Acute Rejection in Kidney Transplantation and Early Beginning of Tacrolimus

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ABSTRACT

Background. Although tacrolimus is an effective immunosuppressive drug used for preventing biopsy proven acute rejection (BPAR) in kidney transplanted patients, its nephrotoxicity may compromise renal function and lead to delayed initiation because of its side effects. This study aimed to evaluate the safety of early initiation of tacrolimus in the occurrence of BPAR during the first 90 days post transplant.

Methods. We conducted a retrospective cohort study involving 315 patients who underwent kidney transplantation from 2015 to 2017. Comparisons were performed between 2 groups according to whether the start time of tacrolimus therapy was delayed or not delayed. Cox proportional hazards models were used to examine the association between variables and the occurrence of BPAR.

Results. The incidence of BPAR was 14.9% (n = 47) and it was significantly higher in the delayed group (19.4% vs 6.4%; $P = .002$). Delayed initiation tacrolimus group was significantly associated with the risk of BPAR (hazard ratio: 2.95; $P < .036$). The overall mortality rate was 2.5% (n = 8) and there was no association between delayed initiation therapy and death ($P = .56$).

Conclusion. Our study confirmed that delayed initiation of tacrolimus in patients with delayed graft function is associated with a high risk of BPAR.

KIDNEY transplantation is the election treatment for end-stage renal disease [1]. Renal allograft survival is affected by repetitive episodes of biopsy proven acute rejection (BPAR), which is a frequent complication in the post-transplant period [2]. Biopsy proven acute rejection (BPAR) causes morbidity, as well as its treatment, which includes high dosages of steroids producing over immunosuppression states that contribute in some cases to infection and other complications [3].

Calcineurin inhibitors (CNIs) like tacrolimus are the cornerstone in the maintenance of immunosuppression treatment in kidney transplantation, and they have improved short-term outcomes since its introduction to the market [4–6]. Even though tacrolimus is widely used in renal transplantation to help prevent acute and chronic rejection, ironically, arterial hypertension and alteration of renal function are its most notable side effects [7]. Described nephrotoxic effects may lead to delay CNIs therapy during the early post-transplant period [8]. Randomized trials have shown that antilymphocyte induction therapy is effective in preventing acute rejection, which can help in delayed initiation of tacrolimus to avoid early tacrolimus-related nephrotoxicity [9–11]. However, avoiding tacrolimus initial therapy may result in inadequate immunosuppression and acute graft rejection [12]. The benefits of delayed initiation of tacrolimus to avoid subsequent nephrotoxicity are still controversial. Additionally, reduction in BPAR rates could

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impact long-term outcomes. This study aimed to evaluate the safety of early initiation of tacrolimus in the occurrence of BPAR during the first 90 days post transplant.

PATIENTS AND METHODS

Study Design and Population

This retrospective cohort analyses involved data from 315 patients who received kidney transplantation at our institution from January 2015 to July 2017. All patients received standard induction therapy with basiliximab or antihuman thymocyte immunoglobulin according to immunologic risk. All patients received a fixed-dose of methylprednisolone perioperatively for 3 days with a transition to fixed-dose oral prednisone by postoperative day 4 up to day 9 post transplant when steroids were withdrawn.

Only patients older than 18 years who underwent their first kidney transplantation were included. Exclusive criteria were graft thrombosis (arterial or venous) and autotransplant.

Patients were divided into 2 groups according to whether the start time of tacrolimus therapy was delayed or not delayed. The no-delay tacrolimus group (NDTG) had their tacrolimus administered within 24 hours of transplantation, and the delayed tacrolimus group (DTG) had their tacrolimus administered after 24 hours of transplantation. Initiation of tacrolimus treatment was implemented once creatinine decreased to less than 3.5 mg/dL. Delayed graft function was defined as a patient requiring dialysis in the first 2 weeks after transplantation.

Outcomes

The primary endpoint was BPAR occurrence within 90 days of transplantation and it was classified under parameters described by Banff (2015) [13,14]. Biopsy was performed on those patients with increase of serum creatinine by >20% from baseline. The secondary endpoint was mortality rate.

Statistical Analysis

Frequencies and percentages were used for categorical variables. The distribution of the numerical variables was obtained by the Shapiro-Wilk test and were reported as medians and interquartile ranges in the descriptive statistics of this study. Comparisons between the 2 groups were performed using independent Student's t test or Mann-Whitney U test. Categorical variables were compared between groups using χ^2 test.

Variables with statistically significant differences were used to perform additional analysis.

BPAR rates in the 2 groups were estimated using the Nelson-Aalen method and compared with the log-rank test. Multivariable analysis was performed using Cox proportional hazard model containing at the outset all covariates significant in the univariate analyses. Log-rank test was used to determine the relation between qualitative variables and BPAR. $P < .05$ was considered as statistically significant. The proportional hazards assumption was assessed. The method of backwards stepwise regression was carried out to select a more parsimonious model.

Ethics Considerations

This study was approved by the ethics research committee of the institution, acting in concordance with local and national regulations, as well as with the Helsinki declaration. Confidentiality of all patients was secured all the time during the execution of the research.

Table 1. Recipient Characteristics

Variable	NDTG n = 109	DTG n = 206	*P* Value
Male sex (%)	52 (47.1)	127 (61.6)	.017*
Age, y (SD)	40 (12.3)	47 (13.4)	.000*
Donor type (%)			.000*
Deceased	18 (16.5)	177 (85.9)	
Living	91 (83.5)	29 (14)	
Cold ischemia time, h (IQR)	1 (1.3)	15 (11)	.000*
PRA I, negative (%)	97 (89)	188 (91.2)	.514
PRA II, negative (%)	92 (84.4)	188 (91.2)	.065
Underlying disease (%)			.077
Glomerular	34 (31)	42 (20.3)	
Diabetes mellitus	6 (5.5)	32 (15.5)	
Arterial hypertension	12 (11)	23 (11)	
Congenital	10 (9.1)	18 (8.7)	
Obstructive	5 (4.5)	7 (3.4)	
Induction therapy (%)			.039*
ATG	96 (88)	162 (78.6)	
Basiliximab	13 (11.9)	44 (21.3)	
Expanded criteria grafts (%)	0	59 (28.6)	.000*
Tacrolimus levels (ng/mL)			
Day 15 post transplant (IQR)	3.5 (3.3)	3.8 (3.8)	.224
Day 45 post transplant (IQR)	5.6 (2.5)	5.2 (2.4)	.058
Delayed graft function (%)	4 (3.6)	79 (38.3)	.000*

Abbreviations: ATG, anti-human thymocyte immunoglobulin; DTG, delayed tacrolimus group; IQR, interquartile range; NDTG, no-delay tacrolimus group; PRA, panel reactive antibody; SD, standard deviation.
*Statistically significant difference.

RESULTS

Clinical features of patients are summarized in Table 1. A total of 315 recipients were included (109 patients in the no-delay tacrolimus group and 206 in the delayed tacrolimus group). There were significant differences between groups in sex (male 47% vs 61%; $P = .017$ in the NDTG and DTG, respectively), mean of age (NDTG 40 vs DTG 47; $P = .000$), donor type (deceased donor: NDTG 16.5% vs DTG 85.9%; $P = .000$), cold ischemia time (NDTG 1 hour vs DTG 15 hours; $P = .000$), induction therapy (basiliximab NDTG 11.9% vs DTG 21.3%; $P = .039$), expanded criteria (DTG 28.6%; $P = .000$), and delayed graft function (NDTG 3.6% vs DTG 38.3% $P = .000$). The mean timing of tacrolimus administered in the DTG was 10 (interquartile range 14) days after transplantation. There was no significant difference between the 2 groups regarding maintenance immunosuppression regimen including tacrolimus dose (not shown) and whole-blood concentration (day 15 $P = .224$; day 45 $P = .058$) during the study period.

The overall BPAR rate during the first 90 days post transplant was 14.9% (n = 47). Median time of presentation of BPAR was at 45 days after the procedure, ranging between 13 days and 90 days. When considering Banff criteria [14] to classify the severity of BPAR, this study found that grade 1A was the most common presentation with 53.1% (n = 25), 11 (23.4%) patients showed a 1B grade BPAR, grade 2B occurred in 1 (2.3%), and the remaining 10 (21.2%) had a biopsy reported as borderline. As shown in

Table 2. Features of Post-transplantation

Outcome	NDTG n = 109	DTG n = 206	*P* Value
BPAR (%)	7 (6.4)	40 (19.4)	.002
Borderline	1 (14.2)	9 (22.5)	
1A	5 (71.4)	20 (50)	
1B	1 (14.2)	10 (25)	
2B	0	1 (2.5)	
Patient survival (%)	107 (98)	201 (97.5)	.734
Delayed graft function (%)	4 (3.6)	79 (38.3)	.000

Abbreviations: BPAR, biopsy proven acute rejection; DTG, delayed tacrolimus group; NDTG, no-delay tacrolimus group.

Table 3. Cox Proportional-Hazards Regression for BPAR Occurrence

Variable	HR (95% CI)	*P* Value
Sex (male)	2.1 (1.12–4.24)	.022
Age	0.98 (0.95–1.0)	.154
Donor (live)	0.90 (0.24–3.3)	.887
Cold ischemia time	0.94 (0.55–1.59)	.823
Expanded criteria	2.39 (1.08–5.29)	.031
Tacrolimus initiation (delayed)	2.9 (1.07–8.11)	.036

Abbreviations: BPAR, biopsy proven acute rejection; CI, confidence interval; HR, hazard ratio.

Table 2 incidence of BPAR over the study period was significantly higher in the DTG (19.4% vs 6.4%; $P = .002$).

A Cox regression model was performed using significant variables previously determined by bivariate analysis. Male patients were found to have 2 times the risk of having BPAR compared with female patients. Patients who had delayed tacrolimus initiation had nearly 3 times the risk of having BPAR compared with the control group (Fig 1). Data are shown in Table 3.

Mortality Rate

The overall mortality rate was 2.5% (n = 8) and there was no association between delayed initiation therapy and death ($P = .56$).

DISCUSSION

As part of our clinical practice, in patients who had early graft dysfunction (creatinine >3.5 mg/dL post transplant) tacrolimus start was delayed based on findings of nephrotoxicity (arteriolar vasoconstriction and raise of oxygen free radicals) that could defer renal function recover [15–17]. An alternative treatment protocol widely established consists in starting CNI the first day after renal transplantation without considering renal function, and this practice keeps BPAR rates close to 10.4% [8]. Discrepancy on those concepts motivated this study in which we looked for the safety of early initiation of tacrolimus in the occurrence of BPAR during the first 90 days post transplant. What we found was that patients who began tacrolimus administration after 24 hours of kidney transplantation had nearly 3 times the risk of developing BPAR compared with those who started tacrolimus before 24 hours after surgery. These findings suggest that patients who had a late start of tacrolimus could be subimmunosuppressed during the initial period after transplantation, and therefore it was considered paramount to find the impact of delayed tacrolimus initiation in BPAR occurrence.

Historically, tacrolimus has been started looking for ideal blood levels early after renal transplant, hoping that this treatment strategy would diminish BPAR incidence [18–21]. However, results are contradictory in some cases, and this affirmation could be questioned as the next authors show. Borobia et al [22] found that patients that presented BPAR had lower tacrolimus levels in the fifth and seventh day post transplant compared with those who did not show alterations in the same period. In the same way, other authors have found similar results suggesting that there is a significant relationship between tacrolimus levels and BPAR prevalence [23–25] Conversely, Boumar et al [8] did not find any significant difference between tacrolimus concentrations at days 3, 10, 14, and 30 and 6 months post transplant, and BPAR occurrence. We did not find a correlation between tacrolimus levels and BPAR rate.

Cumulative incidence of BPAR found by our study was 14.9% compared with the results showed by Flechner et al [26] in the ORION study of 8.8%, which seems to be high. However, as shown by Albano et al [27] BPAR incidence could range between 10.3% and 16.1%. Similarly, Jones-Hughes et al [28] published a systemic review in 2016, and although it reported high heterogenicity in BPAR prevalence ranging between 12.7% and 26%, it showed BPAR incidence similar to what we found in this study. Various other studies have analyzed the relationship between different immunosuppressants during the post-transplant period and BPAR occurrence considering tacrolimus blood levels mainly [6,22,29–32]. Nevertheless, to the best of our knowledge, there is not enough research focused on establishing the ideal moment to start tacrolimus and its

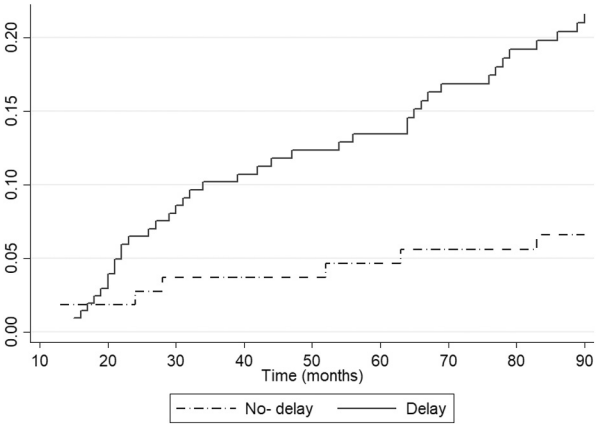

Fig 1. Cumulative probability of BPAR between delay and no-delay groups.

relationship with BPAR. This paper contributes with valuable information of having found that patients who began tacrolimus after 24 hours post transplant have a higher risk of BPAR. Because of the observational and retrospective methodology used in this research, the causality relationship between BPAR and tacrolimus start has limitations. Additionally, because of incomplete data of quantitative panel reactive antibody measures in 100% of cases, the variable could not be included and analyzed on the Cox regression. Finally, and because follow-up was kept for 90 days, graft survival analysis is missed, and future papers should include this outcome.

This study suggests that delayed tacrolimus initiation in kidney transplantation raises the risk of having BPAR during the first 90 days after the procedure, considering the impact of this fact over morbidity and graft survival. We also reaffirm previous findings that CNIs are determinant in protecting patients against BPAR occurrence, especially during the first days after the surgery.

REFERENCES

[1] Abramowicz D, Hazzan M, Maggiore U, et al. Does preemptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP. Nephrol Dial Transplant 2016;31:691–7.

[2] Wang Z, Yang H, Liu X, et al. Role of B and T lymphocyte attenuator in renal transplant recipients with biopsy-proven acute rejection. Med Sci Monit 2018;24:387–96.

[3] Friend P. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet 2014;384:1684–90.

[4] Lamarche C, Orio J, Collette S, et al. BK polyomavirus and the transplanted kidney: immunopathology and therapeutic approaches. Transplantation 2016;100:2276–87.

[5] Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562–75.

[6] Kuypers DRJ, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. Clin Pharmacol Ther 2004;75:434–47.

[7] Hošková L, Málek I, Kopkan L, Kautzner J. Pathophysiological mechanisms of calcineurin inhibitor-induced nephrotoxicity and arterial hypertension. Physiol Res 2017;66:167–80.

[8] Bouamar R, Shuker N, Hesselink DA, et al. Tacrolimus predose concentrations do not predict the risk of acute rejection after renal transplantation: a pooled analysis from three randomized-controlled clinical trials. Am J Transplant 2013;13:1253–61.

[9] Olyaei AJ, de Mattos AM, Bennett WM. Nephrotoxicity of immunosuppressive drugs: new insight and preventive strategies. Curr Opin Crit Care 2001;7:384–9.

[10] Mihatsch MJ, Kyo M, Morozumi K, Yamaguchi Y, Nickeleit V, Ryffel B. The side-effects of ciclosporine-A and tacrolimus. Clin Nephrol 1998;49:356–63.

[11] Katari SR, Magnone M, Shapiro R, et al. Clinical features of acute reversible tacrolimus (FK 506) nephrotoxicity in kidney transplant recipients. Clin Transplant 1997;11:237–42.

[12] Richards KR, Hager D, Muth B, Astor BC, Kaufman D, Djamali A. Tacrolimus trough level at discharge predicts acute rejection in moderately sensitized renal transplant recipients. Transplantation 2014;97:986–91.

