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Combination of Ketoconazole and Tacrolimus Increases the Risk of Kidney Transplant Rejection in African Americans

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Abstract

African Americans have a rapid metabolism and require high dose of tacrolimus after kidney transplantation. Ketoconazole inhibits tacrolimus metabolism and can be used to reduce its dosage and financial cost. The long-term safety of such a practice has not been reported. We study 5-year outcome of ketoconazole and tacrolimus combination in African Americans with kidney transplants. From 2006 to 2010 in our center, ketoconazole was given in 127 African Americans (Group 1), while 82 African Americans did not receive any ketoconazole (Group 2). All received triple maintenance. There was no difference in any basic demographic among the 2 groups. The 5-year incidence of acute rejection was significantly higher in Group 1 than in Group 2 (38.6 vs. 20.7%, p=0.01). Kaplan-Meier estimated 5-year graft survival (69.3 vs. 75.6%, p=0.3) and patient survival (85 vs. 87.8%, p=0.6) were not statistically different between the 2 groups. Addition of ketoconazole was an independent risk of acute rejection (HR 3.13, 95% Cl 1.28-7.60; p=0.012) by multivariable analyses, while higher tacrolimus dose in the 2nd month of transplant was protective (HR 0.79, 95% Cl 0.64-0.91; p=0.036). Therefore, combination of ketoconazole and tacrolimus significantly increased the risk of acute rejection in African Americans after kidney transplantation.

Keywords: African American; Tacrolimus; Ketoconazole; Pharmacokinetics; Cytochrome P450-3A5; Kidney transplant; Acute rejection

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Introduction

Tacrolimus is the most important immunosuppressive drug for kidney transplant patients. It is mainly metabolized by cytochrome P450-3A5 (CYP3A5) enzymes and P-glycoprotein in liver and intestine [1-3]. Ketoconazole can inhibit the CYP3A5 enzymes and P-glycoprotein and decrease the metabolism of tacrolimus. As the cost of ketoconazole is very low, and it has been frequently used to reduce the dose and cost of tacrolimus. There were small studies that demonstrated the financial benefit and short-term safety of such a practice in kidney transplant patients [4,5]. We have previously published a large long-term study of ketoconazole and tacrolimus co-administration in kidney transplant patients and found a significantly higher incidence of acute rejection, which questions the safety of such a common practice [6].

African American (AA) ethnicity is usually considered a risk factor for poor outcome after kidney transplant. AA patients have a higher incidence of rejection and inferior graft survival. Numerous factors have been proposed as explanations, including social and economic status, immunological features and drug metabolism [7-9]. AA patients seem to have more rapid tacrolimus metabolism and may require higher doses of tacrolimus than Caucasians to achieve the similar trough levels. Recent pharmacogenetic studies have found that genetic polymorphism in CYP3A5 expression determines the individual's tacrolimus metabolism [10-14]. AA patients more likely carry CYP3A5*1 allele (CYP3A5 expressers), which leads to rapid metabolism of tacrolimus, while other ethnicities more likely are CYP3A5 nonexpressers, which is associated with normal or low metabolism of tacrolimus [13,14].

Therefore, the co-administration of ketoconazole with tacrolimus can provide greater reduction on tacrolimus dose and financial cost in AA patients. However, the clinical safety of such a practice has not been investigated in this high risk subgroup. Therefore, we analyze the 5-year outcomes of AA patients who received ketoconazole and tacrolimus combination after kidney transplants.

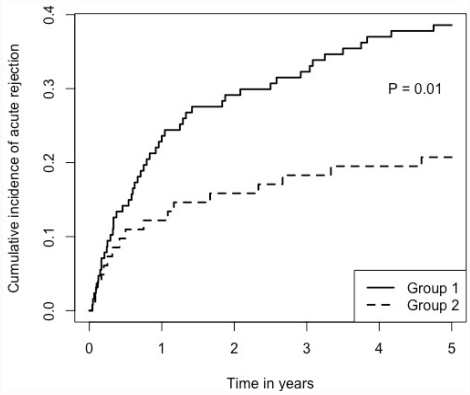

Figure 1: The cumulative incidences of biopsy-confirmed and clinically-treated acute rejection between Group 1 and Group 2. The 1, 3, and 5 year incidences of acute rejection were 23.6%, 32.3% and 38.6% in Group 1, and 12.2%, 18.3% and 20.7% in Group 2 (log rank p=0.01).

