.1 (3.9)	45.5%	8 Mi, 9 Mo, 4 S	4
1-3*	157.8* (347.6)	6.8 (3.6)	35.6%	11 Mi, 5 Mo, 1 S	1
3-6	196.3 (388.4)	6.9 (3.5)	35.1%	8 Mi, 4 Mo, 1 S	1
6-12	185.6 (271.1)	6.1 (3.5)	36.6%	4 Mi, 6 Mo, 3 S	3
12-24	245.1 (579.6)	5.6 (3.0)	36.5%	8 Mi, 12 Mo, 1 S	3

AE, adverse event; AR, acute rejection; C0, tacrolimus trough levels (ng/mL); CV%, percent variation coefficient of dose-normalized tacrolimus concentrations; D, tacrolimus dose (mg/kg); SD, standard deviation; Mi, mild; Mo, moderate; S, severe.
*$P<.05$ compared to the other periods.

patients with AR and patients who did not present an AR ($P<.05$) in the complete study period. However, no significant difference was observed in the C0 and CV% values between both groups ($P>.05$).

Regarding age, patients who presented with an AE had a median (range) age of 3.3 years (0.6-17.6). On the other hand, patients who did not present an AE had a median (range) age of 1.3 years (0.5-14.6). Indeed, there was a significant difference in age between patients experiencing and not experiencing AEs (Mann-Whitney, $P<.05$). Nonetheless, as shown in Figure 3, there was a notorious overlap between the two age groups. A significant difference was found in tacrolimus trough levels between patients with and those that did not develop an AE. Tacrolimus trough levels (median, range) of patients with and without an AE were 8.2 ng/mL (2.5-21.0) and 4.8 ng/mL (1.0-9.8), respectively ($P<.0001$). Regarding patients who experienced PTLD, they had a median (range) age of 1.4 years (0.8-1.6) without difference between girls and boys. The median (range) time of presentation of PTLD was 13.5 months (4.9-19.4) post-transplantation. Noteworthily, PTLD was not influenced by tacrolimus concentrations or dose-normalized trough levels (data not shown).

We analyzed the relationship between AEs (nephrotoxicity, n=13; and hypomagnesemia, n=21) in the maintenance therapy (after 30 days post-transplantation) and C0 exposure. A statistical significant difference was observed between the mean C0 before and during the first week to 10 days prior to the occurrence of nephrotoxicity ($P<.05$) and hypomagnesemia ($P<.05$) (Figure 4). Furthermore, we found that in the 34 AEs observed, 41% (n=14) and 53% (n=18) occurred when FK trough levels were in the range 4-9 ng/mL and 9.1-14 ng/mL, respectively ($P>.05$).

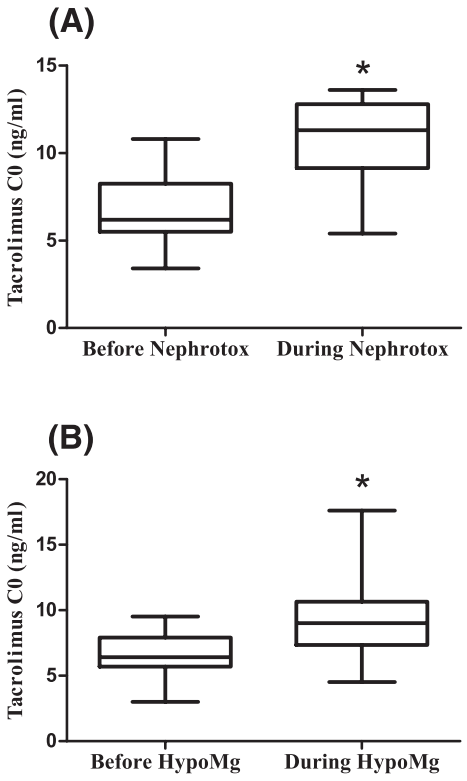

FIGURE 4 Exposure to tacrolimus before and during nephrotoxicity (A) and hypomagnesemia (B). *$P<.05$. Nephrotox, nephrotoxicity; HypoMg, hypomagnesemia; C0, tacrolimus trough concentrations

4 | DISCUSSION

This is the first study that describes AR episodes and the incidence of AE in a large group of pediatric liver transplant patients in the major pediatric transplant center in Argentina, Hospital de Pediatría JP Garrahan.

The potent immunosuppression provided by FK and its specific side effects influences the long-term patient and graft survival.[30] As this is a matter of concern, other authors have described incidence of FK AEs as well. In our population, we observed an incidence of 49% of hypomagnesemia, which represents 51% of the total AEs. In the same way, but in a much-limited-number patient sample, we previously reported a high incidence of this AE in a pediatric kidney and liver transplant population, and 54% of FK AEs correspond to hypomagnesemia,[18] which is consistent with the frequency reported by Margreiter et al. in adult kidney transplant patients.[31] Calcineurin inhibitor-induced chronic nephrotoxicity is also of much interest in long-term survivors of pediatric liver transplantation. According to previous reports, the risk of chronic renal insufficiency in a pediatric liver transplant population increased over time, with a cumulative incidence reaching 25% at 10 years post-transplantation.[32] In the European FK multicenter liver study in adults, the authors reported an incidence of impaired renal function in tacrolimus-treated patients of 35%.[33] In this regard, we observed an incidence of 22%, which is comparable with the results in pediatric patients.[3,5] The incidence of hypertension was low in our study (6%). Similarly, Kelly et al. reported an incident of 7% in pediatric liver recipients.[3] Their study reported an incidence of 9.5% of neurotoxicity, while we observed a 6% of incidence of tremor (Table 1). In total, we observed a decreasing incidence of AE as time post-transplantation increased in this study (Figure 1). As also shown in Table 2, this result was in correspondence with different FK trough concentrations according to time post-transplantation.[34]

