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ORIGINAL ARTICLE

Pharmacokinetic study of mycophenolic acid in pediatric kidney transplantation

Estudio farmacocinético del ácido micofenólico en el trasplante renal pediátrico

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What do we know about the subject matter of this study?

The complex pharmacokinetics of mycophenolic acid is well known, and its safety and efficacy are closely related to the AUC. Studies are only been done in adults and indicates a low correlation between C0 and AUC, no studies have been done in pediatrics".

What does this study contribute to what is already known?

This study provides relevant information to use a single trough plasma level in clinical practice to adjust mycophenolic acid doses, and achieve effective immunosuppression, according to the post-transplant time and the pharmaceutical presentation of the drug used.

Abstract

Mycophenolic acid (MPA) is among the drugs used to achieve effective immunosuppression in kidney transplantation (KT), which is characterized by complex pharmacokinetics and high intra- and inter-individual variability. Monitoring the trough concentration level (C0) of MPA for dosage adjustments is considered controversial, mainly due to its low correlation with the area under the curve (AUC). **Objective**: To correlate the C0 and AUC of MPA in pediatric patients with KT. **Patients and Method:** Prospective study carried out in 54 KT patients under treatment with MPA. Linear regressions and correlations were performed between ABC and C0. Multiple comparisons group analysis was performed according to post-transplant time and the two oral presentations of MPA. **Results:** The plasma level that best correlates with AUC was C0 ($r^2 = 0.52$). There was a significant group of patients with subtherapeutic levels (36.6% of all measurements). It was also determined that the C0 must be between 1.42 and 4.55 µg/ml for the AUC to be within the therapeutic range. It was shown that the correlation between C0 and AUC improves after three months post-transplantation and is even better when administering mycophenolate mofetil. **Conclusion:** The use of C0 is recommended to adjust the dose of MPA in pediatric patients with KT, especially in those with more than 3 months post-transplantation. For patients with early KT or complex clinical pictures, monitoring using ABC is recommended.

Keywords:
Mycophenolic Acid;
Kidney Transplantation;
Pharmacokinetics;
Area Under the Curve

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Introduction

The success of renal transplantation (RT) depends largely on immunosuppressive drug therapy, which seeks to prevent rejection of the transplanted kidney. Among the drugs used mycophenolic acid (MPA), is an ~~enzyme~~ inhibitor of inosine monophosphate dehydrogenase (IMPDH) enzyme which produce cell cycle arrest[1].

MPA has complex pharmacokinetics with large intra- and inter-patient variability[2]. These characteristics involve the use of therapeutic drug monitoring (TDM), which is the periodic measurement of plasma levels of MPA, that correlates with the patient's immunosuppressive therapy status and objectives[3] acting as a tool for evaluating the efficacy and safety of the drug.

In pediatric patients, it is recommended to perform TDM for MPA dose adjustment, since they are considered as a high immunological risk group[4]. One method of doing this is through the measurement of the Area Under the Curve (AUC), which is a pharmacokinetic parameter that reflects numerically the total exposure of a patient to a drug, being recommended for MPA monitoring[5]. The implementation of the $AUC_{0\text{-}12h}$ of MPA, as a routine test in clinical practice is not applicable due to the large number of blood samples required in a 12-hour period after drug administration[1,6,7], along with the need for a transient hospitalization for the patient.

Therefore, alternative methods are used to perform TDM, such as the use of the basal or trough level (C0, plasma concentration of a drug before the administration of the next dose). In general, C0 has a good correlation with AUC and therefore empirically it would be a good parameter to represent drug exposure. However, for MPA, a low correlation between C0 and AUC has been described, so the real clinical usefulness of the C0 measurement of MPA is not clear[8]. For this reason, the use of the abbreviated AUC has emerged as a possible alternative. This abbreviated curve is characterized by requiring a smaller number of samples and has shown an excellent correlations with the AUC calculated in the traditional moder[6]. Therefore, the traditional curve could be replaced by the abbreviated curve, making its implementation applicable in clinical routine.

MPA is used as part of a steroid-free protocol applied to pediatric patients with RT in our Hospital. The standard dose used in these patients is 800 mg/m^2 during the first month, 600 mg/m^2 at the second month, and 400 mg/m^2 at the third month[9,10] and monitoring C0 as a parameter for dose adjustment, with therapeutic range values between 1.4 and 4 µg/ml for trough MPA plasma concentration.