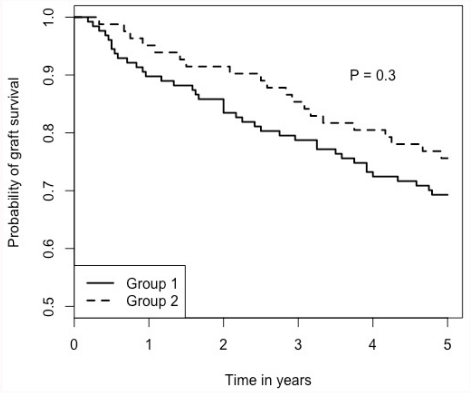

Figure 2: The graft survival analysis by Kaplan-Meier method. The estimated 1, 3, and 5 year graft survival rates were 89.8%, 78.7% and 69.3% in Group 1, and 95.1%, 85.4% and 75.6% in Group 2 (log rank p=0.3).

Patients and Methods

Study population

As described in our previous study, patients were identified from the Tulane University Hospital transplant database between 2006 and 2010 [6]. Briefly, there were consecutive 266 adult AA patients who received a primary kidney transplant at our transplant program during this 5 years' period. Among them, ketoconazole was added in 127 patients after transplant (Group 1), while 82 patients did not receive any ketoconazole (Group 2). Traditional triple combination of tacrolimus, mycophenolate and steroid was used as maintenance therapy in all patients. A total of 57 AA patients were excluded from this study due to the following reasons: primary graft non-function (N=2), death in first week of transplant surgery (N=1), lost fellow-up (N=13), different maintenance immunosuppressive drugs (N=22), or usage of other CYP3A5 inhibitors (such as amiodarone, verapamil) or reducers (such as phenytoin, rifampin) (N=7). We also excluded 12 patients from analysis, in whom ketoconazole was initially started but later discontinued.

Immunosuppressive therapy and acute rejection

The detailed protocols were also reported in our previous study [6]. During that time period, our immunosuppressive protocol was to give induction therapy with 2 doses of basiliximab. Corticosteroids were administrated as intravenous methylprednisolone peri-operatively, and changed to oral prednisone on post-operative day 4, which was tapered down to a maintenance dose of 5mg after the 2nd month of surgery. Each patient was started mycophenolate, either mycophenolate mofetil at 1 gram or sodium mycophenolate at 720mg, twice daily. Oral tacrolimus was started after surgery, and the doses were adjusted to keep the 12hr trough levels at 8 to 12 ng/ml for the first year. The target of tacrolimus trough levels was generally lowered after the first year, to the range of 4 to 7 ng/ml. The decision of adding ketoconazole was made within the first week of transplant in order for patients to rapidly achieve the targeted trough levels before discharge. The dose of ketoconazole was typically 100mg per day. Bacterial, fungal and viral prophylaxes were used in all patients per protocol. Kidney biopsy was performed in all cases of clinically presumed acute rejection. The type and severity of acute rejection was defined according to Banff criteria, and was treated according to our center's established protocol as described previously.

Statistical analysis

We compared the clinical outcomes including the 5-year cumulated incidences of biopsy-confirmed and clinically-treated acute rejection, transplant allograft survival rates and patient survival rates, renal allograft function, clinically captured and treated infections, as well as the risk factor analysis for acute rejection. Statistical analyses were performed using R basic functions and R packages (Survival and Survminer). Chi-squared or Fisher exact test was used for dichotomous data, t-test was used for continuous measures. Product-limit estimates of survival curves were generated by the Kaplan–Meier method and the survival difference was analyzed by log-rank test. Multivariate statistical modeling was performed using Cox proportional hazards model to simultaneously evaluate the effects of multiple factors of acute rejection. A P-value <0.05 was considered statistically significant.

Results

A total of 266 adult AA patients received a primary kidney transplant during the study period, 209 of them met study criteria and were included. The basic demographic characteristics at the time of kidney transplants are summarized in Table 1, and there was no statistical significance between the two groups. The tacrolimus daily dose, 12hr trough blood level and renal allograft function (serum creatinine levels) are reported in Table 2. According to our immunosuppressive protocol, targeted blood trough levels were achieved at all time-points in both groups. However, group 1 needed a higher initial dose of tacrolimus at the first post-operative week. After ketoconazole was added, the required tacrolimus dose decreased as expected. Subsequently, Group 1 had significantly lower dose of tacrolimus in the first post-operative month as well as in all time points afterwards. The renal allograft function as measured by serum creatinine (sCr) levels were similar in the 2 groups.

