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The Association Between the Serum Levels of Generic Tacrolimus (Framebin) in Acute Renal Graft Dysfunction

Delgado-Lara Daniela Lucero del Carmen[1], Cerrillos-Gutiérrez José Ignacio[2], Hernández-Sánchez Gerardo[1], Rodríguez-Razón Christian[1], Rojas-Campos Enrique[3], Miranda-Díaz Alejandra Guillermina[1, *]

[1]Institute of Experimental and Clinical Therapeutics, University of Guadalajara, Guadalajara, Mexico
[2]Department of Nephrology and Transplants, IMSS, Guadalajara, Mexico
[3]Kidney Diseases Medical Research Unit, IMSS, Guadalajara, Mexico

Email address

kindalex1@outlook.com (Miranda-Díaz A. G.)

[*]Corresponding author

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Abstract: Background. There is always the possibility of acute renal graft dysfunction (AGD) after renal transplantation (RT). AGD is suspected because of a decrease in urine volume, an increase in baseline serum creatinine (SCr) or proteinuria. Tacrolimus (TAC) is a calcineurin inhibitor (CI) with immunosuppressive function. Aim. To analyze the association between serum levels of generic TAC (Framebín) with the presence of renal AGD. Material and methods. An analytical cross-sectional study included 41 patients with AGD and 41 without AGD (N-AGD) who were managed with a generic TAC. The post-transplant follow-up was <1 year. TAC levels were determined by EMIT 2000, 12 h after ingestion of the medication. The AGD or N-AGD was confirmed by percutaneous renal biopsy. Results. The serum levels of TAC were found increased in all patients. The TAC levels in the AGD was 16.5±11.8 ng/mL *vs*. N-AGD, 11.6±7.7 ng/mL (p=0.029). When adjusting the TAC levels according to the post-transplant month, no significant difference was found between the two groups (p=0.265). There was a low positive correlation between TAC levels and the SCr levels on the day of measurement (r=0.24, p=0.027). The logistic regression analysis associated the AGD with higher body weight of the patients (OR=1043, 95% CI 1.000-1.088, p=0.050). Having more months after transplant was a protective factor for not presenting AGD (OR=0.763, 95% CI 0.647-0.900, p=0.001). TAC levels were not associated with AGD. In patients with AGD, renal biopsy reported 34% acute rejection (AR) and 64% CI toxicity. The histological result of N-AGD patients reported; 76%, normal biopsy, 12% AR and 12% CI toxicity. Conclusions. Serum TAC levels were found to be increased in all patients without correlation with renal biopsy. Determining TAC levels was not a good marker to detect AGD. The increase in body weight seems to increase the possibility of presenting AGD.

Keywords: Kidney Transplantation, Generic Tacrolimus, Acute Graft Dysfunction, Renal Rejection, Calcineurin Inhibitor Poisoning

1. Introduction

Renal transplantation (RT) is the treatment of choice for patients with terminal chronic renal failure (ESRD). The RT offers clear advantages in relation to other forms of renal replacement therapy (RRT) in quality of life and in reintegration to the productive life of patients [1]. After RT, immunosuppressive therapy is required to preserve graft function, prevent and control the recipient's immune response against the transplanted organ, increase graft survival, and improve the quality of life of the recipient [2]. After RT, there is the possibility of acute graft dysfunction (AGD), with

the potential loss of the transplanted organ. AGD is suspected due to a marked decrease in urinary volume and an increase in baseline serum creatinine (SCr) levels of 15-25%. Among the causes that favor the appearance of AGD are; acute tubular necrosis, acute rejection (AR) and nephrotoxicity caused by calcineurin inhibitors (CI), among other causes. Tacrolimus (TAC) is used as immunosuppressive therapy in RT. CI forms a complex with the FK binding protein of immunophilin [3]. This complex strongly inhibits the activity of calcineurin phosphatase, the expression of interleukin 2, the secretion of cytokines, preventing allograft rejection [4]. TAC has wide variability in absorption, metabolism and pharmacokinetics among transplant patients [5]. The maximum area under the curve (AUC) of the TAC is almost four times greater than the minimum AUC after the first oral dose, which makes that TAC possess a narrow therapeutic index. The sub-dose of TAC favors the rejection of the graft and the overdose can result in nephrotoxicity. Therefore, it is essential to monitor the concentration of TAC in whole blood [6]. The proposed initial dose of TAC is ~0.15-0.30 mg/kg per day orally twice a day. The dose of TACT in adults receiving RT is recommended 1 h before or 2 h after meals [7]. The recommended goal depends on the blood concentration of TAC. For the first month, RT recipients are recommended to receive 12-15 ng/mL, the second month of 8-12 ng/mL, 6-10 ng/mL for the third month and 5-10 ng/mL as a sustained concentration after the third month [8]. The immunosuppressant treatment is complemented with the administration of mycophenolate mofetil (2 g/day) and prednisone (1 mg / kg/day) [9]. When the TAC patent expires as the recommended immunosuppressant (Prograf®), the administration of the generic immunosuppressant becomes possible, although the results have been controversial [10].

The aim of the study was to analyze the association between the serum levels of generic TAC (Framebín) with the presence of renal AGD.

2. Material and Methods

An analytical cross-sectional study included patients who received a TR with a follow-up of <1 year, aged >16 and <50 years, managed with a generic TAC, attended in the Department of Nephrology of the Transplant Division of the High Specialty Medical Unit. (UMAE) of the CMNO of the Mexican Institute of Social Security (IMSS) in Guadalajara, Jalisco (Mexico) that met the inclusion criteria. Patients underwent RT from a living donor (related / unrelated), who agreed to participate in the study and who signed the Consent Under Information. Renal function was measured in all patients from the formula published by the CKD-EPI [11]. Two study groups were formed; 41 patients with AGD characterized by elevated baseline SCr levels, >25% without identified cause or proteinuria, not previously reported [12]. Patients with AGD underwent an indicated percutaneous renal biopsy. 41 other N-AGD patients (without AGD) who attended the outpatient follow-up without presenting elevation of the basal levels of SCr who underwent a protocolized renal biopsy were included. The protocolized renal biopsy was used to detect early chronic graft nephropathy [13].

According to the result of the percutaneous renal biopsy. The result were sub classified into normal biopsy, AR or nephrotoxicity due to TAC. All patients underwent fasting blood sampling by venipuncture 12 h after the last TAC scan to determine the blood concentration according to the recommended levels even the month of follow-up. The blood levels of TAC were sub classified in high, normal or low, according to what was recommended by the clinical practice guide of CENETEC in the immunosuppressive therapy in RT. The recommends maintaining the levels during the first month after transplantation between 10-15 ng/mL, until the third month between 10-12 ng/mL, from the fourth to the sixth month between 8-10 ng/mL, from the seventh to the twelfth month between 6-10 ng/mL. Starting from the year, TAC levels should be maintained between 6-8 ng/mL [14].

2.1. Total Blood TAC Levels

TAC levels were determined by the Emit ® 2000 Syva® from Siemens Health Care Diagnostics Inc, USA. The method is characterized by being a homogeneous enzyme immunoassay containing high specificity mouse monoclonal antibodies for TAC. The TAC of the sample competes with the TAC of the recombinant enzyme glucose-6-phosphate dehydrogenase (G6PDHr). The unbound active G6PDHr converts the oxidized form of nicotinamide adenine dinucleotide (NAD) into the antibody reagent to reduced nicotinamide adenine dinucleotide (NADH), which results in a kinetic change in absorbance capable of being measured by spectrophotometry. The activity of the enzyme decreases proportionally to the binding with the antibody. The TAC concentration of the sample is measured in terms of enzymatic activity. The endogenous serum G6PDHr does not interfere with the assay since the coenzyme NAD works only with the bacterial enzyme (*Leuconostoc mesenteroides*).

2.2. Pretreatment of the Sample

Before the TAC Emit® 2000 Syva® test from Siemens®, pretreatment of the whole blood samples was performed. The calibrators and controls were treated with methanol and cupric sulfate. By the method the cells were lysed, the TAC was extracted and most of the plasma proteins were precipitated. The pre-treated samples were centrifuged and aliquots of the resulting supernatant containing TAC were taken and analyzed with the TAC Emit® 2000 assay. The calibrators, controls and samples were mixed slightly before being used. 200 µL of each calibrator, control and / or sample were transferred to appropriately labeled micro-centrifuge tubes, 200 µL of methanol was added to each tube, then 50 µL of the pre-treated sample (cupric sulfate) was added to each tube and they covered immediately. Each tube was vortexed for at least 10 seconds and incubated at room temperature (18-25°C) minimum for one minute. The sample was centrifuged for two minutes, the supernatant of the tubes

was decanted and the samples were analyzed with the Viva-E® equipment for the detection of drugs and drugs of abuse.

2.3. Statistic Analysis

Quantitative data are presented as mean ± standard deviation (SD) and qualitative as frequencies and percentages. The Kolmogorov-Smirnov goodness of fit test was performed to determine the distribution of the data. The numerical comparisons were analyzed with the Mann-Whitney U test for independent samples. The nominal comparisons were made with the Chi^2 test. The correlation analysis (Spearman) was carried out to determine the strength of association between the serum levels of TAC and the quantitative variables. Logistic regression analysis was performed to determine the influence of the TAC levels in the presence of AGD adjusted by the potential confusing variables. To construct the final model, the dependent variable was AGD. The variables included in the model were variables with value of $p \leq 0.20$ in the univariate analysis or those with biological plausibility of association with proteinuria. The Enter method was used to review the significant association of the variables introduced in the model and the "Forward stepwise" method for the results of the adjusted model. In the final model, an adjusted odds ratio (OR) was performed with a 95% confidence interval (representing the risk conferred by these variables for AGD). The adjusted analysis with OR >1 was considered a risk factor for AGD, while the OR <1 was considered as a protective factor for the appearance of AGD post-transplant, only if the 95% range did not include the value of 1. Any value of $p \leq 0.05$ was considered statistically significant. The SPSS program (version 22) was used for the statistical analysis.

2.4. Ethical Aspects

The study complies with the international standards for conducting research in humans according to the Declaration of Helsinki 64th General Assembly, Fortaleza, Brazil of October 2013, the Belmont Report and the Good Clinical Practice Standards of the International Conference of Harmonization. Corresponds to a study in category III (risk greater than the minimum) in accordance with the provisions of the General Health Law of Mexico in the field of health research, title 2, of the ethical aspects of research in humans, chapter l, and article 17. The nature, purposes and potential risks of the study were explained to each participant so that they gave their Consent Under Information with the signature of witnesses. The project was approved by the Ethics and Research Committee of the National Medical Center of the West, of the IMSS, with registration R-2016-1301-101.

3. Results

One hundred and one patients receiving RT <1 year and were interviewed. We excluded 19 from the study, three for insufficient renal histological sample and 16 for lack of complete data. Eighty-two patients were included, 41 with AGD and 41 N-AGD. Table 1 shows the clinical and demographic characteristics of all patients. No significant difference was found in age, body mass index (BMI) and arterial hypertension. The average age was 27 years, the body weight was significantly higher (~7 kg) in AGD (p=0.017). The RT recipients were predominantly men, 27% of the N-AGD renal recipients were female (p=0.046).