The objective of this study was to evaluate the usefulness of C0 as a suitable parameter for monitoring MPA therapy, implement an abbreviated ABC for MPA, and evaluate the correlation between C0 and AUC of the drug.

Patients and Method

Patients and Ethics

This study was approved by the Ethics Committee for Research in Humans of the University of Chile (May 2017) and the Dr. Luis Calvo Mackenna Hospital. Fifty-four children with RT were recruited between 2017 and 2019, whose parents or legal guardians voluntarily signed informed consent and, in children older than 8 years, signed the informed assent. Patients with MPA immunosuppressive therapy were included and those using cyclosporine or azathioprine as immunosuppressants were excluded due to their pharmacokinetic interactions with MPA. The protocol of immunosuppressive therapy for RT in children[9,10] used in our center is described in the Scheme (see scheme).

Design

Observational, longitudinal, prospective and comparative study. Four 2-mL blood samples collected in EDTA tubes at 0 (C0; trough level, before the next dose of MPA) and 1, 2, and 4 hours after MPA dose administration (C1, C2, and C4) were taken to the patients included. Patients were divided into groups according to the time elapsed post-RT (< 3 months and > 3 months), and according to the MPA drug used [mycophenolate mofetil (MMF) and mycophenolate sodium (MS)].

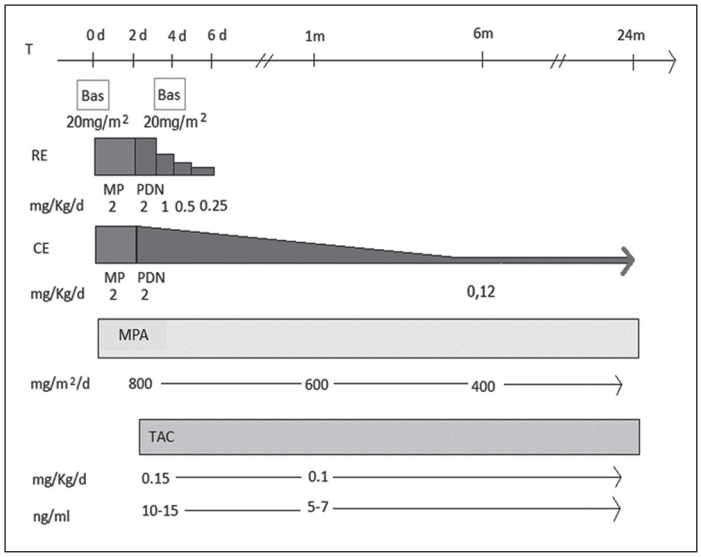
Plasma concentrations measurement

From 200 µl of plasma, the total plasma concentration of MPA in µg/ml was quantified by liquid-liquid extraction and using carbamazepine 20 µg/ml (Sigma Aldrich, MO, USA) as internal standard. Separation and chromatographic analysis were performed by injecting 20 µl on a Brownlee SPP C18 column (2.7um: 4.6 x 30 mm, Perkin Elmer, USA) with acetate buffer (20 mM pH 4.7) - acetonitrile (Sigma Aldrich, MO, USA) mobile phase. High-Performance Liquid Chromatography equipment (1260 Infinity system, Agilent Technologies, CA, USA) and a Diode-Array Detector (DAD) at a wavelength of 214 nm was used.

For the calculation of $AUC_{0\text{-}12h}$ of MPA, the abbreviated AUC formula[6] was used:

$AUC_{0\text{-}12h}$ MPA = $8.217 + 3.163*C_0 + 0.994*C_1 + 1.334*C_2 + 4.183*C_4$.

For the analysis and statistics, the MPA therapeutic ranges of C0 between 1.4 - 4.0 µg/ml and AUC between 30 - 60 µg*h/ml were considered.



Scheme. Immunosuppressive protocol for RT. T: time; d: days; m: months; Bas: Basiliximab; RE: early steroid withdrawal; CE: with steroids; MP: methylprednisolone, PDN: prednisone, MPA: mycophenolic acid, TAC: tacrolimus.

Statistical analysis

The correlation between levels C0, C1, C2, and C4 versus AUC was analyzed by linear regression, with the straight-line equation and Pearson's coefficient (r^2). For statistical analysis of one variable between two groups, the Student's t-test was used and for group analyses with more than one variable, the multivariate test (two-way ANOVA) was selected. The statistical results and graphs were obtained using GraphPad V7.0 software. A p-value < 0.05 and a 95% confidence interval (CI) were considered statistically significant.

