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Profile And Risk Factor Analysis Of Biopsy Proven Acute Rejection& Role Of Basiliximab In Tacrolimus Era - A Multicentric Study:

Sheik Sulthan Alavudeen N[1], Balaraman[2]
[1]*Senior Resident, Department of Nephrology, Govt. Kilpauk Medical College & Hospital, Chennai, India*
[2]*Professor, Department of Nephrology, Govt. Kilpauk Medical College & Hospital, Chennai, India*
Corresponding author: Prof.V Balaraman.

Abstract:
Aim & Objective: *To study the incidence, various risk factors of acute rejections and to show any role of induction agent (Basiliximab) & type of CNI regimen on the incidence of acute rejections.*
Materials & methods: *We performed a retrospective study of biopsy proven acute graft rejection (BPAR) involving 157 patients who underwent living donor renal transplantation in three tertiary care centres in southern part of India during Oct 2007 – Oct 2016. We described the total incidence of acute rejection and analysed various risk factors associated with early and late acute rejections.*
Results: *Among 157, 48(30.6%) biopsy proven acute rejection (BPAR) episodes occurred. Early & late rejections were 28(17.8%) & 20(12.8%) respectively. During the cyclosporine era without induction the rate of BPAR was 37.8% & in the current TAC based regimen with induction agent the BPAR was 22.2%. Among various risk factors, positive Hep C status and regimen without induction were significantly associated with more early acute rejections whereas unrelated donor, CSA based regimen in comparison to TAC based regimen, delayed graft function and low CNI level were correlated with more late acute rejections.*
Conclusion: *About one in every five patients had acute rejection in our cohort and this data is comparable to that of other Indian data. TAC based regimen had reduced late acute rejection episodes when compared to CSA based regimen. Basiliximab had no role in reducing early & late acute rejections on the background of TAC based regimen.*
Keywords: *BPAR – biopsy proven acute rejection, EAR – early acute rejection, LAR – late acute rejection.*

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I. 1.Introduction:

It has been well documented that renal transplantation is the best modality of renal replacement therapy as it increases the longevity & improves the quality of life in patients with ESRD[1]. The most important problem with renal transplantation is the longevity of the graft which in turn is affected by many factors. Graft longevity is measured by means of graft half-life defined as number of years before 50% of the graft that survive at one year will die and is used to predict ten year graft survival[2]. The factors affecting the longevity of the graft are determined by the features of the graft itself and by the early post transplantation course.

A major cause of graft loss is patient death, most often from infections, cardio vascular disease and malignancy[3]. The other major cause of graft loss is chronic allograft failure that is caused by alloantigen dependent and alloantigen independent factors. The alloantigen dependent factors include acute rejection episodes, histocompatibility mismatch, prior sensitisation, sub optimal immunosuppression, drug noncompliance andon-going chronic humoral injury. The alloantigen independent factors are as follows CNI nephro toxicity, graft infections (pyelonephritis, BKV, CMV), disease recurrence, hypertension andtransplant renal artery stenosis[4]. Acute rejection episodes remain the important cause of graft failure in transplant setting.

KDIGO 2009 recommends using induction agent for all renal transplant recipients (IL2R antagonist for low to intermediate immunological risk group & Lymphocyte depleting agents for high immunological groups)[5]to prevent or to reduce the rate of acute rejections.

The present study analyses the various risk factors for acute rejections. It also analyses the role of induction agent and type of CNI regimen on the episodes of acute rejections.

II. Material & Methods:

2.1 Patients:

We performed a retrospective study of biopsy proven acute graft rejection involving 193 patients who underwent living donor renal transplantation in three tertiary care teaching hospitals in southern part of India during Oct 2007 – Oct 2016.