[13] Parajuli S, Astor BC, Kaufman D, et al. Which is more nephrotoxic for kidney transplants: BK nephropathy or rejection? Clin Transplant 2018:e13216. https://doi.org/10.1111/ctr.13216.

[14] Loupy A, Haas M, Solez K, et al. The Banff 2015 Kidney Meeting Report: current challenges in rejection classification and prospects for adopting molecular pathology. Am J Transplant 2017;17:28–41.

[15] Shrestha BM. Two decades of tacrolimus in renal transplant: basic science and clinical evidences. Exp Clin Transplant 2017;15:1–9.

[16] Jacobson PA, Schladt D, Israni A, et al. Genetic and clinical determinants of early, acute calcineurin inhibitor-related nephrotoxicity: results from a kidney transplant consortium. Transplantation 2012;93:624–31.

[17] Naesens M, Kuypers DRJ, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;4:481–508.

[18] Gatault P, Kamar N, Büchler M, et al. Reduction of extended-release tacrolimus dose in low-immunological-risk kidney transplant recipients increases risk of rejection and appearance of donor-specific antibodies: a randomized study. Am J Transplant 2017;17:1370–9.

[19] Egeland EJ, Robertsen I, Hermann M, et al. High tacrolimus clearance is a risk factor for acute rejection in the early phase after renal transplantation. Transplantation 2017;101:e273–9.

[20] Ekberg H, Bernasconi C, Tedesco-Silva H, et al. Calcineurin inhibitor minimization in the symphony study: observational results 3 years after transplantation. Am J Transplant 2009;9:1876–85.

[21] Aktürk S, Erdoğmuş, Kumru G, et al. Average tacrolimus trough level in the first month after transplantation may predict acute rejection. Transplant Proc 2017;49:430–5.

[22] Borobia AM, Romero I, Jimenez C, et al. Trough tacrolimus concentrations in the first week after kidney transplantation are related to acute rejection. Ther Drug Monit 2009;31:436–42.

[23] Staatz C, Taylor P, Tett S. Low tacrolimus concentrations and increased risk of early acute rejection in adult renal transplantation. Nephrol Dial Transplant 2001;16:1905–9.

[24] Böttiger Y, Brattström C, Tydén G, Säwe J, Groth CG. Tacrolimus whole blood concentrations correlate closely to side-effects in renal transplant recipients. Br J Clin Pharmacol 1999;48:445–8.

[25] Cosio FG, Amer H, Grande JP, Larson TS, Stegall MD, Griffin MD. Comparison of low versus high tacrolimus levels in kidney transplantation: assessment of efficacy by protocol biopsies. Transplantation 2007;83:411–6.

[26] Flechner SM, Glyda M, Cockfield S, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. Am J Transplant 2011;11:1633–44.

[27] Albano L, Banas B, Klempnauer JL, Glyda M, Viklicky O, Kamar N. Osaka trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. Transplantation 2013;96:897–903.

[28] Jones-Hughes T, Snowsill T, Haasova M, et al. Immunosuppressive therapy for kidney transplantation in adults: a systematic review and economic model. Health Technol Assess 2016;20:1–594.

[29] Barraclough KA, Isbel NM, Johnson DW, Campbell SB, Staatz CE. Once- versus twice-daily tacrolimus. Drugs 2011;71:1561–77.

[30] Dugast E, Soulillou JP, Foucher Y, et al. Failure of calcineurin inhibitor (tacrolimus) weaning randomized trial in long-term stable kidney transplant recipients. Am J Transplant 2016;16:3255–61.

[31] Jarzembowski T, Panaro F, Raofi V, et al. Long-term results of a prospective randomized trial comparing tacrolimus versus cyclosporine in African-American recipients of primary cadaver renal transplant. Transpl Int 2005;18:419–22.

[32] Ekberg H, Van Gelder T, Kaplan B, Bernasconi C. Relationship of tacrolimus exposure and mycophenolate mofetil dose with renal function after renal transplantation. Transplantation 2011;92:82–7.