Results

Cohort demographics

Fifty-four children with RT were included, with a mean age of 9 years, highlighting pathologies of structural type as main diagnosis. Plasma creatinine levels remained in normal range in all patients during the study period (table 1).

Kinetics and correlation between C0 and AUC of MPA

All patients had an oral administration-associated to MPA pharmacokinetic,with an average C0 value of 2.66 µg/ml, achieving the peak concentration of 8.36 µg/ml at 2 hours after drug administration (C2) and an average AUC of 41.92 µg*h/ml (figure 1 A). The correlation between AUC and C0 was $r^2 = 0.52$ ($r = 0.72$), being the best correlation between AUC and each of the measured levels (figure 1 B-E).

Regarding the therapeutic ranges for AUC, of the total measurements, 54.93% (39/71) were outside the therapeutic range, classifying 36.6% as subtherapeutic and 18.31% (13/71) as supratherapeutic. Likewise for C0 level, 57.74% (41/71) were outside the therapeutic range, with 43.6% classified as subtherapeutic (31/71) and 14.08% (10/71) as supratherapeutic. When considering only patients with a subtherapeutic C0, i.e., < 1.4 µg/ml, 71% (22/31) of them also had a subtherapeutic AUC and only 29% (9/31) had an AUC within the therapeutic range for MPA. Similarly, when considering patients with a supratherapeutic C0, i.e., > 4 µg/ml, 54.54% (6/11) also presented a supratherapeutic AUC and 45.45% (5/11) presented an AUC within the therapeutic range.

Post-transplantation time and its influence on MPA kinetics

Considering the MPA dose adjustment during the first three months post-transplantation, the correlations of C0 with AUC according to time post-transplantation were analyzed.

The measurements of patients with >3 months post-transplant (25/71) presented a correlation ($r^2 = 0.73$) between AUC and C0 of MPA higher than presented by the group with < 3 months post-transplant ($r^2 = 0.45$) (Figure 2 A-B). Mostly, the measurements performed in the group with < 3 months post-transplantation presented a greater dispersion in the data and no statistical differences were observed in the AUC achieved between the two groups (figure 2 C).

Kinetic differences between mycophenolate mofetil and mycophenolate sodium

There are two presentations of MPA, mycophenolate sodium (MS) and mycophenolate mofetil (MMF), and both are metabolized to MPA. The patients included in the study used both MS and MMF, which were administered indistinctly considering, among other factors, the patient's tolerance. When analyzing the results obtained from both presentations, it was possible to see that the kinetics of MMF showed an earlier peak (9.26 µg/ml 1 hour after dose) than that of MS (9.08 µg/ml 2 hours after dose) (figure 3 A), and no significant differences were found in the concentrations achieved for both drugs at any of the times analyzed, nor differences in the AUCs reached by both drugs (figure 3 B). However, the correlation between the C0 and AUC of MMF was higher ($r^2 = 0.88$) than MS ($r^2 = 0.51$) (figure 3 C-D).

Discussion

Currently, the success of RT is achieved in part

to the individualized dosing of immunosuppressive drugs, where should be considered and evaluated the constant changes in children and adolescents[11]. Therefore, adjust drug therapy according to the patient's development is crucial as a short- and long-term prevention for graft rejection.

C0 monitoring is a widespread clinical practice in drugs with narrow therapeutic index and is related to therapeutic success and/or drug safety. However, AUC monitoring in children is an uncommon practice. Several abbreviated curves have been described for adults[12-14]. The implementation of the abbreviated AUC with four samples, using the algorithm proposed by Filler 2004 for pediatric patients, allows studying the correlation between C0 and AUC of MPA in this patients. This abbreviated curve with C0, C1, C2, and C4 times points was selected because of the advantage of using the same sampling times as the abbreviated AUC of tacrolimus (TAC)[15,16], therefore making it possible to determine the plasma concentration and AUC of both drugs from a single blood sample.