2.2 Inclusion criteria:

Living donor renal transplantation recipients
Age > 18yrs

2.3 Exclusion criteria:

Deceased donor transplant recipients
Patients on steroid free protocol
ABO incompatible transplant recipients
Patients on Azathioprine based regimen
Primary non-functioning transplants
Graft loss or death due to surgical causes
Follow up loss

After exclusion 157 patient's records were included for this study. These patients were transplanted during Oct 2007 – Oct 2016 and followed up till Oct 2017 (with minimum of one year follow up). In this design,we measured the incidence of biopsy proven acute rejection.We classified the patients into three groups (as dependent variables); Group 1 - No Acute Rejection (No AR), Group 2 - Early AR (EAR), Group 3 - Late AR (LAR). We have performed the risk factor analysisassociated with the three groups.We also studied the role of anti IL2R agent (basiliximab) versus no induction and TAC+MMF+PDN regimen versus CSA+MMF+PDN regimen on the incidence of BPAR in renal transplant recipients.

2.4 Definitions:

Acute rejection was defined as acute graft dysfunction (which was defined as increase in serum creatinine of > 0.3 mg/dl from the baseline) with confirmed tissue diagnosis based on BANFF 2013 criteria. Indication for kidney biopsy was acute graft dysfunction& no protocol biopsy was done. Borderline rejections were not considered as an AR episode. Early acute rejection (EAR) & late acute rejection (LAR) were defined as acute rejection before & after 3 months respectively. Graft loss was defined as transplant nephrectomy, re transplantation or return to long term dialysis.

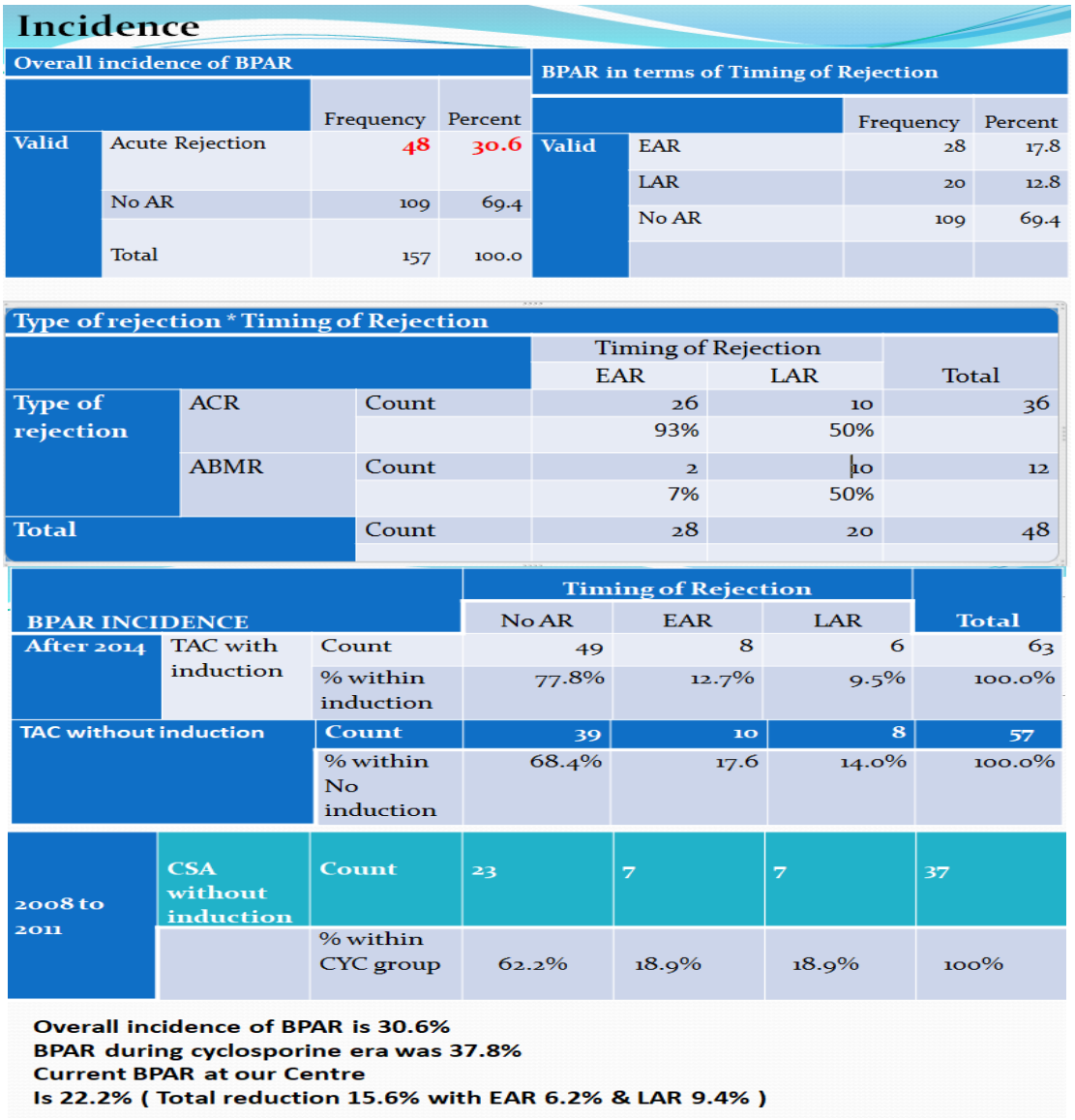
2.5 Statistical analysis:

The clinical characteristics of the three groups were compared using Chi Square test or Exact Fisher t test for categorical variables & ANOVA test for continuous variables.Recipient's age/sex, donor's age/sex, Hepatitis C status, Dialysis vintage, Blood transfusion, Donor type (Related & unrelated), Induction agent (Basiliximab & no induction), Immunosuppressive regimen (TAC+MMF+PDN & CYC+MMF+PDN) were used as independent variables in risk factor analysis. Role of induction agent & immunosuppressive regimen in the incidence of acute rejection among different donor type (related versus unrelated) transplant recipients was studied using Chi Square test. Multinomial logistic regression analysis was performed to determine the predictive values of the independent variables among the three groups. A value of $P < 0.05$ is considered to be significant in all analysis. Statistical analysis was done using IBM - SPSS software, version 23.0.

III. Results:

3.1 Incidence analysis:

Among 157 patients, 48 (30.6%) biopsy proven acute rejection episodes occurred. Early & late rejections were 28 (17.8%) & 20 (12.8%) respectively. During the cyclosporine era without induction the rate of BPAR was 37.8% & in the current TAC based with induction regimen the BPAR was 22.2%. We achieved reduction in the rejection rate by 15.6%.



Incidence

Overall incidence of BPAR

		Frequency	Percent
Valid	Acute Rejection	48	30.6
	No AR	109	69.4
	Total	157	100.0

BPAR in terms of Timing of Rejection

		Frequency	Percent
Valid	EAR	28	17.8
	LAR	20	12.8
	No AR	109	69.4

Type of rejection * Timing of Rejection

			Timing of Rejection		Total
			EAR	LAR	
Type of rejection	ACR	Count	26	10	36
			93%	50%	
	ABMR	Count	2	10	12
			7%	50%	
Total		Count	28	20	48

BPAR INCIDENCE			Timing of Rejection			Total
			No AR	EAR	LAR	
After 2014	TAC with induction	Count	49	8	6	63
		% within induction	77.8%	12.7%	9.5%	100.0%
TAC without induction		Count	39	10	8	57
		% within No induction	68.4%	17.6	14.0%	100.0%
2008 to 2011	CSA without induction	Count	23	7	7	37
		% within CYC group	62.2%	18.9%	18.9%	100%

Overall incidence of BPAR is 30.6%
BPAR during cyclosporine era was 37.8%
Current BPAR at our Centre
Is 22.2% (Total reduction 15.6% with EAR 6.2% & LAR 9.4%)

3.2 Risk factor analysis:

Among various risk factors, positive Hep C status and regimen without induction were significantly associated with more early acute rejections whereas unrelated donor, CSA based regimen, delayed graft function and low CNI level were correlated with more late acute rejections. After the influence of CNI type (TAC Vs CSA) was removed, statistical significance for the rejection episodes associated with Basiliximab usage no longer existed. Basiliximab usage was not associated with reduction in both early and late acute rejection episodes in patients were on TAC based immunosuppressive regimen. But even after the removal of influence of Basiliximab usage, statistical significance for the late acute rejection episodes with TAC based regimen was persisted.

