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24-month monitoring to a late conversion from a Calcineurin inhibitor regime to everolimus in kidney transplant recipients

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Abstract

Introduction: Graft survival has remained stable in the long term, without significant increase in recent years. Among the main causes of renal graft loss after the first year are death with functioning kidney graft from cardiovascular, infectious and neoplastic causes, and chronic graft injury for immunological and non-immunological causes. This has been attributed to the chronic use of calcineurin inhibitors (CNI), increased cardiovascular risk, the incidence of certain infections and increased incidence of post-transplant malignancies. Also, reports show the increased frequency of histological lesions related to nephrotoxicity caused by these drugs. The switch from CNI to mTOR inhibitors may decrease some of these effects in the long term. We conducted a retrospective study of conversion to mTOR inhibitors in patients with a CNI-based scheme.

Materials and methods: A retrospective single-center case study was conducted, including renal transplantation patients with more than 6 months of transplantation, who were switched to everolimus, after an abrupt withdrawal of calcineurin inhibitor with a previous biopsy of the renal graft. Patients with evidence in the biopsy of changes of acute rejection, glomerular disease or relapse of acute tubular necrosis were excluded. Similarly, patients with proteinuria over 1 g in 24 hours and patients with clinical acute rejection within 3 months prior to conversion were excluded. A total of 40 patients were included, monitoring of variables such as glomerular filtration rate, proteinuria, lipids, use of antihypertensive drugs and adverse effects was performed after conversion until Day 720.

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Results: The results, after 720 days of monitoring, show an increased glomerular filtration rate in 65% of the patients and a decrease in 30% of them. The proteinuria increased with respect to the pre-conversion values in all the patients, however proteinuria >1 g was present in 6 of the 40 patients after the same monitoring time. Of the 6 patients with proteinuria, 5 patients had more than 5 years of transplantation and moderate to severe interstitial fibrosis in the pre-conversion biopsy, which would be linked to the increase in proteinuria. The incidence of post-conversion acute rejection was 5%. The conversion tolerance was adequate, with a low frequency of adverse events that could lead to discontinuance of therapy.

Conclusion: Late conversion to everolimus in patients with kidney transplant from a CNI-based scheme is safe, improves renal function without a significant increase in the degree of proteinuria, associated with pre-conversion biopsies evidencing no significant degrees of interstitial chronicity. The tolerance to the scheme is appropriate and the frequency of acute rejection was not significantly increased.

Key words: Renal transplantation, Everolimus, Calcineurin inhibitors, Chronic graft nephropathy, Nephrotoxicity (MeSHsource).

Conversión tardía desde un régimen basado en inhibidores de calcineurina a everolimus en receptores de trasplante renal. Seguimiento a 24 meses.

Resumen

Introducción: La sobrevida del injerto renal a largo plazo ha permanecido estable, sin un aumento significativo en los últimos años. Dentro de las causas principales de pérdida de los injertos renales, en el largo plazo, se encuentran la muerte con injerto renal funcional por causas cardiovasculares, infecciosas y neoplásicas, y la lesión crónica del injerto por causas inmunológicas y no inmunológicas. Se ha atribuido al uso crónico de inhibidores de calcineurina (CNI, por su sigla en inglés), al aumento en el riesgo cardiovascular, a la incidencia de algunas infecciones y al aumento en la incidencia de neoplasias postrasplante. Igualmente, reportes en la literatura evidencian el aumento en la frecuencia de lesiones histológicas relacionadas con nefrotoxicidad por estos medicamentos, en la medida que el tiempo de exposición a los mismos aumenta. Se plantea que el cambio a esquemas basados en inhibidores mTOR puede disminuir alguno de estos efectos en el largo plazo. Por lo que se realizó un estudio de casos retrospectivo, de conversión tardía a inhibidores mTOR, en pacientes con esquema a base de CNI.

Materiales y métodos: Se realizó un estudio de casos retrospectivo de centro único, incluyendo pacientes con más de 6 meses de trasplante renal, quienes fueron convertidos a everolimus despues de suspensión abrupta de CNI previa biopsia del injerto renal. Se excluyeron pacientes con evidencia en la biopsia de cambios de rechazo agudo, recaída de enfermedad glomerular o necrosis tubular aguda. Igualmente, se excluyeron pacientes con proteinuria >1 g en 24 horas y pacientes con rechazo agudo clínico en los 3 meses previos a la conversión. Se incluyeron un total de 40 pacientes, se realizó seguimiento posconversión de variables como tasa de filtración glomerular, proteinuria, lípidos, uso de hipotensores y efectos adversos, hasta el día 720 posconversión.

Resultados: Los desenlaces, a 720 días de seguimiento, muestran aumento de la tasa de filtración glomerular en el 65% de los pacientes y en el 30% se presentó disminución. Se presentó aumentó en la proteinuria con respecto a los valores preconversión en todos los pacientes, sin embargo, proteinuria >1 g se presentó en 6 de los 40 pacientes, en el mismo tiempo de seguimiento. De los 6 pacientes con proteinuria 5 tenían más de 5 años de trasplante y fibrosis intersticial moderada a severa en la biopsia preconversión, lo que estaría relacionado con el aumento de la proteinuria. La incidencia de rechazo agudo posconversión fue del 5%. La tolerancia a la conversión fue adecuada, con poca frecuencia de eventos adversos que llevaran a descontinuación de la terapia.

Conclusión: La conversión tardía a everolimus en pacientes con trasplante renal, desde un esquema a base de CNI, es segura, genera mejoría de la función renal sin aumento significativo del grado de proteinuria, asociado a biopsias preconversión que no evidencien grados importantes de cronicidad intersticial. La tolerancia al esquema es adecuada y no se aumentó de forma importante la frecuencia de rechazo agudo.

Palabras clave: Trasplante renal, Everolimus, Inhibidores de calcineurina, Nefropatía crónica del injerto, Nefrotoxicidad (fuente DeCS).

Introduction

Despite advances in immunosuppressive therapy, graft rejection continues to be one of the main causes of its dysfunction and loss. While it is true that the percentage of rejections, especially the acute cellular type, has decreased significantly in relation with the different protocols for immunosuppression historically being used, chronic antibody-mediated rejection and the patient's death with a functioning graft persist as the main causes of late renal graft loss, resulting in an annual loss rate of 3 to 5%[1].

Most late-lost grafts, except those associated with the death of the patient, are attributed to a progressive renal dysfunction related to interstitial fibrosis and tubular atrophy of immunological or non- immunological etiology[2].