The level that correlates the best with the AUC of

Table 1. Cohort data of patients studied (n = 54)

Parameter	Value
Demographics	
Gender (Female/Male) (n)	24/30
Mean age (years)	9 [2 - 14]
Weight (kg)	29.30 [10 - 61.4]
Type of renal replacement therapy	
Hemodialysis/ Peritoneum	13/41
Diagnosis (%)	
Structurals	66.6
Glomerulopathies (General)	9.2
Segmental Glomerulosclerosis	9.2
Hereditary	5.5
Vascular	3.7
Others	5.5
Induction treatment	
Thymoglobulin/ Basiliximab (%)	2.2/97.8
Pre-transplant at the beginning/end of the study (n)	23/5
Post-transplant at the beginning/end of the study (n)	31/49
Corticosteroids % (yes/no)	15.9/84.1
Creatinine (mg/dl)	0.77 ± 0.38

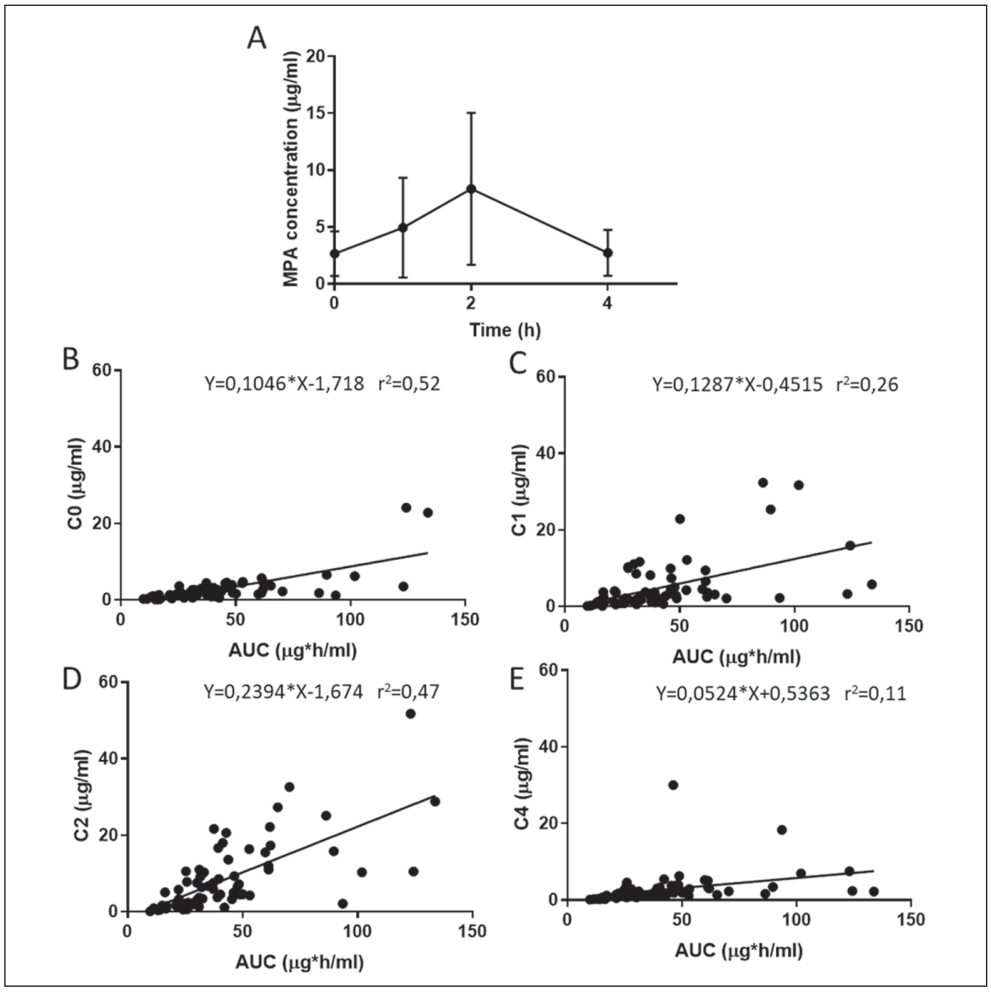


Figure 1. Kinetics of MPA and its correlation between AUC and C0. A) Kinetics of oral MPA plasma concentration over time (mean data +/- SD). B-E) Linear regression and correlation (r2) between AUC and levels C0, C1, C2 and C4. n = 71.

MPA was C0 ($r^2 = 0.52$), which was identical to the r^2 result obtained by Filler 2004, but in their study, the best correlation with the AUC was achieved with the C2 and C4 levels of MPA. This difference could be explained mainly by the fact that in that study, all patients received MMF, which differs from our analysis, where most patients were administered MS (60/71 of the total measurements).

In relation to concomitant immunosuppressive treatment, the study above mentioned applies to patients with TAC due to it has been shown that in healthy volunteers, the administration of this drug does not generate changes in the kinetics of MPA or its). Regarding the use of corticosteroids, there were no differences in the kinetics of MPA, finding similar correlations between C0 and AUC in the patients who had early withdrawal of steroids and patients with prolongeduse of corticosteroids in immunosuppressive therapy (data not shown).

