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ORIGINAL ARTICLE

De novo use of a generic formulation of tacrolimus versus reference tacrolimus in kidney transplantation: evaluation of the clinical results, histology in protocol biopsies, and immunological monitoring

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Summary

The use of generic formulations of immunosuppressive drugs in renal transplantation has been and still is a controversial subject. The lack of clinical studies about safety and efficacy in transplant patients is one of the factors restricting the diffusion of generic drugs in the renal transplant field. Since March 2013, our transplant unit has incorporated generic tacrolimus (Adoport®; Sandoz), replacing the one we were currently using (Prograf®; Astellas). When carrying out our retrospective analysis comparing the two different formulations, we evaluated several clinical results: tacrolimus trough concentrations (*C*0) at 5–7 days; 1, 3, and 6 months post-transplantation; concentration/dose ratio at 6 months; acute rejection incidence; delayed graft function (DGF); renal function (as CKD-EPI); and proteinuria at 6 months in 120 patients (1:1 ratio of Prograf® versus Adoport®), noticing no important differences. We also evaluated the results of protocol biopsies at 6 months in a subgroup of patients, thus verifying the safety and efficacy of this particular generic drug versus the reference product on a histological basis as well. No difference in the development of dnDSA (*de novo* donor-specific antibody) was found between the two groups.

Introduction

The use of generic drugs whose formulation patent has expired usually means important economic savings as the price of generic drugs on the market is around 40–60% less than the reference product [4]. The entry (and the use) of generic drugs on the market pushes the sector toward the investigation of new drugs and, therefore, the development of scientific knowledge.

In spite of this, there is some skepticism regarding the use of drugs with a narrow therapeutic index, such as immunosuppressants [1-3]. This skepticism comes from the fact that the international regulatory agencies (FDA, EMA) approve the use of generic drugs based upon bioequivalence studies in healthy subjects. These are usually two-way crossover studies, where the area under the curve (AUC) and the maximum concentration (C_{MAX}) of the generic versus the reference product is established between

well-defined limits, even though these are arbitrarily defined. For the majority of generic products, bioequivalence is said to exist if the 90% confidence intervals for these values fall within the accepted range of 80–125%. The European Medicines Agency (EMA) has recommended a tighter acceptance margin of 90–111% for certain "critical dose drugs", of which tacrolimus is one example [5,6]. The regulatory agencies do not require pharmaceutical companies to carry out bioequivalence studies on patients nor is it required to analyze clinical studies comparing the safety and efficacy of the generic product to the reference product.

If, on the one hand, two-way crossover studies on healthy subjects completely limit the intra-individual variability, while on the other hand, on a clinical basis, there are many interfering factors (intake of other drugs or clinically unstable conditions which affect the absorption rate), this variability can be relevant [7]. All of the above typically occur following the transplantation of solid organs, such as the kidney.

Since 2011, a new formulation of generic tacrolimus, called Adoport®, has been available in Spain, although it has been and still is very poorly used in the country, especially when compared to other countries where it reaches a diffusion of almost 70% [8].

In this work, we report our experience using Adoport® *de novo*, making a comparison with a group of pre-existing patients treated with Prograf®. We evaluated clinical results (renal function, proteinuria, rejection incidence, and DGF) and tacrolimus levels at several time points post-transplant in both patient groups. Taking into account the limited prognostic value of creatinine and of GFR measured as CKD-EPI, we analyzed the protocol biopsy results at 6 months in a subgroup, thus verifying that there are no differences between Adoport® and Prograf® even at a histological level. We also show that there was no increase in the development of donor-specific antibodies (DSA) generated *de novo* in these two groups, which is a critical aspect taking into account the prognostic impact of dnDSA on graft survival [9].

Material and methods

Patients

This was a retrospective study comparing two historical patient cohorts.

As inclusion criteria, we selected patients whom had been treated since transplant with the same tacrolimus formulation (Adoport® or Prograf®), combined with mycophenolate mofetil and steroids. We dismissed patients who had been treated with mTORi and/or other tacrolimus formulations during the observation period.

