transplantation
india

RENAL TRANSPLANTATION IN PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS- AHMEDABAD EXPERIENCE

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ABBREVIATIONS

FSGS	Focal segmental glomerulosclerosis	SCr	Serum creatinine
ESRD	End stage renal disease	HSCT	Hematopoietic stem cell transplantation

KEY WORDS

renal trasplantation, recurrent focal segmental glomerulosclerosis

ABSTRACT

Background: Primary focal segmental glomerulosclerosis (FSGS), an important cause of end stage renal disease is well known for graft loss due to recurrence. We report our experience of transplantation with adjuvant hematopoietic stem cell transplantation (HSCT) to induce tolerance in patients with primary FSGS.

Patients and methods: Seventeen patients with primary FSGS underwent transplantation at our center between August 1998 and December 2004. They were divided in to 2 groups; group A consisted of 9 patients who opted for adjuvant HSCT with transplantation and group B comprised of 8 patients who underwent transplantation directly. Group A underwent living-related and unrelated (including 1 domino) transplantation. In group B, 3 patients underwent cadaver transplantation and 5 patients underwent living related and unrelated transplantation. Donor-recipient HLA match profile was not comparable between the 2 groups. Mean donor age was 42 years in group A and 40 years in group B. Group A received high dose HSCT in thymus, bone marrow, periphery and portal circulation approximately 1 week before transplantation along with minimum non-myeloablative conditioning with cyclophosphamide, cyclosporine, Treosulphan and target specific low dose irradiation. Both groups underwent transplantation following negative lymphocytotoxicity cross match.

Results: Group A with a mean follow up of 3.14 years had better graft function with mean serum creatinine (SCr) of 1.64 mg %, 2 patients had single mild acute rejection episodes (AR) and no recurrence with less immunosuppression requirement as compared to group B with a mean follow up of 3 years. Mean SCr was 2.3 mg %, 2 patients had single AR episodes each and 5 patients had recurrence out of which graft loss occurred in 1 and, graft + patient loss in 1, over mean follow up of 8.1 months.

Conclusion: Group A had better graft and patient survival with absence of recurrence and minimum requirement of immunosupression as compared to controls. HSCT is safe and efficacious.

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INTRODUCTION

Primary focal segmental glomerulosclerosis (FSGS) is an important cause of end stage renal disease (ESRD) occurring in about 20 % of adults with nephrotic syndrome [1]. Graft loss due to recurrence can affect 15 % to 100 % patients [2-4]. Five year graft survival has been reported from 50 % to 77.4 % [2, 5]. We report single center 7 years experience of transplantation (from August 1998 to December 2004) in 17 patients with primary FSGS. Our primary objective was to create donor specific hypo responsiveness using high dose hematopoietic stem cell transplantation (HSCT) in adults with primary FSGS with ESRD undergoing renal transplantation and also to evaluate its role in preventing recurrence.

PATIENTS AND METHODS

Seventeen patients with biopsy proven primary FSGS underwent renal transplantation at our center between August 1998 and December 2004. They belonged to 2 groups; group A comprised of 9 patients who willingly underwent adjuvant high dose HSCT along with renal transplantation and group B of 8 patients opted out of HSCT and were directly transplanted. Demographics of patients and donors are mentioned in table 1.

Group A:

Out of 9 patients, 7 were males and 2 females, with mean age of 29 years. The mean donor age was 42 years.

HLA match profile: Two patients had complete A, B, DR mismatches, 5 patients had 1 DR, A and B match, 1 had 1B match and 1 had 1 DR match.

Group B:

All 8 patients were males with mean age of 35 years. The mean donor age was 40 years.

HLA match profile: In recipients with 3 cadaver donors, HLA typing could not be performed, 1 patient had complete mismatch, 1 patient had 1 A, DR match, 2 patients had 1 B match and 1 patient had 1 B and DR match.

Pre-transplant HSCT in group A:

All patients had undergone HSCT willingly after giving their written informed consent as per the modified revised declaration of Helsinki. They received bone marrow derived HSCT which was fortified with 2 doses of peripheral blood stem cells as per "Ahmedabad tolerance induction protocol" [6-8]. All of them underwent low dose non-myeloablative conditioning with cyclophosphamide, cyclosporine A (CsA) and low dose target specific irradiation. Hematopoietic stem cells were administered in thymus, portal circulation, marrow and periphery.

	Group A (N=9)	Group B (N=8)
Mean follow up (years)	3.14	3.0
Mean recipient age (years)	29 (17-49)	35 (18-51)
Gender : M/F	7/2	8/0
Mean donor age (years)	42 (28-50)	40 (19-54)
Living/cadaver donor	9/0	5/3
Donor/Recipient HLA match		
A	5 (55.6 %)-1 match	3-not done, 2 (25%)-1 match
B	6 (66.7 %)- 1 match	3-not done, 3 (37.5 %)-1 match
DR	6 (66.7 %)-1 match	3-not done, 3(37.5 %)-1 match

Table 1 Demographics of Patients With Primary FSGS Transplanted with And Without Adjuvant HSCT.