Table 1. *Clinical and demographic characteristics of patients with AGD and n-AGD.*

	AGD n=41	n-AGD n=41	*p*
Age (years) *	26.1 ± 5.8	27.5 ± 8.3	0.766
Gender, n (%)[I]			
Male	37 (90)	30 (73)	0.046
Female	4 (10)	11 (27)	
Weigh (kg)*	69.5 ± 12	62.1 ± 13.8	0.017
BMI n (%)[I]			
Severe malnutrition	1 (3)	1 (3)	
Moderate malnutrition	0	2 (6)	
Mild malnutrition	1 (3)	1 (3)	0.685
Normal	31 (73)	31 (74)	
Overweigh	5 (13)	5 (11)	
Obesity l	3 (8)	1 (3)	
Hipertention n (%)[I]	12 (29)	5 (13)	0.092

Mean ± Standard desviation, *p= Mann-Whithney U test, [I]p= χ^2 BMI: Body mass index, AGD: Acute graft disfunction, N-AGD: Without acute graft disfunction

The patients included were homogenous in relation to the clinical characteristics. Only patients with AGD had significantly greater body weight and a lower proportion of women RT recipients.

3.1. Clinical Characteristics Before and After the RT

The results before the RT were similar in all the patients included the time of evolution of the chronic terminal renal failure, time of hot / cold ischemia. The cold ischemia time was <60 min. More than 50% of the patients were in the peritoneal dialysis (PD) program. The histocompatibility in the majority of patients shared more than two antigens. AGD was detected during the first 6 months in 79% of patients. The N-AGD patients had good function even in the eleventh month of follow-up after RT (p=0.0001). In AGD, the usual SCr levels were 1.2 mg/dL and 1.1 mg/dL in N-AGD (p=0.032). The SCr on the day of measurement was found to be increased >0.8 mg/dL in AGD and served as an indicator for percutaneous renal biopsy (p=0.0001). Renal function after transplantation was evaluated mainly by measuring the SCr. No significant difference was found between the administered dose of TAC in relation to the body weight of the patients (AGD, 0.08±0.04 mg/Kg/day and N-AGD, 0.08±0.03 mg/Kg/day (p=0.772). The 66% of the patients with AGD and 31% N-AGD ingested other drugs with the ability to interact with TAC; of these, >65% of patients received Trimethoprim + Sulfamethazole and Omeprazole

(p=0.005). The levels of TAC were significantly higher in patients with AGD, 16.5±11.8 ng/mL than N-AGD, 11.6±7.7 ng/mL (p=0.029). TAC levels were sub-classified as high, normal or low, as recommended by the CENETEC guidelines. Fifty-nine percent of the patients with AGD and 44% of the N-AGD had increased levels of TAC, which could mean toxicity. The method to diagnose TAC toxicity or the presence of AR depended on the histological report of the graft biopsy. All patients underwent renal biopsy indicated or protocolized according to the AGD or N-AGD. Table 2

Table 2. *Characteristics of groups before and after renal transplantation.*

	AGD	No-AGD	*p*
RRT n (%)[I]			
PD	21 (51)	22 (53)	
HD	19 (47)	18 (44)	0.742
Without RRT	1 (2)	1 (3)	
Evolution time of chronic kidney disease (years)*	3.8 ± 3.6	4.8 ± 3.3	0.187
Ischemia time (minutes)*			
Hot (minutes)	3.8 ± 5.2	4.8 ± 11.3	0.244
Cold (minutes)	60 ± 32.1	42.8 ± 20.2	0.080
Histocompatibility (antigens) n (%)[I]			
0	6 (15)	1 (3)	
2	14 (34)	18 (43)	
4	20 (49)	16 (40)	0.516
6	1 (2)	5 (11)	
8	0	1 (3)	
Months after transplant n (%)[I]			
1-3	18 (46)	9 (18)	
4-6	14 (33)	12 (26)	0.0001
7-11	9 (21)	20 (56)	
Creatinin (mg/dL)*			
Habitual	1.2 ± 0.2	1.1 ± 0.3	0.032
Measurament day	1.8 ± 0.6	1.0 ± 0.3	0.0001
TAC dose / weigh (mg/kg/día)*	0.08 ± 0.04	0.08 ± 0.03	0.772
Interaction with drugs n (%)[I]			
Ye	27 (66)	13 (31)	
No	9 (22)	22 (54)	0.005
Medications are Unknown	5 (12)	6 (15)	
Pharmacological interaction n (%)[I]			
TMP + SMX	13 (48)	0	
Omeprazole	2 (7)	6 (46)	
TMP-SMX-Omeprazole	3 (11)	3 (23)	
Nifedipine	4 (15)	2 (15)	0.005
Losartan	2 (7)	1 (8)	
Verapamil	1 (4)	1 (8)	
Amlodipino	1 (4)	0	
Amlodipino – losartan	1 (4)	0	
TAC level (ng/mL)*	16.5 ± 11.8	11.6 ± 7.7	0.029
TAC level n (%)[I]			
Low	10 (24)	10 (24)	
Normal	7 (17)	13 (32)	0.265
High	24 (59)	18 (44)	
Renal biopsy result n (%)[I]			
Rejection	14 (34)	5 (12)	
Normal	1 (2)	31 (76)	0.0001
Toxicity	26 (64)	5 (12)	