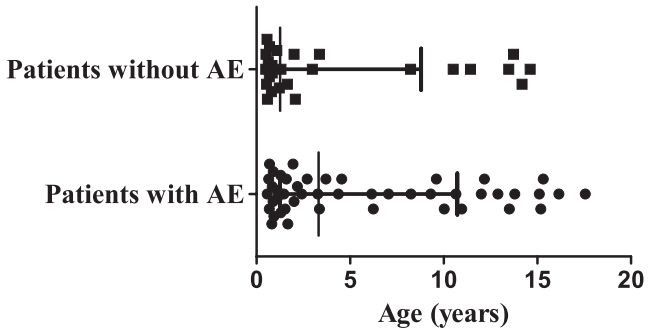

FIGURE 3 Age of patients with and without an adverse event. AE, adverse event

PTLD is the most common pediatric malignancy post-transplantation, and it is the most common cause of cancer-related death, with a mortality rate of 60%.[6,35–37] The incidence of PTLD

reported here was 6%, which is consistent with that reported in a previous report (5.3%) in children who were alive 10 years after pediatric liver transplantation.[7] Besides, the observed time of occurrence of 13.5 months post-transplantation is in line with that reported from our group[18] and that of Molmenti et al.[38] Noteworthily, PTLD is a multicausal event with many risk factors.[39] PTLD occurs as a consequence of the immunosuppressive scheme, which most frequently consisted of induction therapy, tacrolimus, prednisone, and/or mycophenolic acid in our study. Analysis of other causes is necessary, and therefore, it would be a mistake to attribute this malignancy exclusively to tacrolimus.

Long-term evidence to date in children with liver transplantation suggests that tacrolimus is effective in preventing acute and chronic rejection and has a good long-term safety profile.[3] Acute rejection-free survival at one-year follow-up (41.4%) was higher but still comparable to that previously reported by Ng et al., in a large pediatric liver transplant population.[13] We hypothesize that variability and low tacrolimus concentrations may play a role as risk factors of AR. Further studies, including multivariate analysis of AR, would be useful to understand this pattern.

Despite frequent tacrolimus dose monitoring and adjustments, there was a high variability in tacrolimus concentrations corrected by dose, especially during the first month post-transplantation (Table 2). These results are consistent with data reported by other authors in pediatric thoracic organ transplant patients.[40] In addition to the complexity of the patient due to the medication regimens and potential surgical complications including biliary and vascular causes, a high CV% in dose-normalized FK C0 could account for AR in the first month post-transplantation and should not be disregarded. Moreover, the CV% reported in the study period (32%) is comparable to the intra-individual variability previously described in adult transplant recipients.[10,41,42] Noteworthily, FK C0 and CV% did not show significant differences between patients with and without AR, while the FK C0/D parameter was associated with AR. This may play a role in clinical decisions.

We also observed a significant difference in age between patients who experienced at least one AE and those free of AEs during the follow-up period of the present study. This result is in line with a lower incidence of AEs to FK in younger children as shown in the report of the WHO Programme for International Drug Monitoring (http://www.vigiaccess.org/).[43] However, there was a significant difference in FK trough levels between patients with and without AEs, which may have contributed to the higher incidence.

In the low-dose tacrolimus regimen presented here, the incidence of AEs in the maintenance period was studied in 72 pediatric liver transplant patients. We conclude that nephrotoxicity and hypomagnesemia described in this report are related to tacrolimus concentrations, as informed by others.[44–46] Specifically, we observed a significant difference between C0 in the context of and before the AE, which supports the role of therapeutic drug monitoring in individualizing the immunosuppressive therapy and managing tacrolimus therapy as other authors stated.[34]

This study has the same limitations that apply to all retrospective descriptive studies. The potential for selection bias cannot be ruled out based on the criteria defined for adherence. Furthermore, some AEs could have been missed or rejected secondary to misinformation. For instance, diabetes post-transplantation was not confirmed by our clinical reports due to lack of reliable registries; therefore, we could not describe its incidence. Moreover, in pediatrics, FK therapeutic monitoring is based on monitoring trough concentrations (C0) and it has a controversial correlation with toxicity and rejection.[47] Besides, the area under the curve (AUC) of FK blood concentration vs time is a better marker of systemic exposure to FK.[48] However, therapeutic ranges of FK C0 in children are defined based on clinical data,[47] with the subsequent dose adjustment based on the C0 in clinical practice.

In conclusion, this is the first study in a large cohort of Latin American pediatric liver transplant recipients showing the incidence of AEs to FK. We also described the correlation with exposure and the rate of acute rejection-free survival. For the next decade, FK will remain as the primary immunosuppressive agent, and therefore, optimization of FK-based immunosuppressive therapy is of high importance.[30] The main challenges facing pediatric transplantation are to improve the quality of life in the long term, optimize the management of immunosuppression, and prevent AEs, when possible. To this end, pharmacological information on immunosuppressive drugs, with an emphasis on safety, is essential.

AUTHORS' CONTRIBUTIONS

Riva N: Contributed to concept/design, data collection, and data analysis/interpretation; Schaiquevich P: Contributed to concept/design, statistics, data analysis/interpretation, and critical revision and approval of the article; Cáceres Guido P: Contributed to concept/design, data collection, statistics, data analysis/interpretation, and critical revision and approval of the article; Halac E: Contributed to concept/design and critical revision of the article; Dip M: Contributed to concept/design and critical revision of the article; Imventarza O: Contributed to concept/design, data interpretation, and critical revision and approval of the article.

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