Both groups underwent transplantation after negative lymphocytotoxicity cross match; group A underwent transplantation 1 week after HSCT.

Post-transplant follow-up

Both the groups underwent follow up in the same clinic in similar pattern [6-8].

Immunosuppression

Group A received two-drug immunosuppression: CsA, 3 ± 1 mg/kg BW/ day and Prednisolone 0.5 mg/kg BW/ day for first

6 months. CsA was tapered to maintain trough levels of 120 ± 30 ng/ml (measured by EMIT CsA assay, by Syva, Dade Behring, USA- recommended dose: 50-176 ng/ml). Prednisolone was tapered to 0.2 mg/kg BW/ day from 7th month and then kept on 0.1 mg/kg BW/ day thereafter.

Group B was maintained on standard triple drug immunosuppression from the very beginning which included CsA, 5 mg/kg BW/ day, Prednisolone, 0.6 mg/kg BW/ day and Azathioprine, 2 mg/ kg BW/ day.

Rejection was diagnosed following biopsy as per modified Banff criteria and treated with intravenous methylprednisolone (MP), 250 mg/day for three consecutive days [9].

Recurrence of FSGS was defined as significant proteinuria (>50 mg/m²/day) in absence of histological evidence of acute rejection and findings of segmental collapse with hyalinosis, with/ without adhesions to Bowman capsules, in the allograft biopsy.

RESULTS

The mean serum creatinine (SCr) of group A compared with group B at 3, 6, 9, 12 months and at present was better than that of group B (statistically not significant) (figure 1).

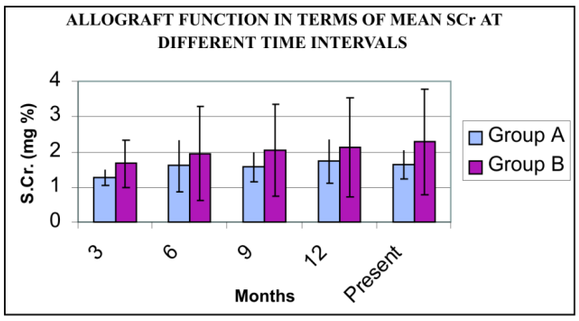

Figure 1

None of the patients in group A had proteinuria over a mean follow-up of 3.14 years. Two patients in group A had borderline acute tubulo-interstitial rejection at 6 weeks post-transplant and 6 months post-transplant respectively, along with acute CsA toxicity which responded to standard anti-rejection therapy and decreasing CsA dose and 2 other patients had acute CsA toxicity which responded to tapering CsA. (figure 2a) All the 9 patients are doing well at present with mean SCr of 1.64 mg % on low dose CsA (1.5 ± 1 mg/ kg BW/day) with/without Prednisolone, 0.1 mg/ kg BW/day.

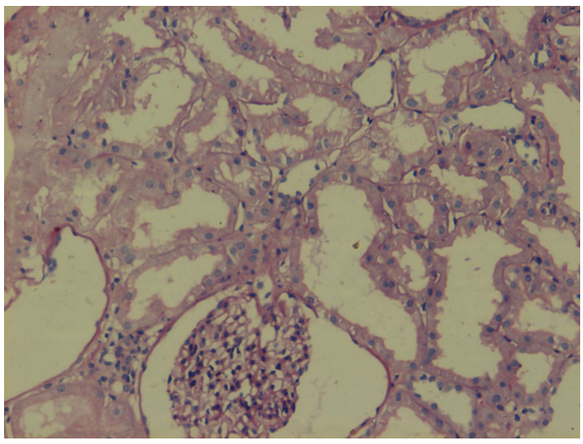

Figure 2a Acute tubular necrosis with CsA induced toxic tubulopathy, x 400, PAS stain.

There was no graft versus host disease or adverse effects related to tolerance induction protocol using high dose HSCT.

Over a mean follow-up of 3 years in group B, 5 (62.5 %) patients developed recurrence of FSGS with urinary protein leak of > 50 mg/m²/day, over a mean follow up of 8.1 months (tables 2, 3). Two patients had recurrence at about 2 months post-transplant. One of them had received it from extended family member and other one had cadaver allograft.

	Group A (N=9)	Group B (N=8)
Immuno-suppression		
≤ 9 months	CsA+low dose Pred. +Aza	CsA +Pred. +Aza
≤ 12 months	Low dose CsA + Pred.	CsA +Pred. + Aza
1 year post Tx.	Low dose CsA± Pred.	CsA +Pred. + Aza
Acute rejection episodes	2	2
Recurrence	0	5 (62.5 %)

Table 2 Post Transplant Follow-up of Both Groups.

