

Correlation of Tough Tacrolimus Level with Early Acute Rejections in Renal Allograft Recipients- A Prospective Study



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Received: January 03, 2018; Published: January 18, 2018

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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 = < 5 ng/ml, Group II = 5-15 ng/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 [1-25].

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 [1-24]. Transplantation with living donor allows anticipated planning of the procedure, which can be performed before dialysis treatment, and prior administration of an immunosuppressant scheme. Pre-transplant administration of immunosuppressant 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 [25-60].

Many transplantation centers advocate the administration of immunosuppressant 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 immunosuppressant therapy are the risk of infection and the nephrotoxicity effects of calcineurin inhibitors during allograft reperfusion. 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 [60-75].

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 the hospital society. All the patients in the study received pre-transplant immunosuppressant starting 3 days prior to transplant. The follow up period was 1 year post transplant [75-90].

Immunosuppression 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, initiated 3 days pre-transplant. Methylprednisalone (1g) was administered intravenous during surgery and after and after that, oral prednisalone was initiated (8mg/kg/d) and gradually tapered to .3mg/kg/d after 3 months of transplant. Doses of Tacrolimus were adjusted according to the 12-hr trough level (C_{min}), aiming to maintain the whole blood trough level between 10-20ng/ml over the initial 3-month post transplantation period and subsequently trough levels were reduced to 5-15ng/ml. Azathioprine dose was reduced or suspended in the presence of leucopenia. The Prednisalone dose was tapered to 0.4 mg/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 [90-115].

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 semi automated fluorescence 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. 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 immunosuppressant therapy.

Statistical Analyses

Demographic, baseline characteristics and outcome characteristics were collected throughout 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.

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). Patients were divided and analyzed in three groups based on base-line trough TAC level on day 0 post-transplant: Group 1 : TAC 0-5 ng/ml (n = 34), Group 2 : TAC 5-15 ng/ml (n =112), Group 3 : TAC >15 ng/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). 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 0.15 mg/kg bid being started 2 days before transplant. TAC doses were subsequently adjusted in all groups to achieve a target TAC of 12-14 ng/ml by one week post-transplant.

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 11.1 and 11.2 respectively (Tables 1-7).

Table 1: 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).

Receptient Sex	Number of cases	Total cases	Percentage
Male	145	179	81.01%
Female	34	179	18.99%

Table 2: Patients were divided and analyzed in three groups based on base-line trough TAC level on day 0 post-transplant: Group 1 : median TAC 3.45 ng/ml (n = 34, range 1.1-5.0 ng/ml), Group 2 : median TAC 7.7 ng/ml (n =112, range 5.1-14.9 ng/ml), Group 3 : median TAC 20.7 ng/ml (n = 33, range 15.6-36.7 ng/ml).

T0 level	Group 1 (<05)	Group 2 (05-15)	Group 3 (>15)
Median TAC (ng/ml)	3.45 (1.1-5.0)	7.7 (5.1-14.9)	20.7 (15.6-36.7)
Patients (n)	34	112	33

Table 3.1: 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.

T0 level	<05	05-15	>15
Male	9	39	13
Female	25	73	20

Table 3.2: 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.

T0 level	<05	05-15	>15
Male	9	39	13
Female	25	73	20

Table 4: 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.

T0 level	<05	05-15	>15
Related	28(82.35%)	76(67.86%)	22(66.67%)
Other than related	06(17.65%)	36(32.14%)	11(33.33%)

Table 5: 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.

T0 level	<05	05-15	>15
<20yrs	09	16	09
20-40yrs	05	77	30
>40yrs	01	21	11
Average age	49.06+/-10.15	47.38+/-9.6	46.42+/-10.2

Table 6: 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.

T0 level	<05	05-15	>15
<40 years	06	29	07
40-60years	24	73	24
>60years	04	10	02
Average age	49.05+/-10.15	47.7+/- 10.14	46.42 +/-10.2

Table 7: 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.

T0 level	<05	05-15	>15
<50 min	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.

Table 8: 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.

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%)

Immunosuppression

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 Tables 9 & 10.

Table 9: 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.

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%)

Table 10: 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.

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: 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.

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

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 Tables 12-15.

Table 12: 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%).

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

Table 13: 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.

Non- infectious complications	<05	05-15	>15	Total case (n=10)
Femoral neuropathy	01	-	01	02
GI side effects of MMF	-	-	03	03
HT encephalopathy	-	01	-	01
Proteinuria	-	-	01	01
TMA	-	01	-	01
TRAS	-	02	-	02

Table 14: 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 lymphocoeel -1; Polyoma virus infection -1. Table 14 shows this distribution.

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
Lymphocoeel	-	01	-	1
VZ-1	-	01	-	1
PV-1	-	01	-	1

Table 15: 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.

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

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 found that cyclosporin levels on day 2 post-transplant were highly predictive of ACR episodes. Similarly, El-Sabrou et al. describe a significant reduction in ACR rates without an increase in toxicity after a loading dose of sirolimus. Staatz et al. identified a strong relationship between median TAC in the first post-transplant month and ACR. Their data were further analyzed by stratification into three groups based on median TAC, and those with the highest (10-15 ng/dl) values experienced no episodes of ACR. We found that biopsy proven ACR were reduced in a linear, graded fashion at all time points and for all TAC increments (Tables 16-25).

Table 16: 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.

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

Table 17: 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.

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

Table 18: 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.

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

Table 19 :

ADPKD	06	179	3.35%
Alport's	05	179	2.79%
CGN	14	179	7.82%
CIN	02	179	1.12%
DM	08	179	4.47%
FSUS	03	179	1.68%
GCKD	02	179	1.12%
HTN	04	179	2.23%
IgA	04	179	2.23%
LUPUS NEPHRITIS	01	179	0.56%
MPGN	09	179	5.03%
O.U	05	179	2.79%
PUV	02	179	1.12%
VUR	08	179	4.47%

Table 23 :

Table 22 :	Induction	Number of cases	Total cases	Percentage
	Induced	67	179	37.43%
	Not induced	112	179	62.57%
Table 22 :	Induction	Number of cases	Total cases	Percentage
	Induced	67	179	37.43%
	Not induced	112	179	62.57%
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	Not induced	112	179	62.57%
Table 22 :	Induction	Number of cases	Total cases	Percentage
	Induced	67	179	37.43%
	Not induced	112	179	62.57%

Table 24 :

Anti proliferative agents	Number of cases	Total cases	Percentage
AZA	81	179	45.25%
MMF	98	179	54.75%

Table 25 :

Post surgical Complications	Number of cases	Total cases	Percentage
With Complication	23	179	12.85%

HYPOPLASTIC KIDNEY	01	179	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%

Table 21 :

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%

No Complication	156	179	87.15%
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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. 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 10-15 ng/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. As mentioned earlier, in our study there was no trend towards increased NODAT in patients with higher baseline trough tacrolimus levels (Tables 17-35).

Table 26:

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%

Table 27 :

Tacrolimus toxicity	Number of cases	Total cases	Percentage
Present	85	179	47.49%
Absent	94	179	52.51%

Table 28 :

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	12	179	6.7%
drug induced	04	12	33.33%
infectious hepatitis	07	12	58.33%
sepsis	01	12	8.33%

Table 29 :

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

Table 30 :

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 lymphocele	01	57	1.75%
PVM	01	57	1.75%

Table 31

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

Table 32

Type of Non-infectious Complications	Number of cases	Total cases	Percentage
Femoral neuropathy	02	20	10.0%
GE secondary to MMF	03	20	15.0%
Hypertensive encephalopathy	01	20	5.0%
Proteinuria	01	20	5.0%
TMA	01	20	5.0%
TRAS	12	20	60.0%

Table 33

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

Table 34

T0 level	<05	05-15	>15
Male	24	94	27
Female	10	18	06

Table 35

T0 level	<05	05-15	>15
<40 years	06	29	07
40-60years	24	73	24
>60years	04	10	02

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. 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 (Tables 36-44).

Table 36

T0 level	<05	05-15	>15
Male	09	39	13
Female	25	73	20

Table 37

T0 level	<05	05-15	>15
Related	28	76	22
Other than related	06	36	11

Table 38

Native Kidney disease	<05	05-15	>15
ADPKD	02	04	-
CGN	02	11	01
Diabetic nephropathy	02	04	02
HTN nephropathy	01	03	-
IgA nephropathy	01	03	-
MPGN	02	04	03
PUV	01	01	-
RN	01	06	01
Unknown	22	62	21
Alport's	-	04	-
CIN	-	02	-
FSGS	-	03	-
GCKD	-	01	01
Obstructive Uropathy	-	03	01
Hypoplastic kidneys	-	01	-
Lupus	-	-	01
Patchy cortical necrosis	-	-	01

Table 39

T0 level	<05	05-15	>15
ATG	01	07	02
Basiliximab	04	14	08

Table 46

Post transplant infections	<05	05-15	>15	No. of cases	Total cases	Percentage
AGE	01	04	-			

Decluzimab	10	14	07
Nil	19	78	16

Table 40

T0 level	<05	05-15	>15
MMF	14	62	22
AZA	20	50	11

Table 41

T0 level	<05	05-15	>15
<50 min	07	25	06
50 – 70min	20	71	23
>70min	07	15	04

Table 42

T0 level	<05	05-15	>15
Tacrolimus toxicity	02	09	05

Table 43

T0 level	<05	05-15	>15
PTDM	17	42	14

Table 44

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

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(.15ng/ml). 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 (Tables 44-50).

Table 45

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

CMV	02	08	04		
FUNGAL	01	-	-		
LRTI	01	01	01		
TB	01	01	-		
UTI	05	11	07		
HBV	-	02	01		
HCV	-	-	01		
Lymphocoel	-	01	-		
VZ-1	-	01	-		
PV-1	-	01	-		

Table 47

T0 level	<05	05-15	>15
Rejection	12	25	05

Table 48

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

Table 49

T0 level	<05	05-15	>15
AMR1	01	03	-
AMR3	-	01	-
TCMR1A	03	07	02
TCMR1B	04	02	-
TCMR2A	02	02	-

Table 50

T0 level	<05	05-15	>15
Full house	01	15	05
Ag1	06	17	03
Ag2	15	38	14
Ag3(haplo)	09	27	08
Ag4	02	07	01
Ag5	01	03	01
Ag6(nil)	00	05	01

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.
- c. TIR or antibody mediated rejection when trough level was > 15 ng/ml.
- d. NOD was not different among various trough levels and trend towards higher nephrotoxicity with higher trough levels.
- e. Only 18 % could achieve the trough level of > 15 ng/ml.

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DOI: [10.32474/IGWHC.2018.01.000111](https://doi.org/10.32474/IGWHC.2018.01.000111)



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