JOJ
Urology & Nephrology
ISSN: 2476-0552

Juniper Publishers
key to the Researchers

Research Article
Volume 5 Issue 1 - January 2018
DOI: 10.19080/JOJUN.2018.05.555652

JOJ uro & nephron

Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation- A Prospective Study

Manish Tripathi*

Department of Nephrology, Emirates European Hospital, Sharjah, UAE

Submission: December 14, 2017; **Published:** January 30, 2018

***Corresponding author:** Manish Tripathi, Department of Nephrology, Emirates European Hospital, Sharjah, UAE, Tel : +971 6 561 9444; Fax : +971 6 561 9300; Email: drmanish@eehospital.com

Abstract

Acute Rejection is the key mediators of long term graft loss. So we aimed the present study to assess the correlation of baseline pre transplant trough tacrolimus level with early rejection. We prospectively analyzed the trough tacrolimus level on the day prior to transplantation of 179 patients transplanted from September 2007 to September 2009. We divided them into three groups according to the trough levels: Group I=<5ng/ml, Group II=5-15ng/ml and Group III=>15ng/ml. Their demography, incidence of BPAR, NOD, infections and biopsy proven CNI toxicity were studied. Incidence of BPAR were the highest in the Group I and lowest in the Group III. None of the patients in Group III had rejection with Banff grade >2. Incidences of post transplant at infection, new onset diabetes were comparable. Trend towards higher incidence of biopsy proven CNI toxicity was noted from Group I to Group III. These results indicate that the incidence as well as severity of early rejection reduces as the pre transplant trough tacrolimus level increases. Trend towards higher nephrotoxicity with higher trough level was noted.

Keywords: Acute rejection; Renal transplant; Pre transplant tough tacrolimus level; Live donors; Graft survival; nephrotoxicity

Abbreviations: BPAR: Biopsy Proven Acute Rejection; NOD: New Onset Diabetes; CNI: Calcineurin Inhibitor; MMF: Mycophenolate Mofetil; WIT: Warm Ischemia Time; CIT: Cold Ischemia Time; PTDM: Post Transplant Diabetes Mellitus; TAC: Tacrolimus; DGF: Delayed Graft Function; OHA: Oral Hypoglycemic Agent; TMA: Thrombotic Microangiopathy; TRAS: Transplant Renal Artery Stenosis; AGE: Acute Gastroenteritis; CMV: Cytomegalo Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; UTI: Urinary Tract Infection; TCMR: T Cell Mediated Rejection; AMR: Antibody Mediated Rejection; TIR: Tubulo-Interstitial Rejection

Introduction

Short-term transplant outcomes have improved such that, if no rejection episodes occur, recipients of live donor grafts can now expect graft function to exceed 95% at 1 year and 90% after 5 years. Several studies have shown that acute rejection is the most significant risk factor for chronic rejection and potential surrogate for long-term graft failure. Several trials are now aimed at the reduction of early acute rejection episodes to improve long term graft survival.

Transplantation with living donor allows anticipated planning of the procedure, which can be performed before dialysis treatment, and prior administration of an immunosuppression scheme. Pre-transplant administration of immunosuppression aims to minimize the incidence and severity of episodes of acute rejection. The risk of acute rejection is greater in the first week post-transplant and progressively decreases after the first months. Thus, the concentration of immunosuppressive drugs must be maximal at this initial phase and tapered during subsequent months, according to the evolution of patient and graft function [1-10].

Many transplantation centers advocate the administration of immunosuppression pre-transplant, with a variation of one to five pre-operative days, while other centers only start the therapy after the surgery. The potential disadvantages of early administration of immunosuppression therapy are the risk of infection and the nephrotoxicity effects of calcineurin inhibitors during allograft reperfusion [11-20].

Up to the present moment, there is only one systematic study that addresses the impact of pre-transplant administration of immunosuppressive therapy consisting of cyclosporine as the CNI, on incidence and severity of acute rejection.

Materials and Methods

Study design

This is an open label randomized study consisting of renal allograft recipients from living donors. This study was carried out by Department of Nephrology, at a tertiary level referral hospital in western India, between January 2008 to September 2009. All patients enrolled were older than 18 years. The

protocol received approval from the Ethical Committee of Muljibhai urological hospital society. All the patients in the study received pre-transplant immunosuppression starting 3 days prior to transplant. The follow up period was 1 year post transplant.

Immunosuppresion scheme

Patients from the study group received Tacrolimus (0.15mg/kg/d) divided into 2 doses and Azathioprine (2mg/kg/d), single dose, or Mycophenolate mofetil (4gm/d) divided into 2 doses, iniciated 3 days pre-transplant. Methylprednisalone (1g) was administered intravenous during surgery and after and after that, oral prednisalone was iniciated (0.8mg/kg/d) and gradually tappered to 0.3mg/kg/d after 3 months of transplant.

Doses of Tacrolimus were adjusted according to the 12hr trough level (C min), aiming to maintain the whole blood trough level between 10-20ng/ml over the initial 3 months post transplantation period and subsequently trough levels were reduced to 5-15ng/ml. Azathiprine dose was reduced or suspended in the presence of leucopenia.

The Prednisalone dose was tapered to 0.4mg/kg/d at the end of the first month, 0.3mg/kg/d at the second month, reaching 0.2mg/kg/d at the third month.

Clinical assessment

Serum creatinine was determined daily during the first 10 days and on day 14, 21, 28, 45, 60, 90, 180, 240 post transplant. C min was measured using a semiautomated fluroscence polarization immunoassay . Baseline trough levels were measured on day of transplant and twice/week thereafter for the first 10 days. Subsequently trough levels were measured as per graft function and clinical requirement [21-40].

The diagnosis of acute rejection was based on clinical and laboratory data. Percutaneous biopsy was always performed to confirm the diagnosis. The Banff 97 classification was used to graduate rejection severity. Acute rejection treatment included methylprednisalone (500mg/d) for 3-5 days or anti-lymphocyte globulin (ATG) in case of severe acute rejection (Banff grade 3) or steroid resistant acute rejection.

The rejection-free graft survival was defined as patients free of rejection based in clinical/laboratory and or biopsy data. Graft loss was defined by the requirement of permanent dialysis after graft failure. Delayed graft function was defined as the requirement of dialysis during the first week after transplant in the absence of rejection and or technical problems.