As exclusion criteria, we considered the following: other organ transplant, ABO incompatible transplant, use of unconventional immunosuppressive drugs (i.e., eculizumab, rituximab), inclusion in other studies which may have interfered in the decision about the type and/or level of tacrolimus, and graft loss due to post-transplant immediate thrombosis.

Protocol biopsy and histological analysis

As a part of routine care in clinical stable kidney transplant patients with steady kidney graft function, biopsies were obtained at a median time point of 6 ($\pm$0.5) months after transplant. Two cores of tissue were obtained under ultrasound guidance with an automated gun using either a 16 or 18 gauge needle. Renal lesions were graded according to the Banff diagnostic categories and updates [10,11]. These categories included the following: normal ($i \geq 0$, $t0$, and either ci ≥ 0 OR ct ≥ 0), borderline (no intimal arteritis, $t \geq 1$ with i0 or i1 and $t1$), subclinical acute rejection ($i \geq 2$, $t \geq 2$, and $v \geq 0$) and IFTA (ct ≥ 1 AND ci ≥ 1). The pathologist was unaware of the tacrolimus formulation used in each patient. C4d staining (immunofluorescence method) was available in all biopsies.

Immunosuppression

Patients received tacrolimus at a dose of 0.05 mg/kg/12 h as initial therapy in cases of low immunological risk. Patients with high immunological risk (retransplant, previous blood transfusions, or positive Luminex® assay) received tacrolimus at 0.1 mg/kg/12 h. All patients received mycophenolate mofetil or mycophenolic acid. The initial dose was 1 g/12 h of mycophenolate mofetil or 720 mg/12 h of mycophenolic acid; after the two-first weeks, this was decreased to 500 mg/12 h or 360 mg/12 h. Induction therapy with thymoglobulin (rATG Genzyme 1.25 mg/kg per day for 4 days) was mandatory for DCD or for high immunological risk, while basiliximab (Simulect® Novartis 20 mg on days 0 and 4) was used for the remaining patients. According to our local protocol, only patients with high HLA compatibility and low immunological risk (>3 HLA matches and negative Luminex® assay) and with a kidney living donor or SCD received no induction therapy. All recipients started tacrolimus treatment within 24 h of transplantation (including patients with DGF). Only patients receiving a kidney from donor after cardiac death (DCD) started tacrolimus 5 days after transplantation.

Clinical outcome, laboratory data, and immunological monitoring

Delayed graft function (DGF) was defined as the use of dialysis in the first postoperative week. We evaluated renal function through the creatinine level and the estimated

GFR measured as CKD-EPI at several time points, that is, 1, 3, and 6 months after the renal transplant. We measured proteinuria as the proteinuria/creatininuria ratio at 6 months (g/mol). The tacrolimus trough level (*C*0) was determined using high-performance liquid chromatography tandem mass spectroscopy (HPLC/MS/MS) at 5–7 days, then 1, 3, and 6 months post-transplantation. Variation coefficients for the tacrolimus trough level were calculated using the *C*0 between 3 and 6 months in patients who maintained the same doses of tacrolimus.

Presence of anti-HLA antibodies was evaluated using a Luminex® screening assay (against class I and class II MHC) the day of transplant. If the screening test was positive, a single antigen bead assay was performed to detect DSA. Screening was repeated on the day of the protocol biopsy (6 months).

Statistical analysis

Results are expressed as mean ± standard deviation. Comparison between groups was performed by means of Pearson's χ^2 test for categorical data. The Fisher test was applied when the number of cases was <5. One-way analysis of variance and *t*-tests were used for normally distributed data, and the nonparametric Kruskal–Wallis test and Mann–Whitney U-test were used for non-normally distributed variables. Regression logistic binomial analysis with stepwise variable selection (level of significance at 0.2) was used to evaluate risk factors for acute rejection. All *P*-values were two-tailed and the statistical significance level was fixed at $P < 0.05$. SPSS 20.0 software (SPSS Inc., Chicago, IL) was used for data management and analysis.

Assuming that the standard deviation for all blood samples (480) was 2 ng/ml for the *C*0 trough tacrolimus level, group sample sizes of 60 and 60 were used to achieve 80% power to detect a difference of 1 ng/ml in the *C*0 trough tacrolimus levels with a significance level (alpha) of 0.05 using a two-sided two-sample *t*-test.

