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Correlation of Base-Line Trough Tacrolimus Level With Early Rejection

Manish Tripathi*

Live donor renal transplantion, Ajman, United Arab Emirates

***Corresponding author:** Manish Tripathi, Live donor renal transplantion, Ajman, United Arab Emirates

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Aim and Objective of the study

To analyze the co-relation of baseline trough (C0) tacrolimus level, with early rejection in living donor transplants.

Materials and Methods

Study area

The study was done at Muljibhai Patel Urological Hospital, Nadiad, Gujarat. It is a tertiary health care centre, for nephrology, with a well established hemodialysis unit. We have done about 1950 renal transplantation so far. Acute rejection is the most significant risk factor for chronic rejection and potential surrogate for long-term graft failure. Aim of our study was to analyze the association between the baseline through (C0) tacrolimus level in the first day post transplant, with early rejection in living donor transplants [1-10].

Study population

All patients enrolled were older than 18 years. The protocol received approval from the Ethical Committee of Muljibhai Patel Urological Hospital Society. All the patients in the study received pre-transplant immunosupression starting 3 days prior to transplant. The follow up period was 1 year post- transplant [11-20].

Sample size and sample technique

179 patients were evaluated. This was an open label randomized prospective study consisting of renal allograft recipients from living donors. This study was carried out by Department of Nephrology at Muljibhai Patel Urological Hospital, Nadiad, between January 2008 to September 2009 [21-30].

Data collection technique and tools

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) [31-40].

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=112), Group 3: TAC>15ng/ml (n=33).

Data Analysis

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 [41-50].

Salient Findings (Table 1-6)

Table 1: Comparison of the baseline demographic features between the 3 groups.

	<5 (n=34)	05-15 (n=112)	>15 (n=33)
Age	49.06+10.15	47.38+9.6	46.42+10.2
Gender (M:F)	24:10	94:18	27:6
Relation Related	28	76	22
Other than related	06	36	11
Donor Age	49.05+10.15	47.7+10.14	46.42+10.2
Donor Gender	9:25	39:73	13:20
Total Ischemia Time	61.32+17.58	57.15+9.7	58.42+13.61

Table 2: Various degree of HLA mismatch in all 3 groups.

	<5 (n=34)	05-15 (n=112)	>15 (n=33)
1	06	17	03
2	15	38	14
3 (haplo)	09	27	08
4	02	07	01
5	01	03	01
6 (nil)	00	05	01

Table 3: Immunosupression protocols used and their related toxicity in the 3 groups.

	<5 (n=34)	05-15 (n=112)	>15 (n=33)
Induction	15	35	17
Anti proliferative -Azathioprine	20	50	11
Anti proliferative - MMF	14	62	22
Biopsy proven CNI toxicity	2(5.9)	9(8.03)	5(15.1)
NOD	17(50)	42(37.5)	14(42.4)

Table 4: Non-infectious complications occurring during hospitalization and outpatient follow-up.

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

Table 5: Infectious complications.

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

Table 6: Number of rejection in each group, their Banff grading and outcomes.

	<5 (n=34)	05-15(n=112)	>15(n=33)
Rejection Episodes	12 (35.3)	27(24.1)	5(15.2)
TCMR 1A	3	10	2
TCMR 1B	3	3	0
TCMR 2A	2	4	0
AMR 1	1	3	0
AMR 3	0	1	0
Graft loss	0	2	0
Post Tx Infections	12 (35.3)	33(29.5)	15(45.4)

Our study showed a significant reduction in the incidence of early rejection as the baseline (pre-transplant) trough tacrolimus level increases. Patients in Group 3 had significantly lower rate of biopsy proven rejections than Group 1 (p=0.001). 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 [51-60].

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 [61-75].

Conclusion

i. Incidences of early rejection reduces as the pretransplant trough tacrolimus level increases [71]

ii. 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 [72]

iii. NOD was not different among various trough levels and trend towards higher nephrotoxicity with higher trough levels [73]

iv. Only 18 % could achieve the trough level of >15ng/ml [74,75]

Recommendation

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. 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.

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