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

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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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1. 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 ESRD¹. 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 survival². 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 malignancy³. 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 and on-going chronic humoral injury. The alloantigen independent factors are as follows CNI nephro toxicity, graft infections (pyelonephritis, BKV, CMV), disease recurrence, hypertension and transplant renal artery stenosis⁴. 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) 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 analysis associated 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, retransplantation 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 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%.
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.
IV. Discussion:

The incidence of acute rejection episodes varies from 8 to 12% in developed nations\textsuperscript{6} whereas in developing countries like India it is in the range of 12 to 15%\textsuperscript{7} and it is even higher among African patients. The major factors proposed for the increased incidence of BPAR in developing countries are the 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\textsuperscript{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\textsuperscript{9}. There are some reports showing despite increase in acute rejection episodes, the long term graft outcome was better with newer agents like Balatacept based regimen\textsuperscript{10}. This signifies that not all the acute rejections lead to poor graft outcome.
In this present study we found that there 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 into 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.

References:


