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Original Article

Internal Medicine Section

Initial Experience with Grafalon as Induction Agent in Kidney Transplantation

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ABSTRACT

Introduction: Renal transplantation is ideal modality of Renal Replacement Therapy (RRT) as it is cost effective and associated with quality of life. Induction immunosuppression is an immunosuppressive therapy given at the time of transplantation to reduce risk of acute rejection. Induction agents include lymphocyte depleting antibodies and Interleukin-2 (IL2) receptor antagonists. Commonly used lymphocyte depleting antibodies are 'Thymoglobulin' and 'Grafalon'. There is no study with Grafalon as induction agent in renal transplantation from India, as until recently it was unavailable in India. Current study is the first report from India, of Grafalon use as an induction agent in renal transplantation.

Aim: The aim of the present study was, to study safety and efficacy of 'Grafalon' as induction agent in kidney transplantation.

Materials and Methods: This was a single center study of 11 patients who have received Grafalon as induction agent for renal transplantation. All received steroid pulse and Grafalon 4 mg/kg as induction. Maintenance immunosuppression consisted of prednisolone, tacrolimus and mycophenolate sodium.

Results: Four patients (36.3%; 95% Confidence Interval (CI), 8 to 65%) developed biopsy proven acute rejection. Three patients had combined acute T-cell and acute antibody mediated rejection and one had acute T-cell mediated rejection. One patient died due to rhinocerebral mucormycosis and one graft was lost due to graft thrombosis. Two patients got urinary tract infection, one with wound infection and another one developed cytomegalovirus syndrome. Cost of Grafalon induction (4 mg/kg) was higher compared to Thymoglobulin (1.5 mg/kg).

Conclusion: Induction with Grafalon was associated with high rate of acute rejection, at the dosage used in the present study. So, cannot be recommended in clinical practice at this dose.

Keywords: Anti-thymocyte globulin, Immunosuppression, T-cell depleting antibody

INTRODUCTION

With increasing prevalence of diabetes and hypertension in India, prevalence of Chronic Kidney Disease (CKD) is expected to rise [1]. Population based study from Bhopal estimated average crude and age-adjusted End Stage Renal Disease (ESRD), incidence rates at 151 and 232 per million population respectively [2]. If same incidence rate is extrapolated to rest of the nation, then with current estimated population of 1.326 billion, India will have around 2,00,000-3,00,000 new patients requiring RRT every year. As per Indian CKD registry, of all stage 5 patients, 61% were not on any RRT, 32% were on haemodialysis (HD), 5% were on Peritoneal Dialysis (PD) and <2% were being worked up for transplantation [3]. Renal transplantation is ideal modality of RRT, as it is cost effective and associated with highest quality of life [4].

High cost of immunosuppressive therapy remains the major problem for developing countries like India. Induction immunosuppression is intense immunosuppressive therapy given at the time of transplant to reduce risk of acute rejection [5]. Several studies have shown that graft survival is negatively influenced by acute rejection [6,7]. Apart from reducing acute rejection, another aim of induction therapy is to prolong graft survival. Cost of graft biopsy and treatment of acute rejection are prohibitive for country like India. However, induction agents are also not without harm, as they increase cost of care and are associated with increased risk of infections and post-transplant lymphoproliferative disorders [8]. Hence, cautious use of induction agents at right dose will be most beneficial in terms of cost saving, graft and patient survival.

Commonly used induction agents include T-lymphocyte depleting antibody (most commonly rabbit anti-thymocyte globulin-rATG) and IL2 Receptor Antagonist (IL2RA). There is wide variation in use of induction agents. In USA, lymphocyte depleting agents (mainly rATG) are used in majority (61.6%) of renal transplantation and IL2RA being used in 33.3 % patients [9]. In Europe, IL2RA is more widely used than rATG or other depleting agents (12.6% depleting antibody and 25.1% nondepleting antibody) [10]. 'Thymoglobulin' and 'Basiliximab' are the induction agents used for renal transplantation in India [11-14]. There is absence of study with Grafalon as induction agent for renal transplantation from India due to lack of its availability. Present study aimed to evaluate safety and efficacy of Grafalon as induction agent in renal transplantation as it has recently become available in India.

MATERIALS AND METHODS

The present study was a single center prospective study of 11 patients who had received Grafalon© (Neovii Pharmaceuticals AG, Switzerland-formerly known as ATG-Fresenius or ATG-F) as induction agent for renal transplantation between December 2016 to June 2017 at Institute of Kidney Diseases and Research Centre, Ahmedabad, India. Patients included in the study were both living donor and Standard Criteria Deceased (SCD) donor renal transplantation recipients [15]. Written consent was taken from all patients and study was approved by internal review board of institution. All transplants were performed in accordance with declaration of Istanbul [16].

Inclusion criteria in living donor transplantation were ABO compatible recipients with negative Complement-Dependent Cytotoxicity (CDC) cross match, flow cytometric cross match and Donor Specific Antibody (DSA) by luminex. Inclusion criteria in deceased donor

transplantation were ABO compatible recipients with negative CDC cross match and flow cytometric cross match (when done).

Patients with positive hepatitis-B surface antigen or hepatitis-C or HIV were excluded from study. Recipients with two haplomatch or leucopenia (total leucocyte count <4000/cmm) or thrombocytopenia (platelet count <100000/cmm) were excluded from the study.

Immunological evaluation: All living donor transplant candidates were evaluated with CDC cross match and flow cytometric cross match. HLA antibody screen was done in all patients by LAB Screen mixed beads for antibody against Class I, Class II and MHC Class-I related Chain A (MICA) antigen using luminex platform (One Lambda Inc., Canoga Park, CA). If antibody screen was positive, then Single Antigen Bead (SAB) assay was done with Class I and II beads to detect DSA. HLA A, B, Bw, Cw, DRB1-5, DQ typing was done by PCR for both patient and donor. In case of deceased donor renal transplantation, it is recent policy to do HLA A, B, Bw, Cw, DRB1-5, DQ typing and antibody screen by LAB screen using mixed beads of wait listed candidates. The SAB assay was done in case of positive antibody screen report. At the time of deceased donor renal transplant, CDC cross match was done in all patients and flow cytometric cross match was done in those for second transplant or for sensitised patients (prior CDC cross match positivity and/or having detectable HLA antibody by SAB assay).

IMMUNOSUPPRESSIVE PROTOCOL

All 11 patients received induction immunosuppressive therapy with methyl prednisolone (500 mg/day intravenously for three days) and Grafalon 4 mg/kg. Grafalon was given in two divided doses each of 2 mg/kg on day of transplant and on day one. Grafalon was diluted in 0.9% Normal Saline (NS) at dilution ratio of 1:7 and infused over 4 hours. First dose was infused intraoperatively before vascular clamp release. Maintenance immunosuppression consisted of prednisolone (20 mg/day, tapered to 10 mg/day at three months post-transplant and continued thereafter), Tacrolimus (TAC) (-0.06-0.08 mg/kg/day) and Mycophenolate Sodium (MPA) (1080-1440 mg/day). Tacrolimus dose was adjusted according to trough level measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Target trough tacrolimus level was 8-10 ng/mL in first three months and 5-8 ng/mL thereafter. All patients received prophylaxis against Cytomegalovirus (CMV) infection (valganciclovir 450 mg once a day for 3 months), fungal infections (fluconazole 100 mg once a day for 3 months), and pneumocystis carinii pneumonia (trimethoprim/sulfamethoxazole 160/800 mg once a day for 9 months). Graft biopsy was done in case of graft dysfunction and graded according to modified Banff classification [17].

STATISTICAL ANALYSIS

Quantitative data was expressed as mean±SD or median (range). Comparison of HLA match between cases with or without acute rejection was carried out using Mann Whitney test. A p-value <0.05 was considered as statistically significant. All analyses were performed with SPSS version 14.0 statistic software.