Non- response of acute rejection to conventional therapy was considered a failure of the protocol and the reason for conversion of the immunosuppression therapy.

Statistical analyses

Demographic, baseline characteristics and outcome characteristics were collected tough out the first year post-transplant. Demographic data included donor and recipient age, gender, relation and underlying native kidney disease. Baseline transplant information included induction used, anti-proliferative used, number of HLA mismatches, graft renal artery number (single or dual), WIT and CIT. Data on complications was also collected including post transplant rejections, surgical complications, infections, liver dysfunctions, PTDM, TAC nephrotoxicity, and delayed graft functions (DGF). DGF was defined as need for dialysis in the first week post-transplant [41-50]. PTDM was defined as requirement for oral hypoglycemic agents or insulin for the first time post-transplant. The outcome was assessed on the incidence and severity of acute rejection in correlation to base-line trough tacrolimus level measured on day 0 of transplantation. The side-effects of the immunosuppressive therapy was also assessed in the form of; episodes of post-transplant infection and their severity; liver dysfunction; PTDM and its severity (transient or persistent; requiring OHAs or insulin) [51-60].

Patients were divided and analyzed in three groups based on base-line trough TAC level on day 0 post-transplant: Group 1: TAC 0-5ng/ml (n=34), Group 2: TAC 5-15ng/ml (n=12), Group 3: TAC>15ng/ml (n=33).

Simple statistical tools were used for calculating demographic parameters. The difference between the two group means was tested using Student's t-test and the presence of episode within two groups by 2x2 Chi-square test. SPSS version 15.0 was used to carry the logistic regression analysis and to find the Pearson's correlation coefficients.

Results

One hundred and seventy-nine patients were included in the study, 145 (81%) males and 34 (19%) were females. The median age of cohort was 47.35 years (range 13-65 years). Table 1 shows sex wise distribution of cases [61-70].

Table 1: Tacrolimus toxicity.

Tacrolimus Toxicity	Number of Cases	Total Cases	Percentage
Present	85	179	47.49%
Absent	94%	179	52.51%

Table 2: Types of tacrolimus toxicity.

Tacrolimus Toxicity Type	Number of Cases	Total Cases	Percentage
Post transplant DM	73	179	40.78%
persistent	55	73	75.34%
transient	18	73	24.66%
Liver Dysfunction	1200.00%	179	6.70%
drug induced	400.00%	12	33.33%
infectious hepatitis	700.00%	12	58.33%
sepsis	100.00%	12	8.33%

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

Patients were divided and analyzed in three groups based on base-line trough TAC level on day 0 post-transplant: Group 1 : median TAC 3.45ng/ml (n=34, range 1.1-5.0ng/ml), Group 2: median TAC 7.7ng/ml (n=12, range 5.1-14.9ng/ml), Group 3: median TAC 20.7ng/ml (n=33, range 15.6-36.7ng/ml). This is as shown in Table 2.

Our decision to take base-line trough tacrolimus level measured on day 0 of transplantation was based on the wide-ranging TAC seen in that time frame, despite all patients receiving the same initial oral dose of 0.15mg/kg bid being started 2 days before transplant. TAC doses were subsequently adjusted in all groups to achieve a target TAC of 12-14ng/ml by one week post-transplant [71-80].

Baseline demographics

Male: female ratio among recipients in Group 1 was 24:10; Group 2 was 94:18; Group 3 was 27:6. Male: female ratio among donors in Group 1 was 9:25; Group 2 was 39:73 and in Group 3 was 13:20, as shown in Table 3.1 & 3.2 respectively [81,82].

Table 3.1: Gender.

T0 Level	<05	15-May	>15
Male	24	94	27-Jan
Female	10	18	06

Table 3.2: Donor gender.

T0 Level	<05	15-May	>15
Male	9-Jan	39	13
Female	25	73	20

Ratio of related donors to unrelated donors in each in each group was: Group 1- 28:6; Group 2- 76:36; Group 3- 22:11. Table 4 depicts this data [83,84].

Table 4: Relation.

T0 Level	<05	15-May	>15
Related	28	16-Mar	22-Jan
Other than related	6-Jan	36	11

Table 5: Age.

T0 Level	<05	15-May	>15
<20yrs	09	16	9
20-40yrs	05	77	30
>40yrs	01	21	11

Average age of recipient age in Group 1 was 49.06+10.15; in Group 2 was 47.38+9.6 and in Group 3 was 46.42+10.2. Table 5 categorizes them into 3 groups i.e. <20yrs; 20-40 yrs and >40yrs.

Average age of donor in Group 1 was 49.05+10.15; in Group 2 was 47.7+10.14 and in Group 3 was 46.42+10.2. This is again categorized into 3 groups as shown in Table 6 [84,85].

Table 6: Donor age.

T0 Level	<05	15-May	>15
<40 years	6	29	7
40-60years	24	73	24
>60years	4	10	02

Total ischemia time (TIT) was comparable in all 3 groups; in Group 1 TIT was 61.32+17.58; in Group 2 TIT was 57.15+9.7 and in Group 3 was 58.42+13.61. TIT in all the groups was divided into 3 groups as mentioned in Table 7.

Table 7 : TIT.

T0 level	<05	05-15	>15
<50min	07	25	06
50 - 70min	20	71	23
>70min	07	15	04
Average TIT	61.32±17.58	57.15±9.7	58.42±13.61

HLA mismatch

HLA mismatch in 3 groups were as follows: Group 1 haplo match was in 9 and nil match was in 0; Group 2 haplo match was in 27 and nil match was in 5; Group 3 haplo match was in 8 and nil match was in 1 patient. Various degree of HLA mismatch in all 3 groups is as shown in Table 8 [86,87].

Table 8: HLA match.

T0 level	<05	05-15	>15
Full house	01(2.94%)	15(13.39%)	05(15.15%)
Ag1	06	17	03
Ag2	15	38	14
Ag3(haplo)	09(26.47%)	27(24.10%)	08(24.24%)
Ag4	02	07	01
Ag5	01	03	01
Ag6(nil)	00(0%)	05(4.4%)	01(3%)

Immunosupression

Use of induction (ATG or IL2 receptor blockers) in 3 groups was as follows: Group 1-15; in Group 2-35; in Group 3-17. Different induction protocols used in 3 groups are as shown in Table 9.