CNI have been the main strategy of immunosuppression in kidney transplant recipients from its introduction[1]. The long-term exposure to CNI, cyclosporine A (CsA) and tacrolimus triggers nephrotoxicity which, not only generates the acute deterioration of the glomerular filtration rate (GFR), but also contributes to anatomical lesions, such as interstitial fibrosis and tubular atrophy[2-5].

A kidney-pancreas transplantation study, with protocol biopsies performed annually, demonstrated histological evidence of CsA toxicity in all renal grafts in 10 years[6]. In order to avoid nephrotoxicity problems of CNI in the long term, a variety of strategies have been explored; including the withdrawal of CNI at some point during the post-transplantation monitoring or just minimizing the exposure. Nevertheless, suspension of CNI, even after 12 months, is often associated with acute rejection[7-17].

Because mTOR inhibitors are less nephrotoxic, especially in the absence of CNI, attention has been focused on its use as a replacement of CNI or as a method of reducing the exposure to those[18-21]. Additionally, cardiovascular disease and neoplasia are important, critical aspects during the monitoring of transplants; mTOR inhibitors may be one important strategy to consider in kidney transplants recipients[22,23] since, through its mechanism of action, they may delay progressive arteriosclerotic injuries and avoid the negative impact of the compliance of large vessels, associated with CsA[24-27]; which are, likewise, associated with a reduced incidence of neoplasias[28,29].

Clinical trials evaluating early conversion (first 6 months after transplantation) of CNI to sirolimus or everolimus, as well as different strategies of late substitution, have shown that CNI can be replaced by a scheme based on mTOR inhibitors in combination with mycophenolic acid, maintaining renal graft function stable without compromising effectiveness and safety[30-37].

This article presents clinical data obtained from late conversion of 40 kidney transplant recipients to everolimus, to test graft survival without increasing the risk of adverse events when removing CNI.

Methodology

Study design

This study seeks to determine whether renal transplantation patients, who are subjected to sustained conversion of immunosuppressive therapy based on treatment with everolimus, have graft failure and involvement of renal function. The development of this retrospective case study was implemented openly in a single institution and with the prior consent of the patients who were monitored.

The late conversion scheme was carried out (over 6 months after the transplant to reduce the risk of early acute rejection) by replacing the previous scheme of immunosuppression based on CsA in combination with azathioprine or mycophenolic acid to a scheme based on everolimus in combination with mycophenolic acid in kidney transplant recipients. The behavior of GFR along the 24-month monitoring is compared to the one registered in the time prior to conversion, being this the main outcome of interest in the study.

Likewise, creatinine, proteinuria levels, WBC, HGB and platelets counts; cHDL, cLDL, TC and TG; use of hypolipidemic and antihypertensive drugs are analyzed during post-conversion monitoring. The most important safety outcomes are reported.

Patients

The study was conducted on 40 men and women, over 18 years old, who reported more than 6 months after transplant, but with no time limits for the permanence of the transplant, with a biopsy of the renal graft before conversion, absence of proteinuria in blood >1 g (except in patients with indication of conversion because of the presence of neoplasia). Patients whose graft biopsies showed evidence of acute cellular rejection, glomerular disease or acute tubular necrosis, and patients with a history of acute cellular rejection in the 3 months prior to conversion, were not converted to everolimus. Pregnant women were excluded, and women who were enrolled in the study were invited to use effective contraception methods during monitoring. All the patients included signed informed consent.

The conversion protocol

The patients involved in the study were consulted, and authorized to be converted to everolimus to replace CsA or tacrolimus in combination with mycophenolic acid with 1 g/day or 720 mg/day, simultaneously. The day before conversion the patients received the last dose of CNI and when the conversion protocol started, the dose of everolimus for all patients was 1.5 mg/d. This dose was adjusted according to the concentration in blood of everolimus recorded during Days 4, 6, 14, 30, 60 and 90, in order to reach whole blood levels of between 3 to 8 ng/ml. The adjustment was maintained during the monitoring, but according to levels of everolimus in blood reported for Days 180, 360 and 720.

During pre-conversion stage, as well as on Days 90, 180, 360 and 720, and during the period immediately after conversion, reports from the examination of renal function, blood count, lipids, hypolipidemic and antihypertensive drugs were collected.

Statistical considerations

Given that the GFR is the main result in the study, it was calculated using the Cockcroft-Gault equation.

The sample size was due to the number of patients of whom the researcher was in charge, who were consulted to participate in conversion and subsequent monitoring of their records. Where the effects on the GFR were higher than 2 or 3 standard deviations from the mean, monitoring was suspended on the grounds that it undermined the ethical basis of the case-study. Descriptive analyses were performed using frequency and distributions of proportions for the categorical variables and measures of central tendency, and dispersion for the continuous variables.

The results for conversion days 0, 90, 180, 360 and 720, were compared using Student's t-tests for the difference in means. Although of the 40 monitored patients, 2 presented graft rejection, the Kaplan-Meier graft survival analysis was developed on the initial sample of 50 patients, in which the time was considered until the moment of rejection. All the analyses were two-tailed, for a 0.05 level of significance.

Results

The initial sample included monitoring 50 patients; However, 2 of them died before the first 90 days after conversion. The first death registration in the study is a 42-year-old white man, with a primary deceased-donor transplant, unknown etiology and indication of conversion determined by histological criteria.

The transplantation is performed on the patient when he is 33 years old, and the treatment with mTOR starts at age 37. The transplant age was 5 years. During the monitoring, no acute rejection episodes, suspension of mTOR, or graft loss were evident; community-acquired pneumonia (CAP) was recorded as the only clinically important infection during monitoring. The dose of everolimus supplied to the patient was always 1.5 mg with trough levels of 3.80 on Day 4 of monitoring and 4.69 on Day 60.

The second record of death in the study corresponds to a 43-year-old white woman, with a primary deceased-donor transplant, unknown etiology and indication of conversion determined by histological crite-

ria. The transplant is performed on the patient when she is 38 years old and the treatment with mTOR starts at 43. The transplant age was 5 years. During the monitoring, no acute rejection episodes or clinically significant acute infections were present, but she presented myeloproliferative disease with initial findings of pancytopenia and hepatitis. Suspension of treatment with mTOR is decided before Day 90 of monitoring. The dose of everolimus supplied to the patient was always 1.5 mg with trough levels of 4.23 on Day 4 and 3.59 on Day 30 of monitoring.

Additionally, the records of 8 patients were discarded for presenting one of the indications that were used as an exclusion criterion from the sample to be monitored in the study. As shown in Table 1, the analysis sample is constituted by 40 patients, as follows: 25 white men, 1 black men and 14 white women, with an average age of 44.5 years and 40.4 years, respectively, at the beginning of conversion. They received, on average, 950.65 days of treatment with mTOR with a transplant average age of 6.8 years.