RESULTS

Demographics: Demographic details of all the patients are mentioned in [Table/Fig-1]. Median age of 11 patients (Male=11, Female=0) was 32 years (range 22-55 years) and 10 donors (Male=4, Female=6) was 49 years (range 30-58 years). Seven were living donor renal transplant (donor: mother=4, spouse=2, brother=1) and 4 were SCD transplant. Two patients were recipient of second kidney transplant. Median duration of maintenance haemodialysis before transplant was 5 months (range 1-30 months). Mean Glomerular Filtration Rate (GFR) of living donor was 99±9 mL/minute. Details of HLA match and anti-HLA antibody screen results are mentioned in [Table/Fig-2]. Surgical details and outcome are mentioned in [Table/Fig-3].

Outcome: At median follow up duration of 103 days (range 54-226 days), patient survival was 91% and graft survival was 82% with biopsy proven acute rejection rate of 36.3% (95% CI 8 to 65%). Details of type of rejection and anti-rejection treatment are mentioned in [Table/Fig-4]. Mean serum creatinine of patients with functioning graft (n=9) was 1.23±0.3 mg/dL. None of the patients developed leucopenia, thrombocytopenia or any infusion related side effects. Delayed graft function was not seen in any of patient. Mean HLA-DR match in those who got acute rejection was 0.5±0.6 and 0.9±0.7, in those who did not get acute rejection (p=0.4). Mean HLA A-B-DR match was 1.5±1.7 in those who got acute rejection and 2±1.5 in those who did not get acute rejection (p=0.5).

One patient died at 6th month post transplant. He had Type 2 Diabetes Mellitus (DM) related nephropathy and received kidney donation from his wife. Both HLA-DR and HLA-ABDR match were zero. On pre-transplant evaluation, he had non-donor specific class II HLA antibody. On post transplant day 6, he developed acute T and B cell mediated rejection with secondary thrombotic microangiopathy and was treated with pulse methylprednisolone, Thymoglobulin, plasmapheresis and Intravenous Immunoglobulin (IVIG). Three months post transplant, he was diagnosed to have pulmonary tuberculosis and was started on anti-tubercular therapy. Six months post transplant, he succumbed to rhinocerebral mucormycosis with aspergillosis, CMV viremia and sepsis induced multiorgan dysfunction including graft failure. One graft was lost due to transplant renal artery thrombosis

Patient No.	1	2	3	4	5	6	7	8	9	10	11
Age (years)	34	30	55	23	35	30	32	32	22	27	50
Gender	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Blood group	A	A	B	A	A	B	AB	A	A	B	B
Native renal disease	Unknown	Unknown	Type 2 DM-DN	Focal global sclerosis	ADPKD	Unknown	Rt PUJ obstruction and small left kidney	Post Transplant CKD	Lupus nephritis	Unknown	Type 2 DM-DN
Prior kidney transplant	No	No	No	No	Yes	No	No	Yes	No	No	No
Dialysis vintage (months)	7	2	1	1	12	4	1	12	12	5	30
Donor age (years)	30	50	47	49	44	40	58	55	55	48	50
Donor sex	Female	Female	Female	Female	Female	Male	Female	Male	Male	Female	Male
Donor relation	Wife	Mother	Wife	Mother	Deceased donor	Brother	Mother	Deceased donor	Deceased donor	mother	Deceased donor
Donor blood group	O	A	B	A	A	B	A	A	A	O	B
Donor GFR (mL/minute)	118	88	98	96	-	96	100	-	-	102	-

[Table/Fig-1]: Demographic data of patients and donors.
M: Male; F: Female; DM: Diabetes Mellitus; DN: Diabetic Nephropathy; CKD: chronic kidney disease; PUJ: pelviureteric junction; GFR: glomerular filtration rate

Patient No.		1	2	3	4	5	6	7	8	9	10	11
HLA-DR match		0	1	0	1	1	1	2	1	0	1	0
HLA-A/B/DRB1 match		1	3	0	3	3	3	4	1	0	3	0
HLA-A/B/DR/DQ match		2	5	1	6	5	5	5	-	1	5	1
HLA-Bw match		1	1	1	1	1	1	1	-	2	1	1
HLA-Cw match		1	1	1	1	1	1	1	-	0	1	0
HLA antibody screen	Class I	Neg	Pos	Neg	Pos	Neg	Neg	Neg	Pos	ND	Neg	ND
	Class II	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Pos	ND	Pos	ND
	MICA	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Neg	ND	Neg	ND
Single antigen (MFI)	Class I	ND	Neg	Neg	Neg	ND	ND	ND	ND	ND	A80-5447 (not DSA)	ND
	Class II	ND	Neg	DR4-1784 DR16-2338 (not DSA)	Neg	ND	ND	ND	ND	ND	DR16-1545, DR4-1480, DQ7-1412 (not DSA)	ND