Table 9: Induction.

T0 level	<05	05-15	>15
ATG	01	07	02
Basiliximab	04	14	08
Decluzimab	10	14	07
Nil	19	78	16
Total used	15(44.11%)	35(31.25%)	17(51.15%)

Use of anti-proliferatives (AZA: MMF) in 3 groups were as follows: in Group 1- 20:14; in Group 2 - 50:62 and in Group 3 - 11:22. This is shown in Table 10.

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

Table 10: Antiproliferatives.

T0 level	<05	05-15	>15
MMF	14(41.18%)	62(55.36%)	22(66.76%)
AZA	20(58.82%)	50(44.64%)	11(33.33%)

Complications

Biopsy proven CNI toxicity in 3 groups was as follows: Group 1 - 2 (5.9%); in Group 2 - 9 (8.03%) and in Group 3 - 5 (15.1%). Table 11 shows its distribution in 3 groups.

Table 11: Tacrolimus toxicity.

T0 level	<05	05-15	>15
Tacrolimus toxicity	02 (5.9%)	09 (8.03%)	05 (15.1%)

New onset diabetes after transplant (NODAT) in 3 groups was as follows: Group 1- 17(50%); Group 2 - 42 (13.5%) and in Group 3 -14 (42.4%) (Table 12) [88-90].

Table 12: Post Transplant DM.

T0 level	<05	05-15	>15
Post Transplant DM	17 (50%)	42 (13.5%)	14 (42.4%)

Non-infectious complications occurring during hospitalization and outpatient follow-up were as follows: Femoral neuropathy - 2; G.I side effects of MMF - 3; Hypertensive encephalopathy - 1; Proteinuria - 1; TMA -1; TRAS - 2. This distribution is shown in Table 13.

Table 13: Non- infectious Complications.

Non- infectious Complications	Number of Cases	Total Cases	Percentage	Number of Cases
Femoral neuropathy	02	20	10.0%	02
GI side effects of MMF	03	20	15.0%	03
HT encephalopathy	01	20	5.0%	01
Proteinuria	01	20	5.0%	01
TMA	01	20	5.0%	01
TRAS	12	20	60.0%	12

Infectious complications were present in 57 patients.They were as follows: Acute gastroenteritis-5; CMV disease -14; Urinary tract infection - 26; Tuberculosis - 2; Lower respiratory tract infection - 3; Herpes Zoster - 1; Post transplant HCV-1; post transplant HBV-3; Infected lymphocoel-1; Polyoma virus infection-1. Table 14 shows this distribution [90-100].

Table 14: Post transplant infections.

Post transplant infections	<05	05-15	>15	Total case (n=57)
AGE	01	04	-	5
CMV	02	08	04	14
FUNGAL	01	-	-	1
LRTI	01	01	01	3
TB	01	01	-	2
UTI	05	11	07	26
HBV	-	02	01	3
HCV	-	-	01	1
Lymphocoel	-	01	-	1
VZ-1	-	01	-	1
PV-1	-	01	-	1

Rejections

Over the course of one year following transplant, there were 44 (24.58%) cases of biopsy proven ACR. When examined by quartile, a significant reduction in the rates of ACR was seen from Groups 1-3. In Group 1 total ACR were 12 (35.3%); in Group 2 total ACR were 27(24.1%); and in Group 3 total ACR were 5(15.2%). This is shown in Table 15 [101-105].

Table 15:

T0 level	<05	05-15	>15	Total rejections
Rejection	12 (35.3%)	27 (24.1%)	05 (15.2%)	44 (24.58%)

Banff grading of these rejection episodes showed that grade 2 and grade 3 rejection were absent in Group 3, as seen clearly in Table 16 [105-110].

Table 16 : BANFF Classification.

T0 level	<05	05-15	>15
AMR1	01	03	-
AMR3	-	01	-
TCMR1A	03	10	02
TCMR1B	03	03	-
TCMR2A	02	04	-

Rates of post transplant infections in each group were as follows: in Group1- 12 (35.3%); in Group 2 - 33(29.5%) and in Group 3 - 15(45.4%). This is seen in Table 17 [111-113].

Table 17:

T0 level	<05	05-15	>15	Total infections
Infections	12 (35.3%)	33 (29.5%)	15 (45.4%)	60 (33.51%)

Graft survival rates at the end of 1 year in each group was as follows: in Group 1 - 97.1%; in Group 2 - 98.2% and in Group 3 - 100% as shown in Table 18.

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation- A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

Table 18: Graft survival.

T0 level	<05	05-15	>15
Graft survival %(1 yr)	97.1%	98.2%	100%

Discussion

ACR is a major factor in determining long-term graft outcome and its occurrence is heavily weighted towards the immediate post-transplant period. The critical influence of maintaining adequate early levels of immunosuppressive medications has been previously emphasized. Perico et al. [10] found that cylosporin levels on day 2 post-transplant were highly predictive of ACR episodes [10]. Similarly, El-Sabrout et al. [11] describe a significant reduction in ACR rates without an increase in toxicity after a loading dose of sirolimus [11]. Staatz et al. [12] identified a strong relationship between median TAC in the first post-transplant month and ACR [12]. Their data were further analyzed by stratification into three groups based on median TAC, and those with the highest (10-15ng/dl) values experienced no episodes of ACR.

Table 19: Native kidney disease.

Native Kidney disease	Number of cases	Total cases	Percentage
ADPKD	600%	27-Jun	3.35%
Alport's	5-Jan	17900.00%	2.79%
CGN	1400.00%	17900.00%	7.82%
CIN	2	17900.00%	1.12%
DM	800.00%	17900.00%	4.47%
FSUS	3	17900.00%	1.68%
GCKD	2-Jan	27-Jun	1.12%
HTN	4-Jan	17900.00%	2.23%
IgA	4-Jan	27-Jun	2.23%
LUPUS NEPHRITIS	1-Jan	27-Jun	0.56%
MPGN	9	17900.00%	5.03%
O.U	5	27-Jun	2.79%
PUV	2	17900.00%	1.12%
VUR	8	17900.00%	4.47%
HYPOPLASTIC KIDNEY	1	17900.00%	0.56%
UND	105	179	58.66%

Table 20:

Donor	Number of Cases	Total Cases	Percentage
Related	126	179	70.39%
Other than related	53	179	29.61%

We found that biopsy proven ACR were reduced in a linear, graded fashion at all time points and for all TAC increments. Our results suggest that targeting baseline (pretransplant) trough (T0) tacrolimus levels similar to those seen in Group 3 (>15ng/ml) immediately post-transplant can yield extremely low ACR rates in the long term. With higher trough levels severity of rejections (based on Banff classification) also reduces and we did not encounter any antibody mediated or severe TIR rejection when the baseline trough levels were more than 15ng/dl. Tacrolimus toxicity like NOD was not different among various trough level groups, though there was a trend towards higher nephrotoxicity with higher baseline trough levels [114-116] (Table 19,20).

Thus we propose that a target baseline trough tacrolimus levels similar to that seen in Group 3 would achieve the optimal balance between efficacy and toxicity. To avoid toxicity, the TAC dose was promptly adjusted to achieve a target range of 10-15ng/ml before the end of first post transplant week. Despite this, a tendency towards increased toxicity was observed and warrants discussion. Despite a slower fall to nadir creatinine with higher baseline trough tacrolimus level, differences were undetectable by the end of the first week post-transplant (Table 21,22).

Table 21: Donor sex.

Donor Sex	Number of cases	Total cases	Percentage
Female	118	179	65.92%
Male	61	179	34.08%

Table 22:

Induction	Number of cases	Total cases	Percentage
Induced	67	179	37.43%
Not induced	112	179	62.57%

As mentioned earlier, in our study there was no trend towards increased NODAT in patients with higher baseline trough tacrolimus levels. The potential for TAC to induce this complication is well known, although it is unclear if this is a dose-related phenomenon. Two recent studies were unable to demonstrate an association between Tacrolimus trough levels and the development of NODAT at any time point out to five years post-transplant. However, in an earlier study of 76 patients, Rodrigo et al. found that Tacrolimus trough levels of >24ng/ml early post-transplant was an independent risk factor for the development of NODAT (Table 23,24).

Table 23: Induction drug.

Induction Drug	Number of cases	Total cases	Percentage
ATG	10	67	14.93%
Basiliximab	26	67	38.81%
Decluzimab	31	67	46.27%

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

Table 24: Anti proliferative agents.

Anti Proliferative Agents	Number of Cases	Total Cases	Percentage
AZA	81	179	45.25%
MMF	98	179	54.75%

Although, all the patients in the study were started with initial dose of tacrolimus of 0.15mg/kg, only 18% could achieve the trough level of >15ng/ml. That an initial dose of 0.15mg/kg should yield such a wide range of early tacrolimus level is testament to the variability in tacrolimus handling in humans. To implement the finding of this study into clinical practice, knowledge of an individual's response to the drug before they are transplanted would be useful. This question is being addressed by an Australian study that is soon to be reported. Increasing recipient age does appear to affect tacrolimus pharmacokinetics in both children and adults, with higher tacrolimus seen in older patients despite equivalent dosing. This suggests that younger patients would benefit from a higher initial tacrolimus dose, targeting tacrolimus similar to those observed in Group 3 (0.15ng/ml) (Table 25,26).

Table 25 : Post surgical complications.

Post Surgical Complications	Number of Cases	Total Cases	Percentage
With Complication	23	179	12.85%
No Complication	156	179	87.15%

Table 26: Type of complications.

Type of Complications	Number of Cases	Total Cases	Percentage
Lymphocele	11	23	47.83%
Wound Gape	04	23	17.39%
Urine leak	03	23	13.04%
Ureteric Stenosis	01	23	4.35%
Bleeding	02	23	8.70%
Graft laceration	01	23	4.35%
Peritoneal opening	01	23	4.35%

This study demonstrates a clear association between baseline (pre-transplant) trough tacrolimus level and reduced long term ACR rates. Targeting high baseline tacrolimus levels (>15ng/ml) and aggressively managing tacrolimus dosing in this critical period of antigen presentation and immunological activation may result in reduced rates of long-term allograft damage (Table 27-34).

Table 27: Post-transplant infections.

Post-transplant Infections	Number of Cases	Total Cases	Percentage
Present	57	179	31.84%
Absent	122	179	68.16%

Table 28 :

Type of Infections	Number of Cases	Total Cases	Percentage
Acute gastritis	05	57	8.77%
CMV	14	57	24.56%
Urinary tract infection	26	57	45.61%
TB	02	57	3.51%
LRTI	03	57	5.26%
Zoster	01	57	1.75%
HCV	01	57	1.75%
HBV	03	57	5.26%
Infected lymphocoel	01	57	1.75%
PVM	01	57	1.75%

Table 29: Non-infectious complications.

Non-infectious Complications	Number of Cases	Total Cases	Percentage
Present	20	179	11.17%
Absent	159	179	88.83%

Table 30:

T0 level	<05	05-15	>15
Permanent PTDM	11	31	13
Temporary PTDM	06	11	01

Table 31: Onset of PTDM.

T0 level	<05	05-15	>15
<01 week	05	11	04
01week-01 month	08	26	07
>01month	04	05	03

Table 32:

T0 level	<05	05-15	>15
ACR	07	05	02
AVR	01	00	00
ACR+AVR	02	01	00
Borderline ACR	02	06	03

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

Conclusion

In summary, our study shows that the incidence of early rejection reduces as the baseline (pre-transplant) trough tacrolimus level increases.

It also shows that with higher trough level severity of rejection also reduces and that there was no severe TIR and antibody mediated rejection when trough level was >15ng/ml.

Our study also showed that the incidence of NODAT was not different among various trough levels; although there was a trend towards higher rate of biopsy proven nephrotoxicity with higher trough levels. It was also seen that only 18% of the patients could achieve a baseline trough level of >15ng/ml inspite of being started on same doses of tacrolimus (0.15mg/kg) pretransplant. This shows a wide variability in tacrolimus handling in humans.

To conclude,

A. Incidences of early rejection reduces as the pretransplant trough tacrolimus level increases

B. With higher trough level severity of rejection also reduces and we did not encounter any severe TIR or antibody mediated rejection when trough level was >15ng/ml

C. NOD was not different among various trough levels and trend towards higher nephrotoxicity with higher trough levels

D. Only 18 % could achieve the trough level of >15ng/ml

References

1. Arrazola L, Sozen H, Humar A, Papalois V, Uknis M, et al. (2000) Both immunologic and non immunologic factors are risks for long-term graft survival - a multivariate analysis. Transplant Proc 32: 1831.
2. Humar A, Ramcharan T, Kandaswamy R, Gillingham K, Payne WD, et al. (2002) Risk factors for slow graft function after kidney transplants: a multivariate analysis. Clin Transplant 16(): 425.
3. Paraskevas S, Kandaswamy R, Humar A, Kristen G, Rainer WG, et al. (2003) Predicting long-term kidney graft survival: can new trials be performed? Transplantation 75(8): 1256.
4. Sayegh MH, Turka LA (1998) The role of T-cell costimulatory activation pathways in transplant rejection. N Engl J Med 338(25): 1813-1821.
5. Kreisel D, Krupnick AS, Gelman AE, Engels FH, Popma SH, et al. (2002) Non-hematopoietic allograft cells directly activate CD8+ T cells and trigger acute rejection: An alternative mechanism of allorecognition. Nat Med 8(3): 233-239.
6. Denton MD, Magee CC, Sayegh MH (1999) Immunosuppressive strategies in transplantation. Lancet 353(9158):1083-1091.
7. Suthanthiran M, Strom TB (1994) Renal transplantation. N Engl J Med 331(6): 365-376.
8. Magee CC, Denton MD, Mieford EL (1999) Immunosuppressive agents in organ transplantation. Hosp Med 60(5): 364-369.
9. Gotti E, Perico N, Gaspari F, Cattaneo D, Lesti MD, et al. (2005) Blood Cyclosporine Level Soon After Kidney Transplantation is a Major Determinant of Rejection: Insights From the Mycophenolate Steroid-Sparing Trial. Transplantation Proc 37(5): 2037-2040.
10. Perico N, Ruggenenti P, Gotti E, Gaspari F, Cattaneo D, et al. (2004) In renal transplantation blood cyclosporine levels soon after surgery act as a major determinant of rejection: Insights from the MY.S.S Trial. Kidney Int 65(3): 1084-1090.
11. El-Sabrout R, Delaney V, Butt F, Qadir M, Hanson P, et al. (2003) Improved freedom from rejection after a loading dose of sirolimus. Transplantation 75(1): 86-90.
12. Staatz C, Taylor P, Tett S (2001) Low tacrolimus concentrations and increased risk of early acute rejection in adult renal transplantation. Nephrol Dial Transplant 16(9): 1905-1909.
13. http://www.centerspan.org
14. Lindholm A, Ohlman S, Albrechtsen D, Tufvenson G, Persson H, et al. (1993) The impact of acute rejection episodes on long term graft function and outcome in 1337 primary renal transplants treated by 3 cyclosporin regimens. Transplantation 56: 307-315.
15. Matas AJ, Gillingham KJ, Payne WD, Najarian JS (1994) The impact of an acute rejection episode on long-term renal allograft survival. Transplantation 57(6): 857-859.
16. Cecka JM (1991) Early rejection: Determining the fate of renal transplants. Transplant Proc 23(1 Pt 2): 1263-1264.
17. Gulanikar AC, MacDonald AS, Sungurtekin U, Belitsky P (1992) The incidence and impact of early rejection episodes on graft outcome in recipients of first cadaver kidney transplants. Transplantation 53: 323.
18. Ferguson RM, Henry M, Elkhammas EA, Tesi RJ (1992) Acute rejection episodes-best indicator of long-term primary cadaveric renal transplant survival. 18th Annual Meeting of the American Society of Transplant Surgeons, Chicago, USA, p: 83.
19. Brady HR, Kamel KS, Harding ME, Cook GT, deVeber GA, et al. (1990) Low Dose Ciclosporin from the Early Postoperative Period Yields Potent Immunosuppression after Renal Transplantation. Nephron 55(4): 394-399.
20. Pirsch JD, D'Alessandro AM , Sollinger HW, et al. (1992) The effect of donor age, recipient age, and HLA match on immunologic graft survival in cadaver renal transplant recipients. Transplantation 53(1): 55.
21. Takahara S, Kokado Y, Kameoka H, Takano Y, Jiang H, et al. (1994) Monitoring of FK506 blood levels in kidney transplant recipients. Transplantation Proc 26(4): 2106-2108.
22. Kerhner R, Fitsimmons WE (1996) Relationship of FK 506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. Transplantation 62(7): 920-926.
23. Winker M, Wonigeit K, Undre N (1995) Comparison of plasma vs. whole blood as matrix for FK506 drug level monitoring. Transplantation Proc 27: 822-825.
24. Undre NA, van Hooff J, Christianns M, et al. (1999) Low systemic exposure to Tacrolimus correlates with acute rejection. Transplant Proc 31(1-2): 296-298.
25. Backman L, Levy MF, Klintmalm (1995) The FK506 Multicentre Study Group. Whole-blood and the plasma levels of FK506 after liver transplantation: Results from the US Multicenter Trial. Transplant Proc 27: 1124.
26. Backman L, Nicar M, Levy M, et al. (1994) FK506 trough levels in whole blood and plasma in the liver transplant recepients. Transplantation 57(4): 519-525.
27. Jain AB, Todo S, Fung JJ, Venkataramanan R, Day R, et al. (1991) Correlation of rejection episodes with FK 506 level and the steroids following primary orthotropic liver transplantation. Transplant Proc 23(6): 3023-3025.
28. Japanese FK506 Study Group (1991) Japanese study of FK506 on kidney transplantation: The benefit of monitoring the whole blood

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

FK506 concentration. Transplant Proc 23: 3023-3025.

29. Bottiger Y, Battstrom C, Tyden G, Sawe J, Groth CG (1999) Tacrolimus whole blood concentrations correlate closely to side-effects in renal transplant recipients. Br J Clinical Pharmacology 48(3): 445-448.

30. Winkler M, Ringe B, Baumann J, Loss M, Wonigiet K, et al. (1994) Plasma vs. whole blood for therapeutic drug monitoring of patients receiving FK 506 for immunosuppression. Clin Chem 40(12): 2247-2253.

31. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, et al. (1997) Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. Transplantation 64(3): 436-443.

32. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS (1997) A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. Transplantation 63(7): 977-983.

33. Jensik SC (1998) Factors affecting the pharmacokinetics of tacrolimus in the first year after renal transplantation. European Tacrolimus Multicentre Renal Study Group. Transplant Proc 30(4): 1261-1263.

34. Mayer AD (1999) Four year follow up of European tacrolimus multicenter renal study. Transplant Proc 31(7A): 27S-28SC.

35. Johnson C, Ahsan N, Gonwa T, Halloran P, Stegall M, et al. (2000) Randomized trial of tacrolimus in combination with azathiprine or mycophenolate mofetil versus cyclosporine with mycophenolate mofetil after cadaveric renal transplant. Transplantation 69(5): 834-841.

36. Schweitzer EJ, Matas AJ, Gillingham KJ, Payne WD, Gores PF, et al. (1991) Causes of renal allograft loss: progress in the 1980s, challenges for the 1990s. Ann Surg 214(6): 679.

37. Massy ZA, Guijarron C, Wiederkehr MR, Ma JZ, Kasiske BL (1996) Chronic renal allograft rejection: Immunologic and non immunologic risk factors. Kidney Int 49(2): 518.

38. Matas AJ, Gillingham KJ, Payne WD, Najarian JS (1994) The impact of acute rejection episode on long-term renal allograft survival (t ½). Transplantation 57(6): 857-859.

39. Cosio FG, Pelletier RP, Falkenhain ME, Henry ML, Elkhammas EA, et al. (1997) Impact of acute rejection and early allograft function on renal allograft survival. Transplantation 63(11): 1611-1615.

40. Opelz G (1997) For the Collaborative transplant study. Critical evaluation of the association of acute with chronic graft rejection in kidney and heart transplant recipients. Transplant Proc 29(1-2): 73-76.

41. O'Keefe SJ, Tamura J, Kincaid RL, Tocci MJ, O'Neill EA (1992) FK-506-and CsA- sensitive activation of the interleukin-2 promoter by calcineurin. Nature 357(6382): 692-694.

42. Clipstone NA, Crabtree GR (1992) Identification of calcineurin as a key signaling enzyme in T-lymphocyte activation. Nature 357(6380): 695-957.

43. Liu J, Farmer JD, Lane WS, Friedman J, Weissman I, et al. (1991) Calcineurin is a common target of cyclophilin-cyclosporin A AND fkbp-fk506 complexes. Cell 66(4): 807-815.

44. Fruman DA, Klee CB, Biere BE, Burakoff SJ (1992) Calcineurin phosphatease activity in T lymphocytes is inhibited by FK 506 and cyclosporine A. Proc Natl Acad Sci U S A 89(9): 3686-3690.

45. Schreiber SL (1992) Immunophilin-sensitive protein phosphatase action in cell signaling pathways. Cell 70(3): 1259-1262.

46. Cecka JM, Terasaki PI (1992) The UNOS Scientific Renal Transplant Registry. In: Terasaki PI, Cecka JM (Eds.) Clinical transplants 1992. Los Angeles UCLA Tissue Typing Laboratory, USA, 1993:1-16.

47. Terasaki PI, Cecka JM, Gjertson DW, Cho Y, Takemoto S, et al. (1993) A ten-year prediction for renal transplant survival. In; Tersaki PI, Cecka JM (Eds.) Clinical transplants 1992. Los Angeles: UCLA Tissue Typing Laboratory pp. 501-512.

48. Basdonna GP, Matas AJ, Gillingham KJ (1993) Relationship between early and late acute rejection and onset of chronic rejection in kidney transplantation. Transplant Proc 25: 910.

49. Almond PS, Matas A, Gillingham K, et al. (1993) Risk factors for chronic rejection in renal allograft recepients. Transplantation 55(4): 752-756.

50. Basdonna GP, Matas AJ, Gillingham KJ, Payne WD, Dunn DL, et al. (1993) Early versus late acute renal allograft rejection: impact on chronic rejection. Transplantation 55(5): 993-995.

51. Land W, Schneeberger H, Schleibner S (1990) Long-term results in cadaveric renal transplantation under cyclosporine therapy. Organ Transplantation pp. 189-199.

52. Matas A (1994) Chronic rejection in renal transplant recipients: risk factor and correlates. Clin Transplant 8(3 Pt 2): 332-335.

53. Vanrenterghem YFC (1995) Acute rejection and renal allograft outcome. Nephrol Dial Transplant 10(suppl 1): 29-31.

54. Lindholm A, Ohlman S, Albrechtsen D, Tufveson G, Persson H, et al. (1993) The impact of acute rejection episodes on long term graft function and outcome in 1347 primary renal transplants treated by 3 cyclosporin regimens. Transplantation 56(2): 307-315.

55. Cecka JM, Terasaki PI (1991) The UNOS scientific renal transplant registry, 1990. In: Treasaki P (Eds.) Clinical transplants 1990. Los Angeles: UCLA Tissue typing laboratory, p. 1-18.

56. Cecka JM, Terasaki PI (1995) The UNOS scientific renal transplant registry. In: Terasaki PI, Cerka JM (Eds.) Clinical transplants 1994. Los Angeles: UCLA Tissue Typing Laboratory, p. 1-18.

57. Japanese FK (1991) Japanese study of FK 506 on kidney transplantation: results of an early phase 2 study. Transplant Proc 23(6): 3071-3074.

58. Laskow DA, Vincenti F, Neylan J, Mendez R, Matas A (1995) Phase 2 FK 506 multicenter concentration control study: one-year follow up. Transplant Proc 27: 809.

59. Jordan ML, Shapiro R, Vivas CA, Scantlebury VP, Rhandhawa P, et al. (1994) FK506 "rescue" for resistant rejections of renal allografts under primary cyclosporine immunosuppression. Transplantation 57(6): 860-865.

60. Japanese FK (1993) 506 Study Group. Japanese study of FK 506 on kidney transplantation: results of an early phase 2 study. Transplant Proc 25: 649.

61. Japanese FK 506 Study Group (1995) FK 506: Long term study in kidney transplantation. Transplant Proc 27: 818.

62. Shapiro R, Jordan M, Scantlebury V, Vivas C, Fung JJ, et al. (1995) A prospective randomized trial of FK 506- based immunosuppression after renal transplantation. Transplantation 59(4): 344: 423.

63. Undre NA, Stevenson P, Schafer A (1999) Pharmacokinetics of tacrolimus: clinically relevant aspects. Transplant Proc 31(7A): 296-298.

64. Aweeka FT, Benet LZ, Gambertoglio JG, Peter K, Okudaira N, et al. (1993) Comparative pharmacokinetics of orally (PO) and intravenously (IV) administered tacrolimus (FK506) in pre- and post-kidney transplant recipients. Clin Pharmacol Ther 53: 151.

65. Lee C, Hewitt J, Aweeka F, et al. (1993) Pharmacokinetics of tacrolimus (FK506) prior to kidney transplantation. Clin Pharmacol Ther 53: 238.

66. Mekki Q, Lee C, Aweeka F, et al. (1993) Pharmacokinetics of tacrolimus (FK506) in kidney transplant patients. Clin Pharmacol Ther 53-238.

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

67. Beysens AJ, Wijnen RMH, Beuman GH, van der HJ, Koots- tra G, et al. (1991) FK506: monitoring in plasma or in whole blood? Transplant Proc 23(6): 2745-2747.

68. Karanam BV, Vincent SH, Newton DJ, Wang RW, Chiu SHL (1994) FK506 metabolism in human liver microsomes: investigation of the involvement of cytochrome P450 isozymes other than CYP3A4. Drug Metab Dispos 22(5): 811-814.

69. Iwasaki K, Shiraga T, Nagase K, Tozuka Z, Noda K, et al. (1993) Isolation, identification and biological activities of oxidative metabolites of FK506, a potent immuno- suppressive macrolide lactone. Drug Metab Dispos 21(6): 971-977.

70. Iwasaki K, Shiraga T, Matsuda K, Nagase K, Tokuma Y, et al. (1995) Further metabolism of FK506 (tacrolimus). Identification and biological activities of the metabolites oxidized at multiple sites of FK506. Drug Metab Dispos 23(1): 28-34.

71. Hill HM, Clark SD, Bentley L (1997) Presented at AAPs annual meeting 1997.

72. Undre NA, Schäfer A (1998) The European Tacrolimus Multicentre Renal Study Group. Factors Affecting the Pharmacokinetics of Tacrolimus in the First Year after Renal Transplantation. Transplant Proc 30(4): 1261-1263.

73. Zucker K, Rosen A, Tsaroucha A, de Faria L, Roth D, et al. (1997) Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous *in vitro* findings. Transpl Immunol 5(3): 225-232.

74. Undre NA, van Hooff J, Christiaans M, Vanrenterghem Y, Donck J, et al. (1998) Low systemic exposure to tacrolimus correlates with acute rejection. Transplant Proc 31(1-2): 296-298.

75. Bottiger Y, Undre NA, Sawe J, Stevenson PJ, Ericzon BG (2002) Effect of bile flow on the absorption of tacrolimus in the liver allograft transplantation. Transplant Proc 34(5): 1544-1545.

76. Morris-Stiff G, Ostrowski K, Balaji V, Moore R, Darby C, et al. (1998) Prospective randomised study comparing tacrolimus (Prograf) and cyclosporin (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: Interim report of the first 80 cases. Transpl Int 11(Suppl 1): S334-S336.

77. Busque S, Shoker A, Landsberg D, McAlister V, Halloran P, et al. (2001) Canadian multicentre trial of tacrolimus/azathioprine/steroids versus tacrolimus/mycophenolate mofetil/steroids versus neoral/ mycophenolate mofetil/steroids in renal transplantation. Transplant Proc 33(1-2): 1266-1267.

78. Margreiter R (2002) Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: A randomized multicentre study. Lancet 359(9308): 741-746.

79. Dunn CJ, Wagstaff AJ, Perry CM, Plosker GL, Goa KL (2001) Cyclosporin: An updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral) 1 in organ transplantation. Drugs 61: 1957-2016.

80. Christiaans M, van Duijnhoven E, Beysens T, Undre N, Schafer A, et al. (1998) Effect of breakfast on the oral bioavailability of tacrolimus and changes in pharmacokinetics at different times post transplant in renal transplant recipients. Transplant Proc 30(4): 1271-1273.

81. Halloran PF, Helms LM, Kung L, Noujaim J (1999) The temporal profile of calcineurin inhibition by cyclosporine *in vivo*. Transplantation 68: 1356-1361.

82. Stein CM, Murray JJ, Wood AJ (1999) Inhibition of stimulated interleukin-2 production in whole blood: A practical measure of cyclosporine effect. Clin Chem 45(9): 1477-1484.

83. Hartel C, Fricke L, Schumacher N, Kirchner H, Muller-Steinhardt M (2002) Delayed cytokine mRNA expression kinetics after T-lymphocyte co stimulation: A quantitative measure of the efficacy of cyclosporin A-based immunosuppression. Clin Chem 48(12): 2225-2231.

84. Sommerer C, Konstandin M, Dengler T, Schmidt J, Meuer S, (2006) Pharmacodynamic monitoring of cyclosporine a in renal allograft recipients shows a quantitative relationship between immunosuppression and the occurrence of recurrent infections and malignancies. Transplantation 82(10): 1280-1285.

85. Labrecque G, Belanger PM (1991) Biological rhythms in the absorption, distribution, metabolism and excretion of drugs. Pharmac Ther 52(1): 95-107.

86. Lemmer B (2000) Relevance for chronopharmacology in practical medicine. Semin perinatol 24(4): 280-290.

87. Reinberg AE, Soudant E, Koulbanis C, Bazin R, Nicolai A, et al. (1995) Circadian dosing time dependency in the forearm skin penetration of methyl and hexyl nicotinate. Life Sci 57(16): 1507-1513.