Several clinical complications and events after transplant surgery are summarized in Table 3. The percentage of patients with DGF that required dialysis support in the first post-operative week was not significantly different among the 2 groups, neither was the incidence of calcineurin inhibitor (CNI) toxicity or infectious complications. The CNI toxicity reported here was the renal toxicity by kidney biopsy and required tacrolimus dose reduction. There was significant difference in the biopsy-confirmed and clinically-treated acute rejections among the 2 groups (Figure 1). The 1, 3, and 5 year cumulative incidences of acute rejection were 23.6%, 32.3% and 38.6% in Group 1, and 12.2%,

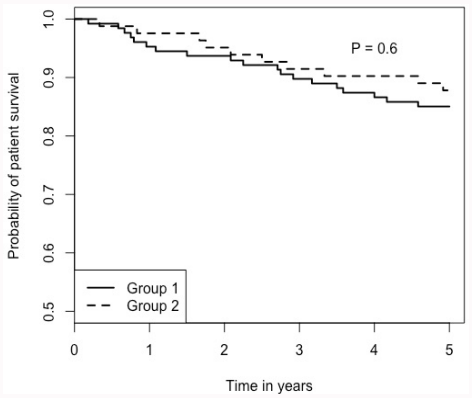

Figure 3: The patient survival analysis by Kaplan-Meier method. The estimated 1, 3, and 5 year patient survival rates were 95.3%, 89.8% and 85% in Group 1, and 97.6%, 91.5%, 87.8% in Group 2 (log rank p=0.6).

Table 1: Demographic characteristics of transplant patients between Group 1 (with ketoconazole) and Group 2 (without ketoconazole).

	Group 1 (N=127)	Group 2 (N=82)	*p*-value
Age, mean ± SD (yrs)	48.1 ± 13.6	49.5 ± 14.7	0.48
Gender (%)			0.47
male	58.3	63.4	
female	41.7	36.6	
BMI (kg/m^2)	29.5 ± 5.6	28.8 ± 6.2	0.4
Peak PRA (%)	17.5 ± 24.3	15.2 ± 28.3	0.53
HLA mismatch	4.2 ± 1.5	4.0 ± 1.8	0.39
Causes of ESRD (%)			0.98
diabetes	23.6	24.4	
hypertension	41.7	45.1	
nephritis	15.7	13.4	
PCKD	7.9	7.3	
others	11.1	9.8	
Induction (%)	89.8	91.5	0.81
Donors (%)			0.87
living	23.6	22	
deceased	76.4	78	
CIT (hrs)	18.3 ± 7.1	19.1 ± 7.9	0.45

18.3% and 20.7% in Group 2 (log rank p=0.01). The types of acute rejection were not different among the 2 groups (Table 3).

Despite of an obvious trend, the graft survival by Kaplan-Meier analysis was not statistically significant in the two groups (Figure 1). The estimated 1, 3, and 5 year graft survival rates were 89.8%, 78.7% and 69.3% in Group 1, and 95.1%, 85.4% and 75.6% in Group 2 (log rank p=0.3). There was no difference in patient survival between the two groups (Figure 2). The Kaplan-Meier estimated patient survival rates at 1, 3, and 5-year were 95.3%, 89.8% and 85% in Group 1, and 97.6%, 91.5%, 87.8% in Group 2 (log rank p=0.6). The causes of renal allograft failure and patient death are summarized in Table 3.

Cox proportional hazards model was used to further analyze the risk factors for acute rejection, and several significant factors were identified (Table 4). Addition of ketoconazole was found as an independent risk of rejection (HR 3.13, 95% Cl 1.28-7.60; p=0.012). We also examined the required daily dose of tacrolimus at each time point. Interestingly, it was noted that the tacrolimus dose in the 2nd post-operative month was a significant factor (HR 0.79, 95% Cl 0.64-0.91; p=0.036), the higher the daily dose of tacrolimus, the lower the risk of acute rejection. As commonly described in literatures, we also found that live donor kidneys were associated with lower risk of acute rejection compared to the deceased donor kidneys, while development of DGF or infectious complications after kidney transplant increased the risk of acute rejection.