Results

Patients and donor characteristics

From March 2013 to April 2014, 60 patients treated with Adoport® (ADO) fulfilled the inclusion criteria to enter the study and therefore were selected for the analysis. The control group consisted of 60 patients (1:1 ratio) treated with Prograf® (PRO) transplanted within 1 year and 3 months before the inclusion of the first ADO patient. The two cohorts did not present statistically significant differences regarding age at the time of transplant, sex, or previous number of transplants (Table 1). Most patients in both groups had been on hemodialysis (PRO: 88% vs. ADO: 82%); 8% were transplanted predialysis. Patients on peritoneal dialysis were 4% of the PRO group and 10% in the ADO group ($P = 0.058$).

Table 1. Patient's Baseline and donor's characteristics.

	ADO (60)	PRO (60)	*P*
Age (mean)	56.1 ± 12.6	59.2 ± 13.7	0.35
Sex (% M/F)	70/30	62/38	0.44
Kidney transplantation (% 1/>1)	83/17	82/18	0.81
DSA at time of KT (% Y/N)	2/98	5/95	0.30
HLA MM (Median)	3	3	0.18
Type of dialysis			
Hemodialysis (%)	82	88	
Peritoneal dialysis (%)	10	4	0.057
Pre-emptive (%)	8	8	
Induction therapy (%Y/N)	97/3	89/11	0.18
ATG (% Y/N)	31/69	18/81	0.09
Basiliximab (% Y/N)	43/57	78/21	0.01
Corticoid at 6 m. (% Y/N)	90/10	82/18	0.12
Age (Mean ± SD)	59.9 ± 15	60.4 ± 13	0.13
CIT (Mean ± SD)	18 ± 6.3	17 ± 7.3	0.24
Type of donor			
Deceased donor (%)	82	88	0.43
Living donor (%)	8	10	0.36
DCD (%)	10	2	0.09

Table 2. Logistic Regression analysis with stepwise variable selection for acute rejection.

	OR	CI (95%)	*P*
DSA at time of transplant (Yes versus No)	187	5.77–6149	0.003
Tacrolimus formulation (Adoport versus Prograf)	0.68	0.27–1.65	0.39
DGF (Yes versus No)	19.3	2.24–166.4	0.007
CIT (for each hours)	0.94	0.82–1.08	0.41
*C*0 Tacrolimus 5–7 day from Tr (for each μg/L)	0.95	0.72–1.26	0.75
HLA MM (for each mismatch)	0.67	0.35–1.30	0.11

DSA, donor-specific antibody; DGF, Delayed graft function; CIT, Cold isquemia time; HLA MM, HLA mismatch (0/6).

Donor characteristics were similar for both groups, although ADO patients had received more DCD kidneys (PRO: 2% vs. ADO: 10%; $P = 0.08$). There were no significant differences in donor age, cold ischemia time, or HLA mismatch (Table 1). The PRO group presented DSA at the time of transplant more frequently than the ADO group (5% vs. 2%, respectively), although the difference was not statistically significant ($P = 0.3$).

Immunosuppression

Most patients had received induction therapy (PRO: 97% and ADO: 89%; $P = 0.18$). The ADO patients received

thymoglobulin (rATG®) more frequently than the PRO patients (31% vs. 18%, respectively; $P = 0.09$), although, regarding basiliximab, the difference between the two groups was statistically significant (ADO: 43% vs. PRO: 78%; $P = 0.01$) (Tables 1 and 2).

Some patients in both groups required a reduction in mycophenolate mofetil or mycophenolic acid (500 or 360 mg/day) during the first 6 months (mostly from 3 to 6 months after transplantation; PRO 18% ADO 16% $P = 0.45$). There was no difference in the rate of discontinuation of prednisone in the two study groups (Table 1). Steroid withdrawal was performed early at day 7 after transplantation.