Only 2 of the 40 patients have a secondary transplant and 18 of the 40 received living-donor transplants. Non-melanoma skin cancer, solid organ cancer, and post-transplant lymphoproliferative disorder (PTLD) records were taken from Day 180, finding that none of the 40 patients had one of these cancers or PTLD during the study. In Table 1 the demographic characteristics of the population in the study are presented.

The suspension of mTOR due to acne is reported on Day 720 in a 53-year-old patient, who during the earlier stages of the monitoring reported, not only acne, but also vertigo. From Day 180, the occurrence of cardiovascular events (acute coronary event, cerebrovascular event and peripheral vascular event) is monitored, finding that none of the 40 patients show cardiovascular events during the 720 days following conversion.

Renal function

In Figure 1 a reduction in the levels of creatinine is observed and it is maintained until day 720, after conversion to mTOR inhibitors.

Table 1.

Demographic characteristics			
Patients converted to everolimus		Male (n= 26)	Female (n= 14)
Age (mean; SD)		**46.38; 10.67**	**41; 9.01**
Ethnicity	White	25	14
	Black	1	0
Transplantation	Living-donor	10	8
	Deceased-donor	16	6
Transplant time (mean; SD)		6.88; 2.99	6.63; 2.60
Receiving CsA		25	14
Receiving Tacrolimus		1	0
Receiving Azathioprine		15	13
Receiving mycophenolic acid		10	0
Receiving Statins		24	13
Receiving Fibrates		1	1
Biopsy	Yes	21	6
	No	5	8
CAN	Grade I	5	2
	Grade II	10	3
	Grade III	1	0
	Not recorded	10	9
CNI	Toxicity	6	3
	No toxicity	13	3

The GFR was constant only in 2 (5%) of the patients observed in the study, decreased in 12 patients (30%) after 720 days from conversion and increased in 26 patients (65%), as shown in Figure 2.

During the monitoring, it was possible to observe that both the average level of creatinine and the GFR have an abrupt change after conversion, decreasing and increasing respectively, as can be seen in Figures 1, 2 and 3. The average levels of both variables tend to stabilize after day 360. The average level of proteinuria does not show a significant change after conversion. Only from day 360 a significant increase is reported, maintaining this behavior until day 720. Regarding the tendency, after conversion the GFR and proteinuria increased throughout the monitoring. The variability of the average levels of creatinine, proteinuria and GFR is low.

As evidenced in Figures 4 and 5, in the case of proteinuria, none of the patients in the study maintained the same levels. The level of proteins decreased in 22 patients; i.e., 55% of the study sample. This level increased in the remaining 18 patients (45%).

The hemoglobin count after 720 days from conversion increased in 16 patients; i.e., 40% of the patients in the study. This count decreased in 18 subjects (45%) and remained unchanged in six of them (15%). The white blood cell count remained the same only in 2 patients, 5% of the patients in the study, after 720 days from conversion. The count increased in 10 patients (25%) and decreased in 28 patients (70%). The platelet count remained unchanged in 2 patients (5%) after 720 days from conversion. This count increased in 26 patients (65%) and decreased in 12 of them (30%). Table 3 shows the basal and post-conversion hematological parameters.

The average of each of the variables of the complete blood count decreased immediately after conversion. However, the averages of the white blood cells and hemoglobin count on day 180 increased again (being the increase of white blood cells count slightly lower). Then the average of these two variables decreased again, and continued with a stable behavior until day 720. The average of the platelets count remained stable after the decline subsequent to con-

Figure 1.

Behavior of Creatinine Level during monitoring

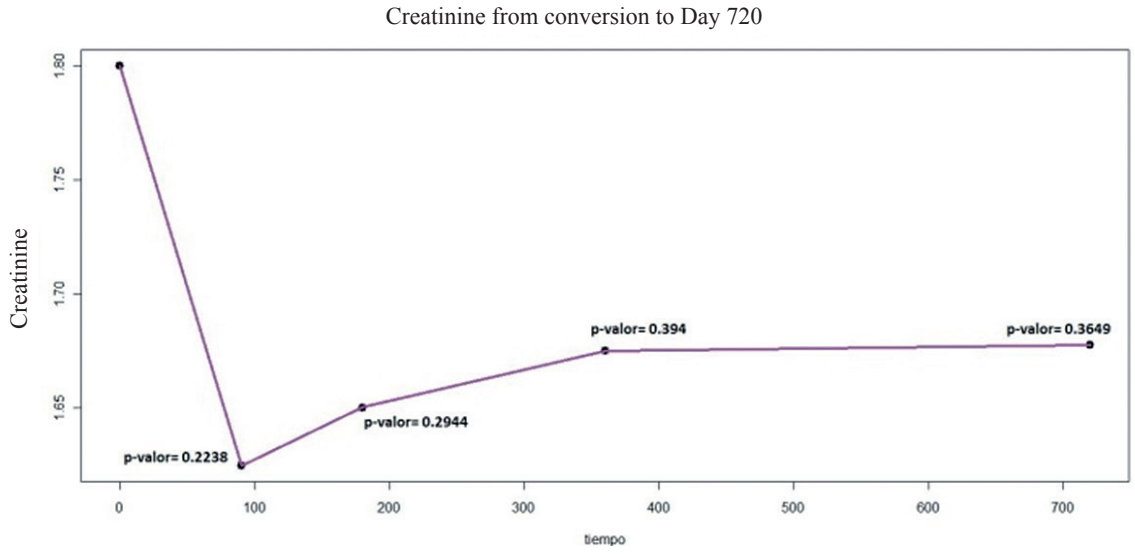


Figure 2.

Behavior of GFR during monitoring

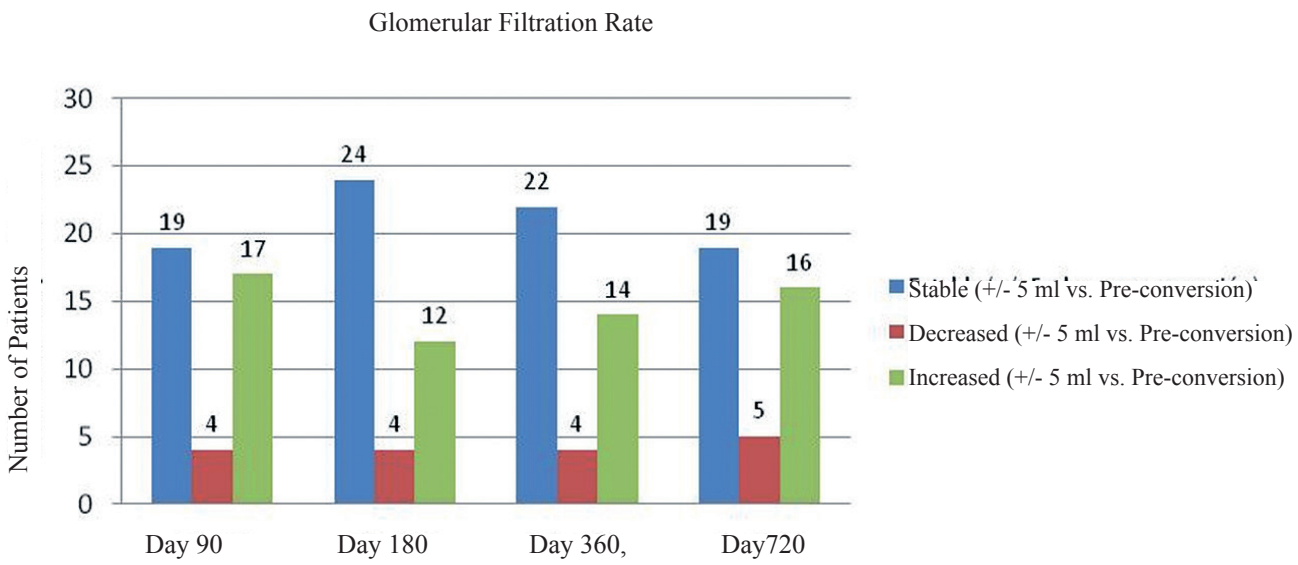


Figure 3.

Diferencia de medias para los niveles de TFG

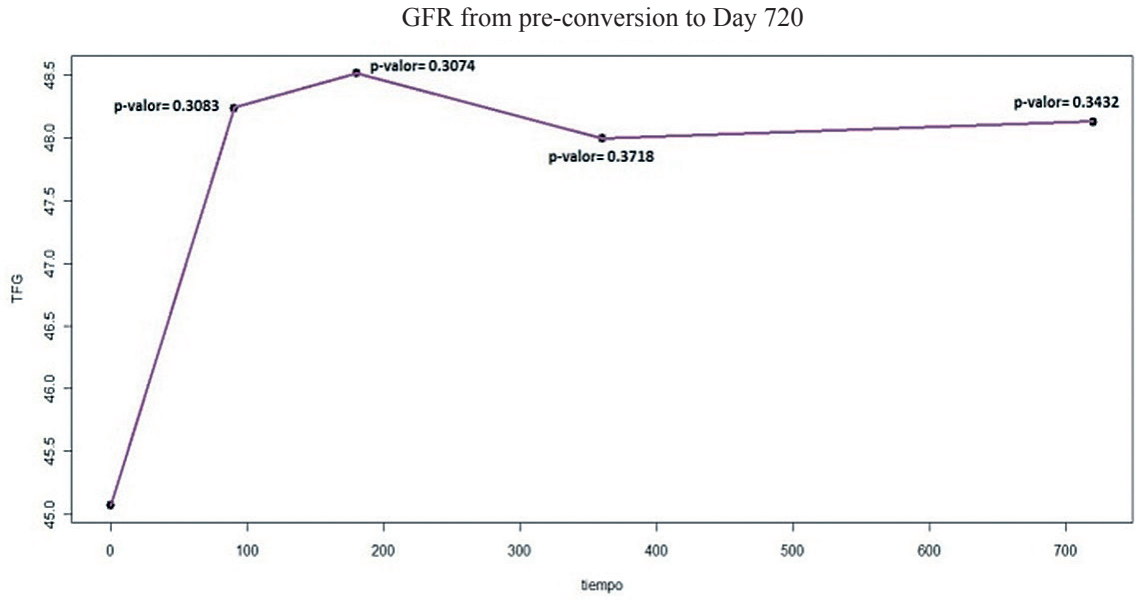


Figure 4.

Number of patients per interval of interest of proteinuria

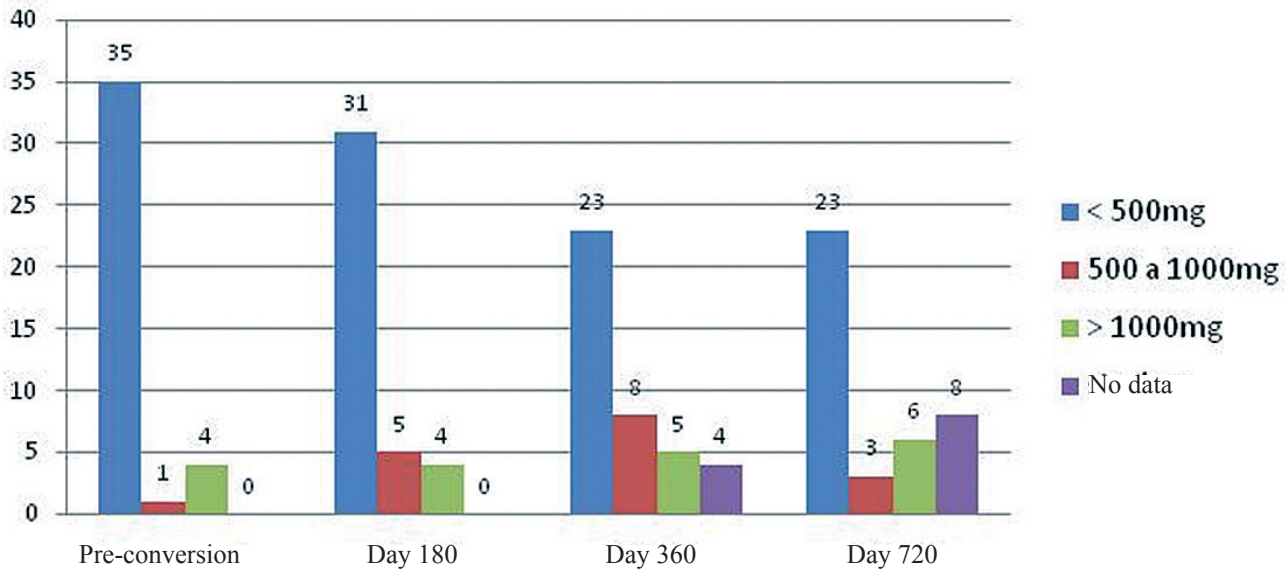


Figure 5.

Difference of means for proteinuria levels

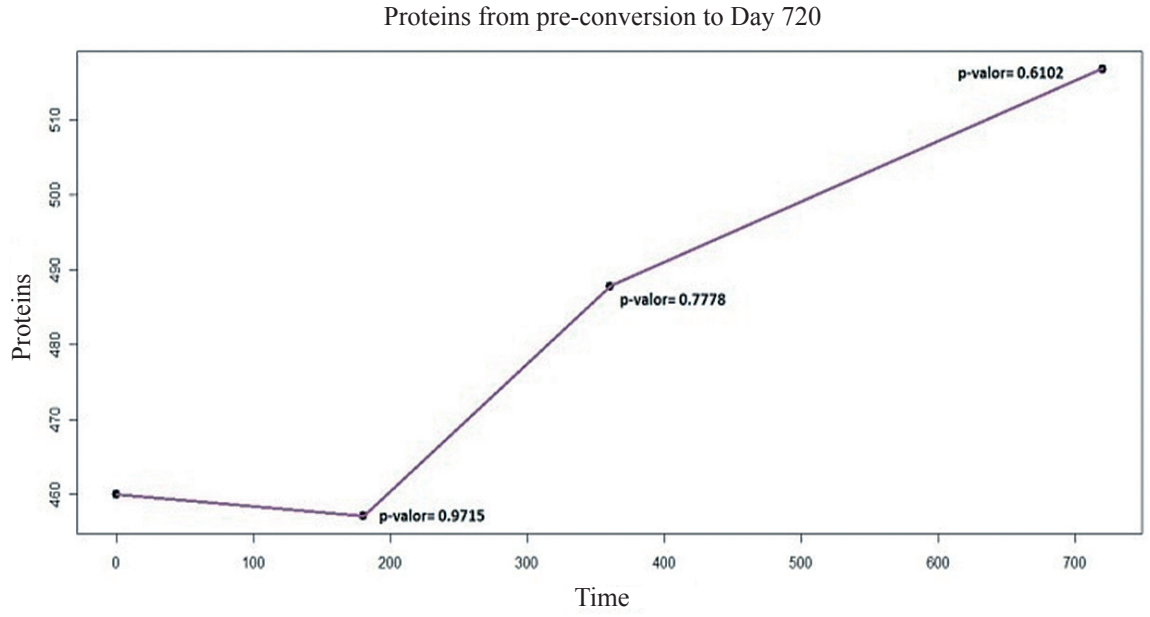


Table 3.

Blood Count						
	Mean		SD		95 % Confidence Interval	
	Day 0	Day 720	Day 0	Day 720	Day 0	Day 720
Leukocytes	8.08	6.95	2.65	1.61	(7.24 ; 8.93)	(6.44 ; 7.47)
Hemoglobin	14.17	13.87	1.73	2.08	(13.62 ; 14.73)	(13.20 ; 14.53)
Platelets	270.55	290.67	57.30	63.28	(252.22 ; 288.87)	(270.44 ; 310.91)

version and until day 180, and then started showing a growing behavior until day 720.

Lipids

The average HDL-C and LDL-C increases immediately after conversion, but then the HDL cholesterol begins to decrease, until day 720 when its average is even lower than in the pre-conversion time. In contrast, the average of LDL-C continues increasing as time passes after conversion (Figures 6 and 7).

TG and TC averages show similar behaviors: they decrease immediately after conversion, show an increase on day 180, and then stabilize from day 360 to day 720.

Use of hypolipidemic drugs

The use of hypolipidemic drugs decreased along the monitoring, the most widely used throughout the study was lovastatin (from being used in 87.5% of patients, it came to be used in 60% of the patients). In parallel, the hypolipidemic drug that increased in its frequency of use was gemfibrozil (from being used in 5% of patients, it came to be used in 35% of these) (Figure 8).

Use of antihypertensive drugs

Controlling blood pressure was achieved by reducing the number of antihypertensive drugs after conversion. ACE and LITA inhibitors were indicated in all the patients receiving more than 1 antihypertensive drug. The doses were higher in the second year, compared to the first one, to achieve similar therapeutic ranges. The average number per patient of antihypertensive drugs during the post-conversion monitoring are shown in Figure 9.

Analysis of graft survival

As shown in Table 4, only two suspected episodes of graft rejection were reported within the 40 monitored patients, without histological confirmation, without graft loss or compromise of the associated renal function. This is equivalent to 5% of the patients with acute rejection after conversion over a period of 720 days. The graft survival rate at day 135 (from a total of 720) is 97.5%; at day 540, it is 97.4%.

Everolimus dose and blood levels

Both the doses levels of everolimus and trough level were monitored from day 4 of conversion and then on days 14, 30, 60, 90, 180, 360 and 720 after conversion.

On day 4, all the patients receive 1.5 mg/day of Everolimus, showing an average blood level of 4.38. From day 14, daily doses administered to the patients start changing, going from 1.5 mg/day to 3.0 mg/day. These changes continue along the monitoring time and therefore, different patients receive 0.75 mg/day, 1.5 mg/day, 2.0 mg/day, 2.5 mg/day or 3.0 mg/day (Table 5).

Figure 10 demonstrates the immediate effect of conversion on the average blood levels, reflected on the increase from day 0, recording a decrease from day 90 and up to day 180, to return to its growing behavior on day 360, but having at the end of the monitoring period a dramatic decrease of the average trough levels. The general trend is that after conversion, the average trough levels decrease. In terms of the

Figure 6.

Difference of means for LDL-C

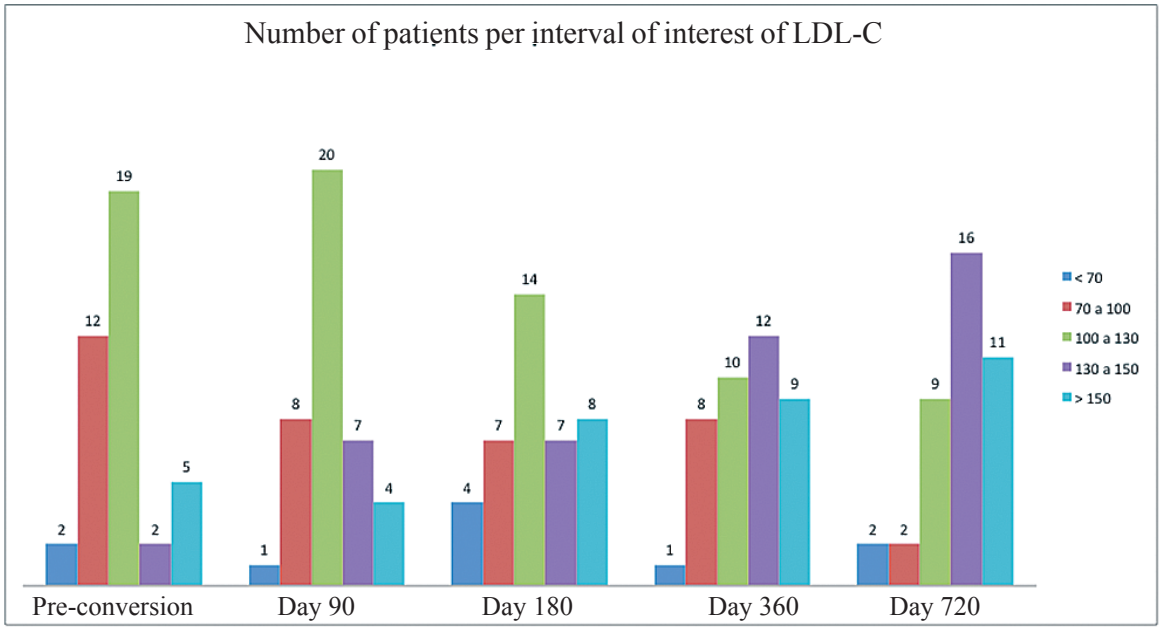


Figure 7.

Difference of means for TG

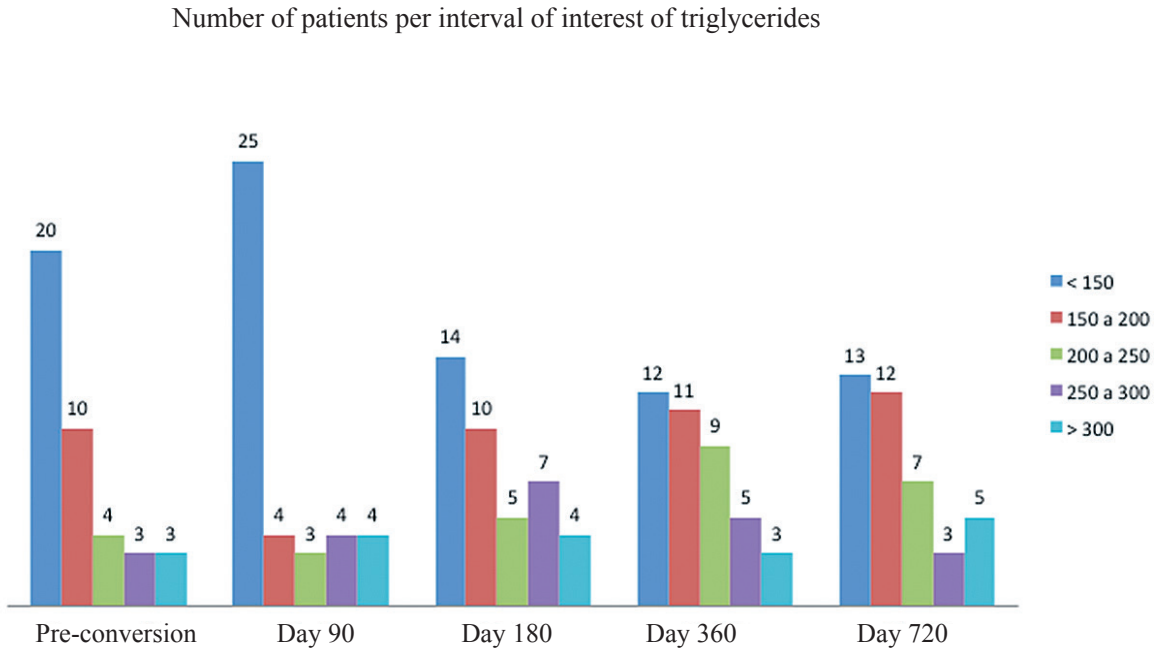


Figure 8.

Frequency of use of hypolipidemic drugs

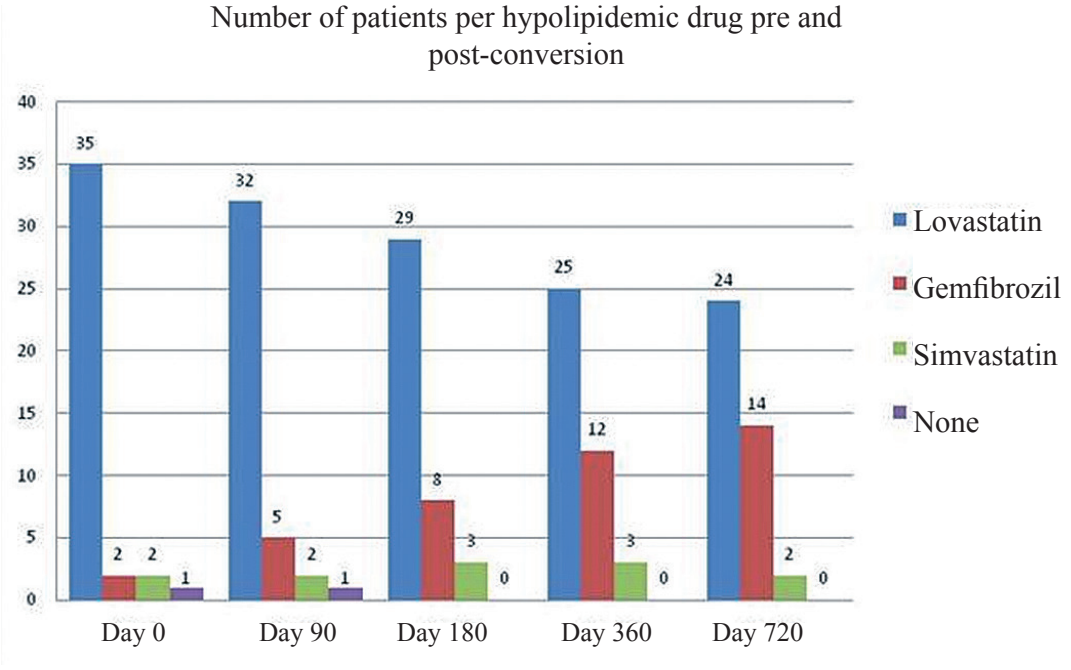


Figure 9.