Discussion

Tacrolimus remains the backbone of modern immunosuppressive therapy in solid organ transplants. Due to its side effects, narrow safety margin and large variability in its absorption and metabolism, clinical monitoring for tacrolimus exposure is necessary [1-3]. The pharmacokinetic curve of tacrolimus normally has a peak-and-trough pattern. A rapid peak phase after an oral dose reflects the absorption by the gastrointestinal tract, which is followed by a slow slope towards trough level that reflects its metabolism. Tacrolimus dosing ideally should be based on a 12-hour area under the curve (AUC) that reflects its real exposure. However in our daily practice, oral doing is usually guided by monitoring its 12-hour trough levels due to the assumed correlation between trough level and AUC [2,3,10,15]. Recent pharmacogenetic studies have found that genetic polymorphism in CYP3A5 expression determines the individual's tacrolimus metabolism [10-14]. AA patients more likely carry CYP3A5*1 allele (CYP3A5 expressers), which leads to rapid metabolism of tacrolimus. AA patients usually require higher doses of tacrolimus than Caucasians to achieve the similar trough levels. Therefore, the addition of ketoconazole to inhibit CYP3A5 enzymes can provide greater reduction on tacrolimus dose and financial cost in AA transplant recipients.

Our current study indicates that the combination of ketoconazole and tacrolimus increases the risk of acute rejection in AA patients. This is the first study to question the safety of such a common practice in this population. The 5-year acute rejection was significantly higher in group 1 with ketoconazole than in group 2 without ketoconazole (38.6% vs. 20.7%; p=0.01), although similar targeted trough levels of tacrolimus were achieved at all time-points according to our protocol. The patients in group 1 required higher dose of tacrolimus than the patients in group 2 during the first week of surgery. When ketoconazole was added, their daily tacrolimus dose decreased. Subsequently, group 1 required significantly lower dose of tacrolimus in the first month and at all time-points after that. We further analyzed the risk factors for acute rejection and found that ketoconazole usage was an independent risk of acute rejection (HR 3.13, 95% Cl 1.28-7.60; p=0.012). The daily tacrolimus dosage in the 2nd month was protective from acute rejection (HR 0.79, 95% Cl 0.64-0.91; p=0.036), i.e. the higher the daily dose of tacrolimus, the lower the risk of acute rejection. Therefore, the higher incidence of acute rejection may be related to the lowered dose of tacrolimus from ketoconazole co-administration.

There were studies from Egypt, which reported the safety as well as cost reduction of cyclosporine with ketoconazole in patients who received living-related donor kidneys [16,17]. The combination of ketoconazole and tacrolimus was also studied in a total of 70 patients with living donor kidney transplants [4,5]. The addition of ketoconazole had significant reduction of tacrolimus dose (by 58.7%) and financial cost (by 56.9%) compared with those without

Table 2: Tacrolimus dose, trough level and kidney function in the two groups.

	1 week	1 month	2 month	1 year	3 year	5 year
Tacrolimus Dose (mg/day)						
Group 1:	12.5±5.9	7.6±4.3	6.6±3.9	6.2± 3.8	5.6±3.6	5.2±3.1
Group 2:	9.6±4.6	8.9±4.0	8.6±3.8	8.2 ± 3.4	7.8 ± 2.7	7.1 ± 3.1
p-value	0.0002	0.048	0.0003	<0.0001	<0.0001	<0.0001
Tacrolimus Trough level (ug/dl)						
Group 1:	10.6±2.4	11.3±1.9	9.6±1.8	8.5±2.1	5.7 ±1.9	5.1±1.5
Group 2:	11.8±1.9	10.5±2.1	9.8±1.9	8.9±2.2	5.4±1.7	4.9 ±1.6
Serum Cr (mg/dl)						
Group 1:	2.5±1.4	1.9±1.2	1.6±0.8	1.5±1.2	1.6±1.1	1.7±0.9
Group 2:	2.2±1.3	1.8±1.3	1.7±0.9	1.6 ±1.1	1.7±0.9	1.8±1.0

Table 3: Post transplant events and causes of graft loss and patient death.