SR. NO.	AGE/SEX	DONOR	DONOR AGE	RECURRENCE DURATION POSTTX. (MONTHS)	PRESENT SCr (mg %)	MAINTENANCE HD
1 (AR)	29/M	*EXT. FAM.	31	2	5.2	YES
2 (DV)	51/M	CADAVER	35	2		DIED AT 11 MONTHS POSTTX
3 (VP)	32/M	CADAVER	50	8	2.42	NO
4 (MS)	40/M	* EXT. FAM.	40	8	1.1	NO
5 (KB)	35/M	MOTHER	54	11	1.52	NO

Table 3 Data Showing Recurrence of FSGS in Group B.

* EXT. FAM. : Extended family member
* Post Tx. : Post transplant

Two patients had recurrence at approximately 8 months post-transplant, out of which one was cadaver donor and one was from extended family member. One patient with mother's graft had recurrence at 11 months post-transplant (figures 2b).

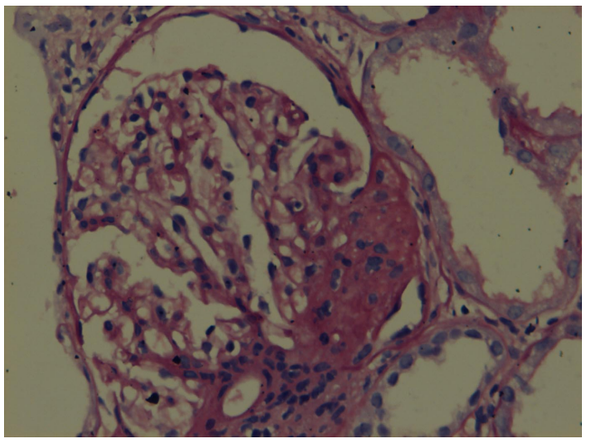

Figure 2b Recurrence of FSGS with perihilar adhesion of capillary tuft, x 200, H & E Stain.

One cadaver graft recipient succumbed to recurrence and associated CMV infection at 11 months post-transplant and other one is on maintenance hemodialysis. One patient died in road accident with functioning graft. Two patients with living related grafts, who had mild acute tubulointerstitial rejection, type IA, each; at 1 month post-transplant and 14 days post-transplant respectively, responded to standard anti-rejection treatment and have now stable graft function with mean SCr of 1.47 mg %.

DISCUSSION

Primary FSGS is considered to be one of the primary glomerulopathies with highest rate of recurrence after transplantation [2-4, 10]. The risk factors identified by various workers are: age at onset, time interval between diagnosis to end stage renal failure, duration of dialysis, immunosuppressive therapy, mesangial proliferation in native kidney and donor age. We have found 62.5 % chances of recurrence in our population. The time of recurrence noted was from 2 months to 11 months and HLA matching had no role in preventing recurrence. The number of cadaver donors was also limited to define the effect of cadaver kidney versus living related donor kidney. In our experience we have found that recurrence cannot be prevented in cadaver graft also. In India it is difficult to compare the effect of duration of maintenance dialysis since majority of our patients cannot afford to get adequate maintenance dialysis.

It is very clear from the present study that adjuvant HSCT has definite role in preventing recurrence of primary FSGS in addition to preventing severe AR episodes with an advantage of low dose minimal immunosuppression. Over a mean follow up of 3.14 years; none of the 9 patients who underwent transplantation from living related donor allografts with donor age above 40 years, had recurrence. Moreover their immunosuppression requirement has also been minimal. They have minimum acute rejection episodes and there is absence of CMV or any other viral infections in this group of patients.

Primary FSGS is a lesion of obscure pathophysiology. One of the hypotheses for post-transplant recurrence of FSGS is that lymphocytes in such grafts are found to be resistant to CsA induced inhibition of interleukin 2 production [11]. Our tolerance induction model is based on the principle of apoptotic deletion of peripheral T lymphocytes sustained by presence of donor chimeric cells. We believe that this may be the probable

mechanism of preventing post-transplant recurrence of FSGS in addition to creating donor specific hypo responsiveness.

Our primary objective of adjuvant HSCT in renal transplantation was to create donor specific hypo-responsiveness resulting in to minimum/ no immunosupression requirement. This objective was achieved in all patients across MHC barriers and in addition, interestingly we found that recurrence of primary FSGS was preventable using "Ahmedabad tolerance induction protocol".

CONLCUSION

This is the first report showing prevention of post-transplant recurrence of primary FSGS in addition to creating donor specific hypo responsiveness in living related renal allograft recipients across MHC barriers using adjuvant high dose HSCT with low intensity nonmyeloablative conditioning. HSCT is safe and efficacious.

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