Use of antihypertensive drugs per number of patients

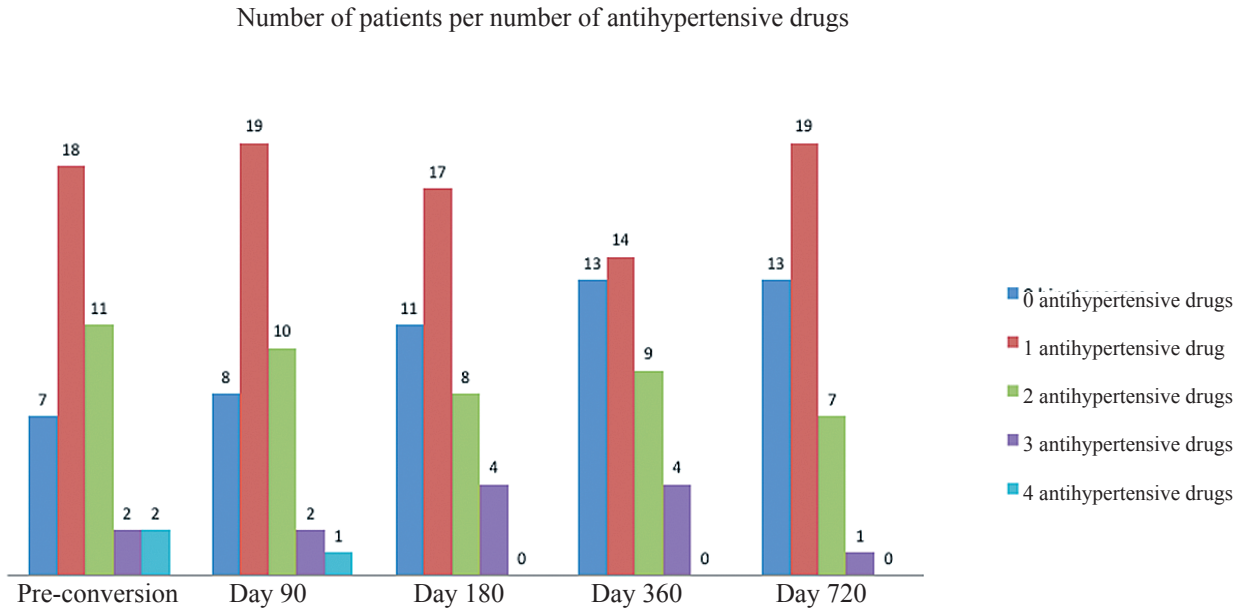


Table 4.

Kaplan- Meier's analysis of survival			
Survival average time	Typical deviation	Lower threshold (95%)	Upper threshold (95%)
529,875	14,139	502,163	557,587

Table 5.

Everolimus Dose and Blood Level at Day 4, post-conversion				
Starting dose and starting levels of everolimus				
	Minimum levels (ng/ml) (4-5 d)			
Starting dose (mg/d))	< 3.0	3.0 - 8.0	> 8.0	n
1.0 - 2.0 (1.5 mg/d)	9(24,3%)	25 (67,6%)	3(8,10)%	37

statistical difference, the averages reporting a significant difference compared to the average trough level at the start of conversion, are the ones on days 60 and 90.

On the other hand, to make a total count of the adverse events reported by each of the 40 patients during the four stages of the post-conversion treatment, it is possible to observe that 75.6% of the patients do not report any clinically important adverse event, and that, with a low frequency, the most common ones are mouth ulcers, diarrhea, acne and nausea (Figure 11).

DISCUSSION

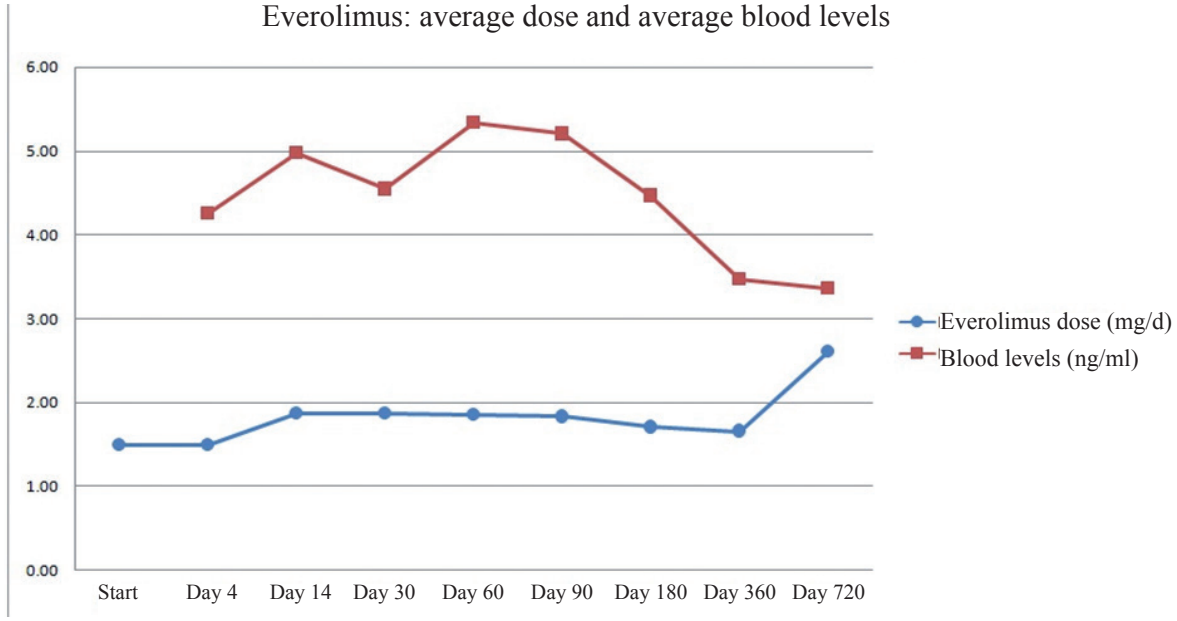
The late CNI withdrawal in a scheme based on everolimus and mycophenolic acid was associated with stability and improvement of the renal function at 24 months, in most patients, with a cellular rejection rate of 5%.

The results of our experience have significant observations to take into account when deciding late CNI withdrawal and mTOR inhibitors introduction. Positive results in renal graft function, a reduction of nephrotoxicity, without the presence of cardiovascular events or neoplasia, and adequate tolerance to the drug were found. These results are favorable compared to those obtained in the CONVERT30 study, where no significant difference was observed in the renal graft function in the late CNI withdrawal and the introduction of sirolimus, suggesting no benefit in renal graft function.

A probable explanation of the outcomes could be associated with renal graft function, to proteinuria levels prior to conversion and to the exploration of histological findings, excluding subclinical acute cellular rejection, glomerular disease relapse and acute tubular necrosis of renal graft. Once again, the use of mTOR inhibitors requires conditions that must be previously evaluated in order to obtain positive results. We emphasize that this is not a useful strategy for all patients receiving CNI, we exclude those with severe impairment of renal graft function30, significant proteinuria[32], glomerular inflammatory disease of the renal graf[38], acute tubular necrosis[39] and, possibly, subclinical acute cellular rejection. We still have no evidence about the clinical behavior in kidney transplant recipients with humoral component who receive mTOR inhibitors.

Figure 10.

Everolimus dose and blood levels



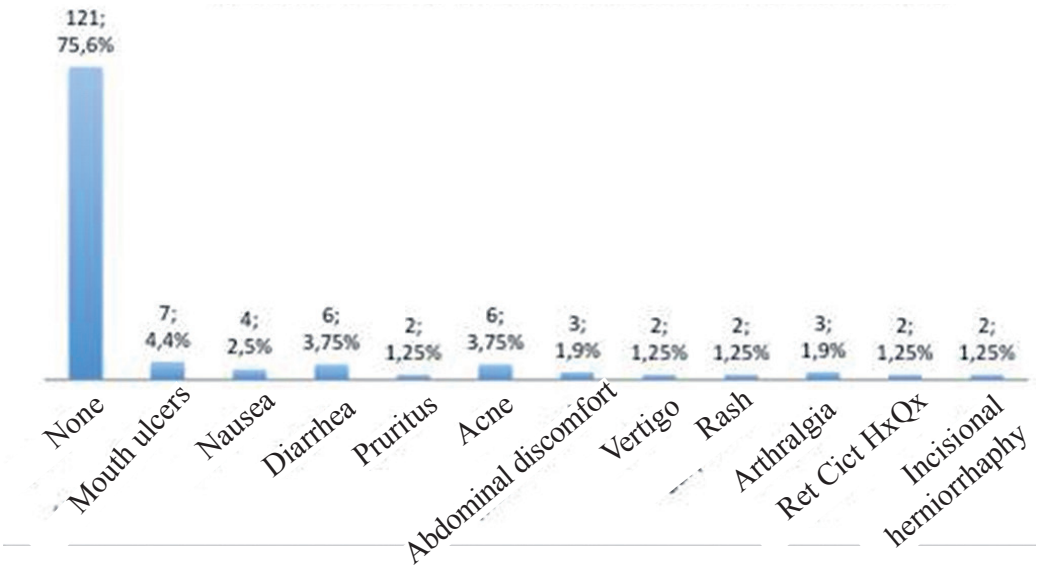
The use of mTOR inhibitors is associated with significantly higher acute cellular rejection, in a de novo scheme with low and free doses of CNI, compared to schemes based on CNI[21]; however, at higher concentrations the rejection rate is similar[18, 39-43], finding tolerance as the main obstacle, and triggering high rates of medication withdrawal because of adverse effects.

This study was conducted expecting an exposure to everolimus between 3 and 8 ng/ml, considering that immunologic events in renal transplant are characterized by a high immune early response stage (first year after transplantation), and a late stage of lower intensity; this level of exposure contributed to prophylaxis for acute cellular rejection in the vast majority of patients, obtaining adequate tolerance in almost all of these, unlike previously reported rates, where higher exposures with medication withdrawal rates close to 25% 30 were used.

It is important to note the increase in the average levels of proteinuria by the end of the monitoring, compared to pre-conversion values. However, the presence of severe proteinuria (>1 g) was reported in only 6 out of 40 patients in 24 months. Five or more years after transplant, the 6 patients, except for one, had interstitial fibrosis and moderate tubular atrophy in the pre-conversion biopsy, proteinuria >800 mg in 2 of them before the start of everolimus, and no electron microscopy, c4d and donor specific antibodies studies were performed to establish a diagnosis of chronic glomerulopathy, the latter being one of the limiting conditions to be considered at the moment of conversion in our monitoring. Two of the 6 patients had a significant reduction in the GFR. In 3 out of 6 the function was stable, and in 1 out of 6 renal graft function improved significantly, despite the presence of significant proteinuria. The clinical impact of mild levels of proteinuria is unknown, and deserves an adequate analysis in the long term[44]. Performing a new renal graft biopsy was not possible in any of the patients with significant proteinuria at the end of the monitoring.

Figure 11.

Total frequency after conversion of adverse events.



As for the results of hemoglobin levels, only 1 patient presented hemoglobin levels <11 g/L at the end of the monitoring. Similar results were reported in renal transplant recipients with late introduction of everolimus, finding that the anemia caused by everolimus is characterized by microcytosis, low serum iron, high ferritin levels, and high PCR levels, consistent with anemia associated with chronic inflammatory conditions. This alteration occurred in the first 3 months after conversion, disappearing at 6 months[45].

Furthermore, LDL cholesterol levels and, predominantly, triglycerides, have a progressive increase in each of the recorded time points. This demanded a change of strategy, related to the drugs used before conversion, since 37 out of 40 patients received statins (only 14 out of 40 patients reached the target LDL cholesterol ranges), reducing the use of these to 26 patients and increasing the use of oral fibrates at the end of the monitoring in 14 of the 40 patients. However, despite the increase in the use of oral fibrates, the target triglyceride levels are only reached by 13 of the 40 patients, and the target LDL cholesterol levels are only reached by 4 patients in 24 months.

It is important to add that the use of lovastatin, which was the only statin included in the Compulsory Health Plan in our country during the period of the study, is ineffective for reaching adequate LDL levels proposed by Kidney Disease Outcome Quality Initiative (KDOQI) for the treatment of dyslipidemia in patients with chronic renal failure[46]. This is based on the recommendations of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)[47], who assumed reasonably that the attainment of these targets must reduce the risk of adverse cardiovascular outcomes. The use of other types of statin, such as fluvastatin in renal transplant recipients describes an average reduction in LDL cholesterol levels from 159 mg/dl before the start of the hypolipidemic drug to 98 mg/dl at the end of the monitoring, associated with a lower risk of cardiovascular events48. Although, during the 24 months of monitoring, the study group showed no adverse cardiovascular outcomes, long-term monitoring and

analysis must be performed to conclude on the direct effects on lipids behavior.

The control of blood pressure was achieved by reducing the number of antihypertensive drugs after conversion, being ACE inhibitors and LITA the drugs formulated in all patients receiving one or more antihypertensive drugs.

The starting doses of everolimus (0.75 mg bid) did not help to achieve the target levels in 25% of the patients. Therefore, after the analysis of the results, the starting dose has been modified for future patients in late conversion (1 mg bid). Similarly, the levels were higher in the second year compared to the first year to achieve similar therapeutic ranges, but the explanation of this behavior is not clearly identifiable, as there is no data supported by pharmacokinetic studies.

In conclusion, the use of everolimus in combination with mycophenolic acid in a reduced dose allows the withdrawal of CsA in selected renal graft recipients, in a late and safe way, allowing improvement or stabilization in graft function without increasing the risk of adverse cardiovascular outcomes or presence of neoplasia, and with a suitable tolerance.

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Interest conflict

The authors declare no conflict of interest.

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