	Group 1 (N=127)	Group 2 (N=82)	*p*-value
Post transplant Events, n (%)			
Delayed graft function	44(34.6)	25(30.5)	0.55
Acute rejection	49(38.6)	17(20.7)	0.01
type of rejection:			0.95
cellular rejection	31	10	
antibody rejection	5	2	
both rejections	13	5	
CNI toxicity	8(6.3)	10(12.2)	0.21
Infectious diseases	38(29.9)	33(40.2)	0.14
type of infection:			0.96
Bacteria	16	14	
BKV	11	8	
CMV	7	6	
HSV	3	3	
Fungus	1	2	
Total Graft Loss, n (%)	39(30.7)	20(24.4)	0.32
causes of graft loss:			0.98
DWFG	15	8	
CAN	12	6	
rejection	9	4	
Infection	3	2	
Total Patient Death, n (%)	19(15)	10(12.2)	0.64
causes of death:			0.97
CVD	13	7	
infections	3	2	
malignancy	2	1	
others	1	0	

Table 4: Multivariable analysis of risk factors for acute rejection.

	Hazard ratio	95% CI	*p*-value
Donor (living vs. deceased)	0.36	0.19-0.91	0.04
Ketoconazole (yes vs. no)	3.13	1.28-7.60	0.012
Delayed graft function (yes vs. no)	2.34	1.20-3.83	0.01
Infection (yes vs. no)	1.78	1.10-3.50	0.041
Tacrolimus dose (mg/d) in 2nd month	0.79	0.64-0.91	0.036

ketoconazole at 6 months [4]. After 2 years of kidney transplants, the ketoconazole group demonstrated similar benefits of both tacrolimus dose reduction and financial saving [5]. Coadministration of ketoconazole was not associated with higher risk of rejection or inferior graft survival in any of their studies. Our study is different from theirs. We include much more patients, have a longer follow-up, and more importantly, we focus on AA patients who are well-known to be associated with poor outcomes after kidney transplants. Also, the allografts from deceased donors (76.4% and 78% in Group 1 and 2) rather than from living donors were the main sources of our transplants, and more than 30% of our patients had DGF after surgery. Therefore, our patients had much higher risk for acute rejection [18,19].

The idea of studying this issue originates from our experience in the NIH funded investigation of organ transplants in HIV positive patients [20-22]. Unexpectedly higher incidences of acute rejection in both kidney and liver recipients were noted, and many of those rejection episodes happened early after transplant, and were aggressive and difficult for treatment [20,21]. Although the targeted trough levels of CNIs in HIV infected recipients were consistent with those in non-HIV patients, but their daily doses of CNI were much lower due to concurrent administration of anti-retroviral protease inhibitor, which inhibits CNI metabolism by CYP3A5 enzymes. Further study revealed that the pharmacokinetic curves of tacrolimus in these patients looked like a flat line, which did not have a normal peak-and-trough pattern as in non-HIV patients [23]. Recently, the pharmacokinetics of tacrolimus in HIV patients treated with ritonavir was examined, and it was found that their tacrolimus curves did not have the peak phases of absorption. When similar trough levels were targeted, their tacrolimus exposures (12-hour AUC) were about 44% lower than the exposures in non-HIV recipients [24]. It was estimated that the trough levels of tacrolimus in the HIV infected patients with ritonavir therapy should be 40% higher than in the non-HIV recipients in order to achieve comparable tacrolimus exposures (12-hour AUC). Higher targeted trough levels of tacrolimus were previously shown to decrease the risk of rejection (HR, 0.90; 95% CI, 0.81-1.00; p=0.04) in HIV infected recipients [20]. A recent study has suggested the integrase inhibitor-based therapy that does not inhibit CYP3A5 enzymes as the preferred antiretroviral regiment in HIV-infected patients for kidney transplants [25].

The similar altered pharmacokinetics could also exist in our

patients. We speculate that the addition of ketoconazole decreased tacrolimus dose, flatted its peak-and-trough curve, reduced the exposure (12-hour AUC) of tacrolimus, and consequently increased the risk of acute rejection. AA patients are well known to be associated with high incidence of acute rejection and poor graft survival. Our study suggests that the combination of ketoconazole and tacrolimus is another independent risk for acute rejection, which may further contribute to the inferior long-term graft survival in this high risk population. Our study is limited by single center data, retrospective nature, and lack of multi-timed tacrolimus levels for AUC calculation. Nevertheless, it is the first study suggests the usage of ketoconazole to reduce tacrolimus dose is an independent risk factor, and the combination of ketoconazole and tacrolimus significantly increases the incidence of acute rejection in AA transplant recipients. This is an important issue for clinicians who take care of these patients with financial difficulty. Further study is needed to define the pharmacokinetic curve of tacrolimus with ketoconazole so that proper tacrolimus trough levels can be proposed and/or determined for clinical practice.

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