Clinical outcome

Overall, the incidence of DGF was 27% without differences between the two study groups (ADO: 31% vs. PRO: 23% 0.3). The acute rejection rate was 8/60 in the PRO group and 3/60 patients in the ADO group ($P = 0.2$). All acute rejections were confirmed by biopsy and treated according to the type of rejection. Most rejections were diagnosed during the first 3 months after transplantation. There were seven cellular rejections (3 IA, 2 IB, 3 IIB), one humoral rejection, and three mixed rejections. None of the patients with acute rejection lost the graft, but they showed worse 6-month renal function than the patients with no rejection (creatinine 132 μmol/l vs. 192 μmol/l; $P = 0.001$). The *C*0 trough tacrolimus levels at 5–7 days after renal transplant were numerically lower in the group of patients with rejection (6.5 ± 1.4 ng/l vs. 7.3 ± 3.8 ng/l, respectively; $P = 0.5$).

We performed a logistic regression analysis with stepwise method including several known factors influencing acute rejection risk (the presence of DSA pretransplant, DGF, tacrolimus *C*0 at 5–7 days, and HLA compatibility) and the use of the different formulations of tacrolimus. In the model, only the presence of DSA at the time of renal transplant and DGF were factors capable of predicting the development of acute rejection (Table 2).

At 6 months, death censored graft survival was 100% in both groups. There were no identified cases of polyoma virus nephropathy or cancer in patients receiving either Adoport® or Prograf®. Three patients died within 6 months of transplantation. One patient in the Adoport® group died 7 days after transplant due to intestinal ischemia. One patient in the Prograf® group died at 3 months due to pneumocystis carinii pneumonitis and another one due to sudden cardiac death at 1.5 months after transplantation. These patients were not included in the study analysis and replaced by newly recruited patients.

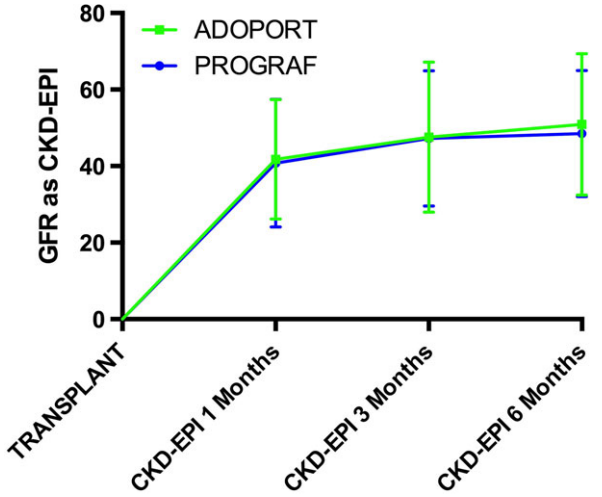

Figure 1 Renal function as eGFR measured as CKD-EPI (mean ± 2 SD) during the study.

Kidney allograft function and proteinuria

At all time points, no differences were detected between the ADO and PRO groups regarding the eGFR (Fig. 1). Proteinuria at 6 months was comparable in the two groups (ADO: 26.8 ± 49 g/mol vs. PRO: 29.3 ± 42.2 g/mol $P = 0.76$). In the majority of patients, the degree of proteinuria was in the range of normal or minimal; only two patients in the Prograf® group and three patients in the Adoport® group had proteinuria greater than 1 g/day.

*C*0 trough tacrolimus levels during the study

There were no significant differences in the *C*0 trough tacrolimus levels at any of the analyzed time points (Fig. 2). Five to seven days after introducing tacrolimus, 49% of ADO patients vs. 35% of PRO patients were on target (tacrolimus *C*0 between 6–10 ng/ml). In 36% of ADO vs. the 46.5% of PRO patients, the *C*0 was <6 ng/ml, while 18.5% of PRO vs. 14% of ADO patients presented a tacrolimus *C*0 > 10 ng/ml (all nonstatistically significant). Although the *C*0 tacrolimus trough level at 2–4 days was not determined per protocol (the steady state is usually not reached until day 5), we had data from a subgroup of patients (24 Prograf® and 29 Adoport®). Again, the mean tacrolimus level at this time point was similar in both groups (Prograf® 6.1 ± 4 vs. Adoport® 5.4 ± 3; $P = 0.2$).

Overall, there were 42 patients (35%) older than 65 years. *C*0 tacrolimus level at 5–7 days tended to be higher in older patients (8.05 ± 3.1 in the older group vs. 7.1 ± 4 in the rest of the patients; $P = 0.06$), thus suggesting a lower capacity to metabolize the drug in the elderly. However, thereafter older patients had lower tacrolimus levels (at 1 month 7.2 ± 2.2 vs. 6.9 ± 2.3 $P = 0.25$, at

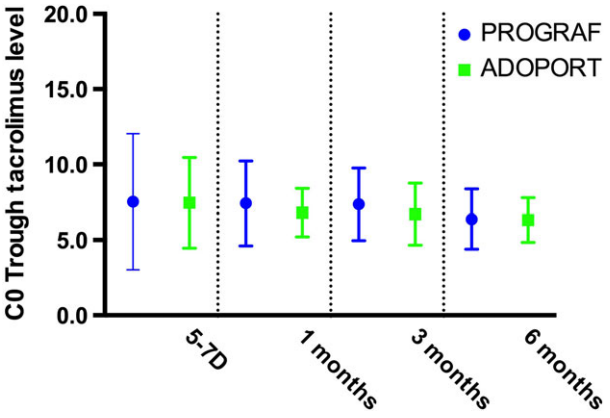

Figure 2 *C*0 tacrolimus trough level (mean ± 2SD) at different time points in the two study groups.

3 months 7.1 ± 2.1 vs. 6.7 ± 2.3 $P = 0.5$, at 6 months 6.7 ± 1.6 vs. 5.7 ± 1.7 $P = 0.03$), reflecting usual clinical management of immunosuppression in patients older than 65 years. When we analyzed only the elderly group according to the type of tacrolimus (27 Adoport® vs. 15 Prograf®), we found that the *C*0 trough tacrolimus levels were nearly identical at all time points (data not shown). No differences in the *C*0 levels were detected according to the type of donor (living versus deceased) or to presence or not of DGF (data not shown).

The intra-individual variation of coefficient of *C*0 tacrolimus between 3 and 6 months for the two study groups was similar (PRO: 21% vs. ADO: 16%; $P = 0.15$). When we analyzed the patients who maintained the same dose between 3 and 6 months, the variation coefficient was 20% for Prograf® group vs. 15% for the Adoport® group ($P = 0.28$). The variation coefficient was slightly higher for the patients who needed an adjustment in dose between 3 and 6 months (Prograf® 22% vs. Adoport® 17%; $P = 0.7$).

Between 3 and 6 months, 51% of the patients treated with Prograf® needed an adjustment in dose vs. 48% of patients treated with Adoport® ($P = 0.86$). The magnitude of the dose correction was −1.27 ± 1.8 mg/day for Prograf® group and −1.32 ± 1.7 mg/day for the Adoport® group ($P = 0.88$). At 6 months, no difference was found in the daily dose adjusted by weight between the two groups (PRO: 0.055 ± 0.037 mg/kg vs. ADO: 0.061 ± 0.04 mg.kg; $P = 0.41$) as well as in the trough tacrolimus concentration/dose average (PRO: 151.7 vs. ADO: 142.7 [ng/mL]/[mg/kg/d], $P = 0.64$).

Six-month protocol biopsies and immunological monitoring

Of the 120 patients included in the study, 50.8% had a protocol biopsy suitable for analysis, 32 in the ADO group, and 29 in the PRO group. The remaining patients were not submitted to protocol biopsy for the following reasons: patient denial ($n = 15$), contraindication caused by antiplatelet and/or anticoagulant therapy ($n = 23$), urological problems such as frequent urinary tract infection, pyelocaliceal ectasia, or vesicoureteric reflux ($n = 5$). The results from the protocol biopsy on patients who had suffered from previous rejection ($n = 11$) and biopsies with an insufficient tissue sample ($n = 5$) were dismissed from the analysis. We analyzed each Banff score variable for the two groups, without detecting significant differences in any of the Banff items (Table 3), although we noticed a trend toward a higher prevalence of tubulitis in the Prograf® group (32% vs. 45% $P = 0.058$). No patient presented a positive C4d result, peritubular capillaritis, or transplant glomerulopathy.

Table 3. Banff's items at protocol biopsy at 6 months.

	ADO (% of patients)	PRO (% of patients)	*P*
Ag 0/>1	90/10	80/20	0.42
Ai 0/>1	68/32	72/28	0.74
At 0/>1	68/32	52/48	0.058
Ti 0/>1	50/50	50/50	0.78
Ptc 0/>1	100/0	96/4	0.28
AV 0/>1	100/0	100/0	–
AHV 0/>1	83/17	92/8	0.17
CG 0/>1	100/0	100/0	–
CI 0/>1	52/48	61/39	0.46
CT 0/>1	58/42	60/40	0.83
CV 0/>1	90/10	83/17	0.59
MM 0/>1	86/14	88/12	0.88
C4d % +/% –	0/100	0/100	–

We then classified biopsies into four groups: normal, borderline changes, subclinical acute rejection (SCAR), and IFTA. The whole cohort showed a 36.4% prevalence of normal biopsies (all Banff items equal to 0), without significant differences between the two groups (ADO 18/32 patients versus PRO 17/29 patients $P = 0.35$). There were no differences in the prevalence of borderline changes (ADO 12/32 patients versus 10/29 patients $P = 0.47$). The prevalence of subclinical acute rejection was low (1 in the ADO group and 2 in the PRO group), while IFTA was 41.8% (ADO 14/32 patients versus PRO 13/29 patients $P = 0.68$) (see Fig. 3). Subclinical rejections were managed by increasing basal immunosuppression.

In the PRO group, three patients (5%) presented DSA at the time of transplant. At 6 months, two of them still presented DSA, while the other had become negative. In the ADO group, one patient presented pretransplant DSA and still had it at 6 months. At the 6-month follow-up, one patient in each group developed *de novo* DSA (both class II). The total dnDSA incidence in the whole cohort was 2.8% (Fig. 3).

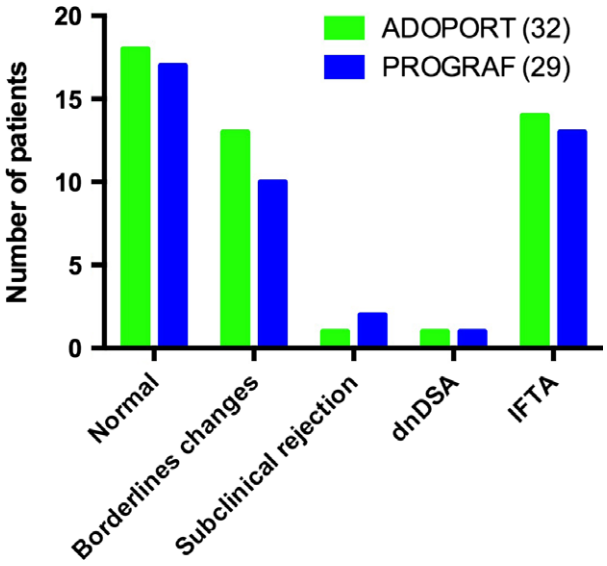

Figure 3 Histology results and dnDSA at protocol biopsy. The categories normal, borderline changes, and subclinical rejection are mutually exclusive and expressed as number of patients. Incidence of dnDSA and IFTA are not related with the others BANFF categories in the graphic.

Discussion

Tacrolimus still is the cornerstone of immunosuppression in solid organ transplantation [12]. As its immunosuppressive properties on the T-cell response due to a reduction in IL-2 expression were discovered [13], the decrease in the incidence of acute rejection and improved graft survival after 1 year (renal and any other organ) have plateaued [14]. The Symphony trial demonstrated that tacrolimus is more effective when combined with mycophenolate mofetil rather than other drugs, such as cyclosporine or mTORi [15].

The Prograf® patent, owned by Astellas, expired in 2008, and therefore, other pharmaceutical companies have started to produce and commercialize their own generic tacrolimus formulations. In 2011, the tacrolimus produced by Sandoz under the name of Adoport® officially entered the market in Europe after being approved by the European Medicines Agency. Since then, many authors have performed clinical studies to test the efficacy and safety of Adoport® in different situations: conversion studies from Prograf® to Adoport® [16–18], as well as *de novo* use [19] and bioequivalence studies (postconversion) [20].