Mean ± Standard deviation, *p= Mann-Whitney U test, [I]p= χ^2 RT: Renal transplant, AGD: Acute graft dysfunction, No-AGD: Without acute graft dysfunction. RRT: Renal replacement therapy, PD: Peritoneal dialysis, HD: Hemodialysis, CKD: Chronic kidney disease, TAC: Tacrolimus, TMP + SMX: Trimethoprim + Sulfamethoxazole.

All patients were similar before the RT. There were differences between the patients in the months after the RT, in the normal SCr and on the day of the measurement, in the presence of pharmacological interactions in the serum levels of TAC and in the result of the indicated or protocolized renal biopsy.

3.2. Kidney Biopsy

The result of the renal biopsy in AGD reported 34% of AR and 64% TAC toxicity. In one patient, the histological report was normal (high levels of TAC). In the N-AGD patients the histological report found 76% normal biopsy, 12% AR and

12% TAC toxicity. Table 3 shows the TAC levels (high, normal or low) according to the month of RT.

Table 3. *TAC Levels in relation to the result of renal biopsy.*

Result of renal biopsy	AGD	N-AGD	*p*
Rejection n (%)[I]			
Low levels	4 (29)	1 (20)	
Normal levels	2 (14)	2 (40)	
High levels	8 (57)	2 (40)	
Normal n (%)[I]			
Low levels	0	8 (26)	
Normal levels	0	9 (29)	0.265
High levels	1 (100)	14 (45)	
Toxicity n (%)[I]			
Low levels	6 (23)	1 (20)	
Normal levels	5 (19)	2 (40)	
High levels	15 (58)	2 (40)	

Frequency (%), [I]p= χ^2

The majority of patients presented high levels of TAC.

When the renal biopsy report was normal in N-AGD (the levels of TAC in 45% were increased), in 29% normal levels and in 26% low levels. In 57% of patients with AGD and 40% N-AGD with histological report of AR, we found increased levels of TAC. In 23% of patients with AGD and 20% N-AGD, the histological report showed toxicity for TAC with decreased levels. Table 4 shows positive correlation between SCr levels on the day of measurement (defined AGD or N-AGD), the body weight (rs=0.42, *p*=0.0001) and with the usual SCr (r_s=0.62, *p*=0.0001). There was a low positive correlation with TAC levels (r_s=0.24, *p*=0.027).

Table 4. *Clinical data correlated with the scr levels of measurement day.*

	r_s	*p*
Age (years)	0.24	0.833
Weigh (kg)	0.42	0.0001
BMI (kg/m^2)	0.21	0.063
Time evolution of CKD (years)	-0.16	0.153
Hot Ischemia (min)	0.01	0.919
Cold Ischemia (min)	-0.03	0.818
Histocompatibility	-0.05	0.643
Time after transplant (months)	-0.20	0.062
Serum creatinin (habitual) (mg/dL)	0.62	0.0001
TAC dose / weigh (mg/kg/day)	-0.07	0.512
TAC level (ng/mL)*	0.24	0.027

The Spearman rho was used to compute the correlations between data. BMI: Body mass index

Only weight, usual serum creatinine and TAC levels were correlated with serum creatinine on the day of measurement

Table 5 presents the logistic regression analysis where the factors associated with the presence of AGD. Age, gender, weight, arterial hypertension, post-transplant months and TAC levels were measured. In the "Forward" step it was observed that the higher body weight, higher the risk of AGD (OR=1.043, 95% CI 1.000-1.088, *p*=0.05) and longer time after transplantation; lower probability of developing AGD (OR=0.76), 95% CI 0.647-0.900, *p*=0.001). In contrast, the TAC levels were not related to AGD.

Table 5. *Logistic regression analysis evaluating factors associated with presence of acute graft dysfunction (agd) in renal transplant patients.*

	Enter method			Forward Stepwise method		
Predictor criterion	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	0.978	0.893-1.071	0.631	Not in the model	-	-
Gender	1.621	0.359-7.309	0.530	Not in the model	-	-
Male						
Weigh	1.035	0.986 – 1.086	0.171	1.043	1.000 – 1.088	0.050
Arterial hypertention	0.530	0.140 – 2.007	0.350	Not in the model	-	-
Months after transplant	0.787	0.663 – 0.934	0.006	0.763	0.647 - 0.900	0.001
TAC levels	1.047	0.980 – 1.119	0.175	Not in the model	-	-

OR: Odds-ratio; 95% IC, Confidential Intervals; HTA: Arterial hypertension; TAC: Tacrolimus.

The dependent data was the presence of acute graft dysfunction (SCr >25%). Included in this analysis were those data that had a p-value <0.20 in the univariate analysis or those considered with biological plausibility for the development of proteinuria.

4. Discussion

In the present study, predominantly young adults were included. The women were mostly kidney donors and the men were recipients (AGD, 90%, N-AGD, 73%). In 2010, the gender-specific differences observed among organ donors were reported, two thirds of donors were women and one third were men. Of the recipients of organs; two thirds of the recipients were men and one third women, without the authors having clarified the possible medical, psychosocial or cultural reasons in relation to the distribution by gender for the RT of living donor related [15].

It is striking that patients undergoing RT are at high risk for development of overweight and obesity. The increase in body weight is a condition that favors the appearance of changes in lipid and glucose metabolism conditioned primarily by the administration of immunosuppressive therapy and by the increase in food intake that are allowed after the RT [16]. Weight gain after RT is considered a risk factor for poor results because the increase in weight favors oxidative stress that is associated not only with CKD and with RT, but also with obesity and cardiovascular disease. It is essential to incorporate early clinical prevention strategies to reduce oxidative stress in this kind of patients [17].

The detection and early intervention of renal AGD continues to be a key challenge for nephrologists. Changes in the levels of SCr and proteinuria often occur late in the progression of the disease and may incorrectly represent the accuracy of the underlying kidney damage. The fundamental aspect to preserve the adequate function of the renal graft is probably based on distinguishing between the immunological or toxic changes that occur in patients undergoing RT. The early identification of renal deterioration can condition early changes in immunosuppressive therapy [18]. In this paper, the renal function after transplantation was evaluated mainly by measuring the SCr and renal biopsy. However, it must be considered that the levels of SCr in the post-transplant increase late in the lesion and are not specific for the type of injury. The SCr are not able to predict or determine the progression of the chronic lesion, which means that the SCr determination is neither specific nor predictive [19].

The renal biopsy is considered the gold standard for the evaluation of the transplant. Nevertheless, the renal biopsy has several disadvantages. Renal biopsy it is not useful to control the progression of the lesion because it is an invasive method, serial biopsies cannot be performed, the procedure is not completely free of complications, in addition, there could has problems and biases in the evaluation of the sample [20]. The predictive power of renal biopsy is poor. In the clinical trial of National Institutes of Health (NIH) "*Immunosuppression without steroids vs. steroids in pediatric RT"* (SNSO1): kidney biopsies were not able to measure "hidden" tissue injury in clinically stable patients [21]. In a study reported by Naesens, et. al., the authors used renal biopsies of protocol and reported that the molecular examination of the tissue was able to reveal anomalies of the innate and adoptive immune response long before the abnormalities appear at the histological level [22]. Therefore, the development of predictive and non-invasive biomarkers for early diagnosis and monitoring of any clinical condition after RT is essential for individualized personalized treatment [23]. Among the biomarkers susceptible to analyze that were not performed in the present exploratory study are (proteomics, genomics, transcriptomics and metabolomics) [24]. The appearance of AR is considered one of the main causes of AGD. In Mexico, one out of every six patients receiving RT from a living donor presents an episode of AR in the first year after transplantation [25]. Other specific risk factors for RT receptors that influence the occurrence of AGD are included in the dialysis processes to which patients are subjected before and after the RT [26]. On the other hand, it has been reported in previous publications that the ischemia / reperfusion process contributes early and late to the subsequent loss of the graft by reducing the renal functional mass, graft vascular injury, chronic hypoxia and posterior fibrosis. Ischemia / reperfusion induces renal allograft dysfunction and AR, reducing graft survival [27].

TAC is an immunosuppressive agent widely used to prevent the rejection of allografts after RT, it is an important CI, and it has selective action on T lymphocytes. TAC is essential for its physicochemical properties of the generic formulations. They are essential characteristics of the generic TAC; it must be identical to the original brand formulation, Prograf® (patent) where the AUC and Cmax are significantly higher. The Prograf® brand has demonstrated uniformity of its content as opposed to the content of generic TAC formulations that vary widely. The generic TAC formulations tested are not bioequivalent to Prograf®, suggesting that the use of TAC generics may represent potential risks for transplant patients. The physicochemical characteristics of generic drugs are characterized by slower dissolution and lower solubility, which favors sub-optimal absorption and sub-therapeutic levels in blood, which delays reaching optimal drug concentrations. Therefore, TAC generics show inconsistent therapeutic effects compared to patent TAC [25].

The generic Framebin® is characterized by slower and incomplete dissolution; it releases 24-51% of TAC within 2 h. The solubility of Framebin® at 2 h is 12.6 μg/mL and decreases to 2.3 μg/mL at 24 h. While the solubility of Prograf® is 35.7 μg/mL at 2 h and 29.5 μg/mL at 24 h [28]. Many of the commonly used (generic) innovative drugs mean significant cost savings for the patient or health sector institutions [29]. The above statement justified the use of the generic brand mark Framebin. The substitution of the patent TAC for the generic one is considered an essential component to maintain the integral care of the transplanted patients, especially within the public health systems, where the economic resources are limited and should be distributed in an equitable manner [30]. However, the policies of the institution should minimize the risk of insufficient immunosuppression of patients, until sufficient evidence of strict bioequivalence of the generic to be used has been established [28].

5. Conclusions

Serum generic TAC levels were found to be increased in AGD and N-AGD without correlation with renal biopsy. Determining TAC levels was not a good marker to detect AGD. The increase in body weight seems to increase the possibility of presenting AGD.

The limitations of the study include the low number of patients, and the fact that it is an analytical cross-sectional study. The strength of the study is to offer a small panorama of the behavior of the generic TAC in patients with AGD and N-AGD.

Perspectives

With the results found in this study, we consider it worthwhile to explore the expression of innate and acquired immunity in urine and renal biopsies in patients undergoing renal biopsy with AGD and N-AGD

Conflict of Interest Statement

The authors have no conflict of interests to report.

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