Multinomial logistic regression model

Likelihood Ratio Tests

Effect		Model Fitting Criteria: -2 Log Likelihood of Reduced Model	Likelihood Ratio Tests: Chi-Square	df	Sig.
Intercept		224.109[a]	0.000	0	
Recipient Age		227.771	3.662	2	.160
Dialysis Vintage		226.007	1.898	2	.387
Donors Age		224.133	.024	2	.988
Recipient Sex		227.756	3.647	2	.161
Hep C status	EAR	230.143	6.034	2	.029
Type of Donor Related/Unrelated	LAR	225.498	1.389	2	.034
Donors Sex		228.712	4.603	2	.100
Induction agent Y/N	EAR	230.814	6.705	2	.035
CNI	LAR	224.123	.014	2	.013
CNI level	LAR	213.647	3.521	2	.039
GF DGF	LAR	228.835	4.727	4	.037

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.
a. This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

Role of Basiliximab after CNI influence removed

TAC with or Without induction

			Timing of Rejection: No AR	EAR	LAR	Total
ISDS	TAC with induction	Count	49	8	6	63
		% within induction	77.8%	11.7%	10.5%	100.0%
	TAC Without induction	Count	39	10	8	57
		% within No induction	68.4%	17.6%	14%	100.0%
Total		Count	86	21	13	120

Results

	No AR	EAR	LAR			Row Totals
TAC with Ind	49 (45.15) [0.33]	8 (11.02) [0.83]	6 (6.82) [0.10]			63
TAC without Ind	37 (40.85) [0.36]	13 (9.98) [0.92]	7 (6.18) [0.11]			57
Column Totals	86	21	13			120 (Grand Total)

The chi-square statistic is 2.6484. The *p*-value is .3266011.
The result is not significant at $p < .05$.

IV. Discussion:

The incidence of acute rejection episodes varies from 8 to 12% in developed nations[6] whereas in developing countries like India it is in the range of 12 to 15%[7] and it iseven higheramong African patients. The major factors proposed for the increased incidence of BPAR in developing countries arethe higher incidence of life threatening infections that limit the usage of highly potent immunosuppressive drugs in the recommended dosage, cost of the drug & drug level monitoring and the racial factors, at least in African patients. The predictive factors for acute rejections are HLA mismatch, DGF, sensitised patients (positive PRA, positive DSA), retransplant, previous pregnancy, young recipients and older donor[8]. Episodes of acute rejections are important factors that determine the longevity of the graft and hence reduction in acute rejection incidence must have been increase the graft survival. But the current studies showed there is only a modest improvement in long term graft survival despite a significant reduction in acute rejection episodes[9]. There are some reports showing despite increase in acute rejection episodes, the long term graft outcome wasbetter with newer agents like Balatacept based regimen[10]. This signifies that not all the acute rejections lead to poor graft outcome.

In this present study we found thatthere were significant differences in the occurrence of early rejection & late ejection among patients with different donor type (related & unrelated), induction protocol (Basiliximab & No induction) and immunosuppressive regimen (Tac based & CSA based). We specifically looked in to the role of induction agent in occurrence of rejection episodes among different donor type (related & unrelated). We found that usage of induction agent reduced the incidence of early acute rejections in both related & unrelated donor type when combined with TAC based immunosuppressive regimen but there was no statistical significance achieved after the influence of TAC eliminated.This is in concurrence with recent large prospective studies conducted in western countries[11].TAC based immunosuppressive regimen reduced the incidence of both early and late acute rejection even the influence of Basiliximab eliminated. The beneficial effect is more prominent in unrelated donor type.

The limitations in our study, first the data were collected retrospectively and hence the association found may not prove causality. Second, the number of events especially late rejection episode were small.

V. Conclusion:

About one in every five patients had acute rejection in our cohort and this data is comparable to that of other Indian data. TAC based regimen had reduced late acute rejection episodes when compared to CSA based regimen. Basiliximab had no role in reducing early & late acute rejections on the background of TAC based regimen. This is in concurrence with recent large prospective studies conducted in western countries. Hence we may be able to reduce the cost of the transplant in resource poor settings by avoiding induction agent at least in low immunological group. Larger prospective data from our country is needed to confirm the results.

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