88. King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, et al. (1997) Positional cloning of the mouse circadian clock gene. Cell 89(4): 641-653.

89. Goto T, Kino T, Hatanaka H, Hatanaka H, Nishiyama M, et al. (1987) Discovery of FK506, a novel immunosuppressant isolated from Streptomyces tsukubaensis. Transplant Proc 19(5 Suppl 6): 4-8.

90. Kumar D, Wingate D, Ruckebusch Y (1986) Circadian variation in the propagation velocity of the migrating motor complex. Gastroenterology 93: 926-930.

91. Belanger PM, Labrecque G, Dore F (1984) Rate limiting steps in the temporal variations of the pharmacokinetics of some selected drugs. In: Chronobiology 1982-1983. pp. 359-363.

92. Cambar J, Lemoigne F, Toussaint C (1979) Etude des variations nychtemerales de la filtration glomerulaire chez le rat. Experientia 35(12): 1607-1609.

93. Born J, Lange T, Hansen K, Molle M, Fehm HL (1997) Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol 158(9): 4454-4464.

94. Goldsmith MA, Greene WC (1994) Interleukin-2 and the interleukin-2 receptor. In: Thomson A (Eds.), The Cytokine Handbook, London: Academic Press, UK, pp. 57-80.

95. Uthgenannt D, Schoolmann D, Pietrowsky R, Fehm, HL, Born J (1995) Effects of Sleep on the Production of Cytokines in Humans. Psychoso Med 57(2): 97-104.

96. Lemmer B (1999) Chronopharmacokinetics: Implications for Drug Treatment. J Pharm Pharmacol 51(8): 887-890.

97. Lemmer B, Nold G (1991) Circadian changes in estimated hepatic blood flow in healthy subjects. Br J Clin Pharmacol 32: 627-629.

98. Goo RH, Moore JG, Greenberg E, Alazraki NP (1987) Circadian Variation in Gastric Emptying of Meals in Humans. Gastroenterology 93(3): 515-518.

99. Bekersky I, Dressler D, Mekki Q (2001) Effect of time of meal consumption on bioavailability of a single oral 5 mg tacrolimus dose. J Clin Pharmacol 41(3): 289-297.

100. Wong SHY (2001) Therapeutic drug monitoring for immunosuppressants. Clinica Chimica Acta 313: 241-253.

101. Hawley CM, Wall DR, Johnson DW, Campbell SB, Griffin AD, et al. (1995) Recovery of gastrointestinal function after renal transplantation in a patient with sclerosing peritonitis secondary to continuous ambulatory peritoneal dialysis. Am J Kidney Dis 26(4): 658-661.

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652

102. Fujimura A, Ebihara A (1994) Administration time-dependent toxicity of a new imunosuppressive agent, tacrolimus (FK 506). Life Sci 55(7): 485-490.

103. Fujimura A, Shiga T, Ohashi K, Ebihara A (1993) Chronopharmacokinetic study of a new immunosuppressive agent, FK 506, in mice. Jpn J Pharmacol 61(2): 137-139.

104. Uchida H, Kobayashi E, Ogino Y, Mizuta K, To H, et al. (1993) Chronopharmacology of tacrolimus in rats: toxicity and efficacy in a mouse-to-rat intestinal transplant model and its pharmacokinetic profile. Transplant proc 31(7): 2751-2753.

105. Jorgensen K, Povlsen J, Madsen S, Madsen M, Hansen H, et al. (2002) C2 (2-h) levels are not superior to trough levels as estimates of the area under the curve in tacrolimus-treated renal-transplant patients. Nephrol Dial Transplant 17(8): 1487-1490.

106. Iwasaki K, Matsuda H, Nagase K, Shiraga T, Tokuma Y, et al. (1993) Effects of twenty three drugs on the metabolism of FK506 by human liver microsomes. Res Commun Chem Pathol Pharmacol 82(2): 209-216.

107. Tada H, Yanagiwara S, Itoh K, Suzuki T (1999) Role of diltiazem on tacrolimus pharmacokinetics in tacrolimus-induced nephrotoxic rats. Pharmacol Toxicol 84: 241-246.

108. Regazzi MB, Iacona I, Alessiani M, Spada M, Vaccarisi S, et al. (1996) Interaction between FK506 and diltiazem in an animal model. Transplant Proc 28: 1017-1018.

109. Hebert MF, Lam AY (1999) Diltiazem increases tacrolimus concentrations. Ann Pharmacother 33(6): 680-682.

110. Bailey DG, Spence JD, Munoz C, Arnold JM (1991) Interaction of citrus juices with felodipine and nifedipine. Lancet 337(8736): 268-269.

111. Di Marco MP, Edwards DJ, Wainer IW, Ducharme MP (2002) The effect of grapefruit juice and Seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein. Life Sci 71(10): 1149-1160.

112. Wong KM, Shek CC, Chau KF, Li CS (2000) Abbreviated tacrolimus area under the curve monitoring for renal transplant recipients. Am J Kidney Dis 35(4): 660-666.

113. Ku YM, Min DI (1998) An abbreviated area-under-the-curve monitoring for tacrolimus in patients with liver transplants. Ther Drug Monit 20: 219-223.

114. Knapp MS, Cove-Smith Jr, Dugdale R, Mackenzie N, Pownall R (1979) Possible effect of time on renal allograft rejection. Br Med J 1: 75-77.

115. Tada H, Satoh S, Iinuma M, Shimoda N, Murakami M, et al. (2003) Chronopharmacokinetics of tacrolimus in kidney transplant recipients: occurrence of acute rejection. J Clin Pharmacol 43(8): 859-865.

116. Kim JS, Aviles DH, Silverstein DM, Leblanc PL, Matti Vehaskari V (2005) Effect of age, ethnicity, and glucocorticoid use on tacrolimus pharmacokinetics in paediatric renal transplant patients. Pediatr Transplant 9(2): 162-169.

DOI: 10.19080/JOJUN.2018.05.555652

How to cite this article: Manish T. Correlation of Pretransplant Trough Tacrolimus Level with Early Acute Rejection In Live Donor Renal Transplantation-A Prospective Study. JOJ uro & nephron. 2018; 5(1): 555652. DOI: 10.19080/JOJUN.2018.05.555652