To test the usefulness of the linear regression equation obtained by plotting C0 versus AUC, we interpolated the C0 values necesary to obtain an AUC within the therapeutic range (between 30 and 60 µg*h/ml), obtaining that C0 should be between 1.42 and 4.55 µg/ml. This finding coincides with that used as a reference for C0 (range: 1.4 - 4.0 µg/ml) and confirms that the calculated equation is valid and useful for clinical practice.

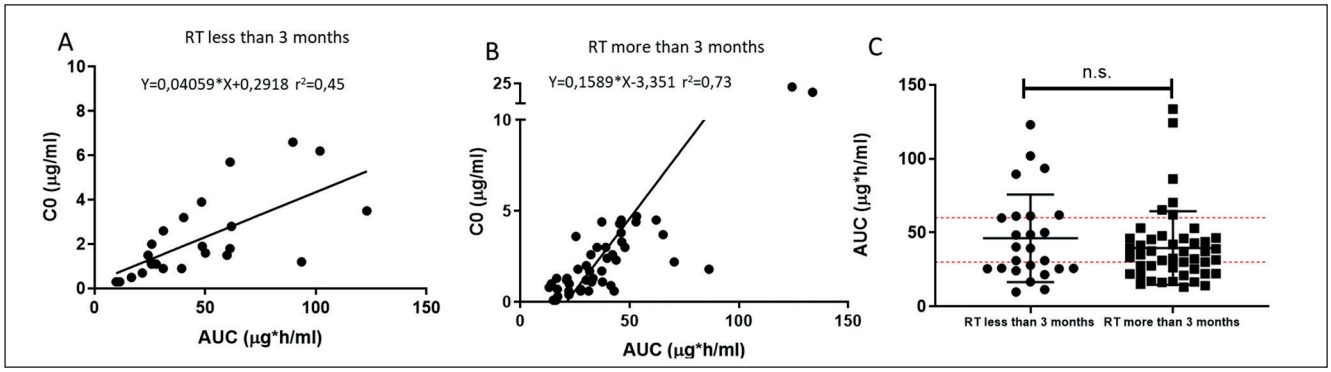


Figure 2. Correlation of C0 and AUC in patients less or more than 3 months post-transplant. A-B) Linear regression between AUC and C0 of MPA in patients who are less (n = 25) or more than 3 months (n = 46) post-transplant. C) Comparison of AUC between patients with less or more than 3 months post transplant.

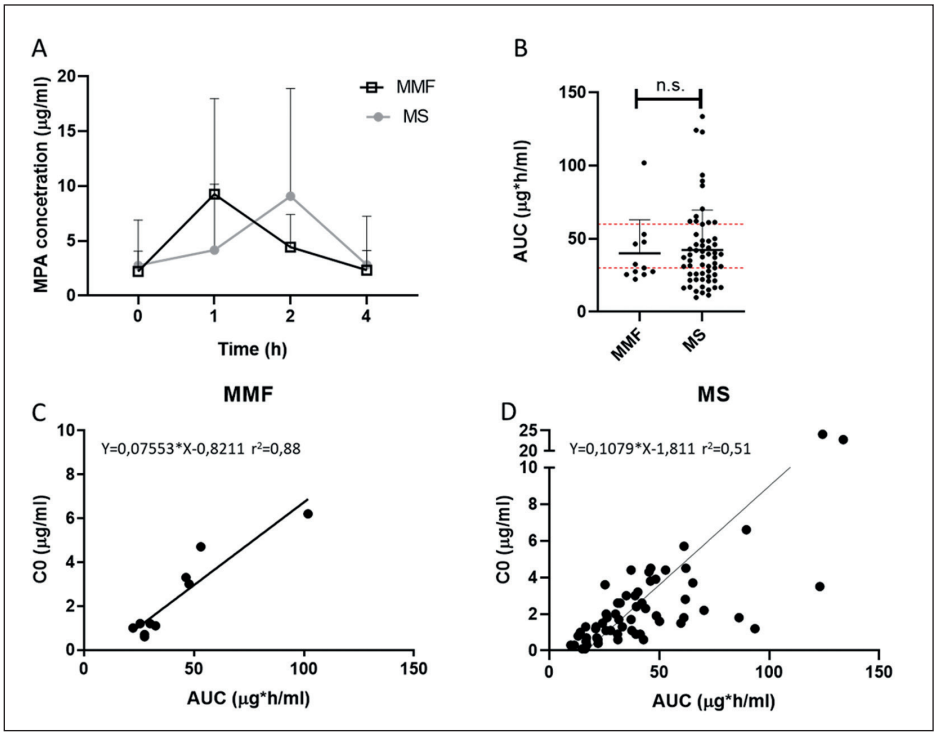


Figure 3. Kinetics and correlation between MPA drugs: mycophenolate mofetil (MMF) and mycophenolate sodium (MS). A) MPA plasma concentration kinetics over time for MMF (n = 11) and MS (n = 60). B) Comparison of MPA AUC values between MMF and MS. C-D) Correlation and linear regression between AUC and C0 of MMF and MS.

Subtherapeutic MPA levels are related to episodes of acute graft). In the group studied, 36.6% of the levels would be classified as subtherapeutic for AUC and 43.66% subtherapeutic for C0, despite receiving MPA doses adjusted according to body surface area, this could suggests that there are other factors associated with drug metabolization that may influence the plasma levels of the patients.

In this study, the age of the patients included was widely heterogeneous (between 2 and 14 years). It has been reported that enzymatic, metabolic, and hormonal development, among others, depends on the stage of growth of the children and can affect drug pharmacokinetics in different ways[19]. Hepatic metabolism of drugs and their clearance is age-dependent[20] and would be increased in children under 10 years of age[20].

Regarding glomerular filtration rate (GFR), it increases rapidly during the first two weeks of life and then increases steadily until adult values are reached between 8 and 12 months of age[21]. As the cohort of patients recruited was at least 2 years old, the influence of immature renal clearance processes would be low and the influence of metabolic processes on plasma MPA levels would be more important. In our experience, no patient had impaired renal function or leukopenia, and creatinine levels remained within the normal range throughout the study period, with no significant statistical differences found when comparing C0 and AUC levels achieved between children younger and older than 5 years (data not shown).

Interindividual variability associated with pharmacogenetic factors including SNPs in the UGTs enzyme, an enzyme responsible for the main metabolizing pathways of this drug, has been documented for MPA. It has been proposed that the combination of polymorphisms in the UGT1A9, UGT2B7, and MRP2 (ABCC2) isoforms may be important predictors of interindividual variability of MPA in the pediatric population[22,23]. Results in pediatric patients seen in our center have shown that carriers of the *UGT1A9-275A* variant allele had a lower $AUC_{0\text{-}12h}$/dose MPA than patients carrying only the *UGT1A9-275T* ancestral allele genotype with a marginal difference of statistical significance ($p = 0.05$)[24]. These results suggest that patients carrying that polymorphism may have lower C0 and AUC levels of MPA than expected and therefore require higher doses than those standardized per body surface area.

In the post-transplant period, the doses of immunosuppressants decrease and dose escalation are performed monthly. Accordingly, it was found that after 3 months post-transplant, the correlation between AUC and C0 improves, which is possibly due to the dosage and stable plasma levels of the immunosuppressants. Considering our results and the feasibility of measuring C0 compared with AUC, in outpatients it would be convenient to measure only the C0 level. On the contrary, before three months post-transplantation, AUC would be more appropriate to monitor MPA.

Another factor that could influence plasma levels and the correlation between C0 and AUC of MPA is the administration of MMF or MS drugs. MMF is characterized by its rapid absorption at the gastric level, while MS releases MPA in the small intestine[25-27]. Differences between MMF and MS have been reported, mainly because the pharmacokinetics of MPA when MS is administered is extremely variable and unpredictable compared with MMF administration in patients with stable RT[28]. Although the correlation between AUC and C0 is better with MMF, there were no significant differences in plasma levels or AUC of MPA achieved when comparing the two drugs. The main difference found was that the peak level was achieved earlier with MMF, which is explained by the earlier absorption of this drug in the gastrointestinal tract when compared with the delayed absorption of the coated MS. In our cohort, it was determined that the peak concentration was reached at the C2 point, mainly because most of the patients were administered MS over MMF due to the known gastrointestinal adverse reactions of MMF.

In conclusion, the use of drug monitoring for MPA is complex in pediatric patients with RT.The implementation of an abbreviated AUC proved to be adequate as a response to these problems, being the ideal parameter for monitoring the drug during the first 3 months post-RT. The trough C0 level was characterized by having the best correlation with the AUC and was more useful and convenient for adjusting the dose of immunosuppressive therapy in pediatric patients with RT greater than 3 months.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This docu-

ment is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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