Although they presented obvious limits (i.e., patients with other organ transplants [16,17], lack of a control group [17,18], retrospective studies [18], and highly variable periods post-transplant [20]), conversion studies have shown that conversion to generic tacrolimus does not translate into a higher risk of rejection (no postconversion rejections occurred). The need for a 10–40% adjustment in the dose has been reported (depending on the study and the type of transplant) in patients submitted to conversion. The conclusions of these studies and of a consensus document from the European Society of Transplantation (ESOT) [21] support the use of this generic drug, even if a postconversion tacrolimus *C*0 control level is required, with all the effort that it implies (increase in the number of visits, extra analysis, and increased costs). For this reason, the most effective strategy when introducing generic tacrolimus is its use *de novo*. From this point of view, although the data on widespread Adoport® use in some countries are strong, few studies have been published on *de novo* use and comparison with a control group [19].

With the exception of some abstracts which include a very small number of patients [22,23], only one study has shown the clinical results from the use of Adoport® (51 patients) versus a historical group treated with Prograf® (49 patients) [18]. This study reported no significant differences in the tacrolimus *C*0 at 1, 3, and 6 months, in postrenal transplant acute rejection or in the DGF. At 6 months, the Prograf® group showed slightly better renal function, although this was not significant.

Beginning from March 2013, our transplant unit has used Adoport® as the reference tacrolimus. The present work is a retrospective comparison of the *de novo* use of Adoport® versus Prograf®. Unlike the study by Connor *et al.*, our work also includes patients treated with rATG, as the use of rATG with generic tacrolimus has not been reported in other published studies. The use of rATG was slightly higher in the ADO group due to a greater prevalence of DCD.

Noteworthy, we found similar clinical outcome as well as *C*0 tacrolimus levels in ADO and PRO groups (DGF, acute rejection, renal function, proteinuria). Another important issue, which was not reported by other authors, was the evaluation of the tacrolimus trough level *C*0 at 5–7 days post-transplant. The KDIGO clinical practice guidelines for the care of kidney transplant recipients specifically states that the earlier therapeutic blood levels of a calcineurin inhibitor (CNI) can be attained, the more effective the CNI will be in preventing acute rejection [24]. We observed that a slightly higher percentage of patients in the Adoport® group reached therapeutic levels (6–10 ng/ml) at 5–7 days after tacrolimus was introduced than in the Prograf® group. No significant differences were found in the two groups regarding the number of patients under (<6 ng/ml)- or overexposed to tacrolimus at 5–7 days (>10 ng/ml). Finally, we carried out an analysis of the intra-individual variation of *C*0 between 3 and 6 months with no difference found between the two formulations. All these results were in agreement with the similar clinical outcome. Moreover, the comparison of the histological results between the two groups provided

rather similar scores in 6-month protocol biopsies. The incidence of *de novo* DSA was very low in both groups and was slightly lower than that reported by other authors [25]. This divergence from the literature data may be secondary to the use of the screening technique, and therefore, it is possible that some patients with negative screening but with dnDSA were not properly detected. Both protocol biopsy analysis and immunological monitoring reinforce the similar performance of both tacrolimus formulations reported previously [19].

This study has some limitations. First of all, the type of the study (retrospective with a historical control group) does not permit us to draw firm conclusions. Secondly, we did not perform accurate pharmacokinetic assessment, although it was already reported [20]. However, our data strongly suggest similar safety and efficacy in a clinical setting. Finally, we did not perform an economic cost analysis because this was not within the scope of the study. Nevertheless, the mean weight adjusted daily dose and the mean tacrolimus concentration/dose were equivalent between the two study tacrolimus formulations.

In conclusion, our study shows similar outcomes in renal transplantation in patients treated with Prograf or Adoport. Our results may support the use of Adoport® in a real clinical setting.

Authorship

EM: designed study, performed study, collected data, analyzed data, and wrote the paper. JC: collected data. DS: collected data. AM and NSB: collected data and analyzed data. RM: performed study (protocol biopsy). AP: analyzed data and wrote the paper. JMG and OB: designed study. JMC: designed study and analyzed data and wrote the paper.

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