[Table/Fig-2]: Details of HLA match and anti-HLA antibody screen by SAB.
HLA: Human leucocyte antigen, Pos: positive, Neg: negative, SAB: single antigen bead, DSA: donor specific antibody, MICA: MHC class-I related chain A, Std: standard, ND: not done

Patient No	1	2	3	4	5	6	7	8	9	10	11
WIT (minutes)	3	3	35	2	3	3	2	1	5	2	5
CIT	64 minutes	90 minutes	58 minutes	62 minutes	11 hours	60 minutes	106 minutes	11 hours 45 minutes	12 hours 40 minutes	54 minutes	10 hours
AT (minutes)	24	21	26	29	40	35	19	40	42	25	30
S. Cr at last follow up	0.73	1.15	2.59 Mortality due to mucormycosis	1.47	0.96	1.15	2.36	5.0 Graft loss due to thrombosis	1.14	1.6	1.1
Follow up days post transplant	226	198	189	201	211	50	103	54	72	61	61

[Table/Fig-3]: Surgical details and outcome.
WIT: Warm ischemia time, CIT: Cold ischemia time, AT: Anastomosis time

Patient No.	3	5	9	10
Type of rejection:	ABMR and Acute TCMR with secondary Acute thrombotic microangiopathy	Acute pyelonephritis+ Acute borderline TCMR	Acute ABMR+ borderline TCMR	Acute ABMR+ Acute TCMR
Modified Banff Class and score	Type 4+6 ag1 at0 av0 aio PTC score 0	Type 4+6 ag1 at1 av0 ai1 PTC score 0	Type 2+3 ag1 at1 av0 ai2 PTC score 1	Type 2+4 ag2 at1 av0 ai3 PTC score 1
C4d by IHC	Negative	Negative	10%	50%
Timing of biopsy	Day 6	Day 13	Day 14	Day 9
S. Cr at biopsy	2.95	1.46	2.7	2.07
S.Cr at discharge	1.9	1.34	1.23	1.36
S.Cr at last follow up	2.59 12/7/17	0.96 23/8/17	1.14 18/8/17	1.56 28/8/17
Anti-rejection	4 PP+4 IVIG+3MP+ Thymoglobulin	3 MP	3 MP+ IVIG+ Thymoglobulin	3 MP+4 PP+4 IVIG
Post-transplant DSA anti-HLA ab -	DQ6 2798	Not done	Negative	Negative
Post-transplant Non DSA anti-HLA ab (MFI)	DR16 5272 DR43075 DP19 2460 DQ5 2067 DR52 2005 DQ7 1660	Not done	B76 1364 DP11 1253	A80 3233 A3 2165 DR4 1557 DR16 1432
Follow up biopsy	Day 28 Unremarkable	ND	ND	ND
Immunologic risk as per KDIGO	High	High	High	High
Trough tacrolimus level at time of biopsy (ng/mL)	9.76	8.4	9.76	10.27

[Table/Fig-4]: Details of type of acute rejection, anti-rejection therapy used and response.
ABMR: Antibody medicated rejection, TCMR: T cell mediated rejection PP: plasmapheresis MP:iv methylprednisolone, IVIG:intravenous immunoglobulin, ND: not done, KDIGO: Kidney Diseases Improving Global Outcomes, MFI: Mean fluorescence intensity, S. Cr: serum creatinine

and pseudoaneurysm after 54 days of transplant. There was no evidence of fungal or bacterial infection on histopathologic examination.

Cost analysis of Thymoglobulin and Grafalon at different induction doses have been mentioned in [Table/Fig-5]. At commonly used induction doses, Grafalon is costlier than Thymoglobulin. If cost of Grafalon at dose of 4 mg/kg is compared with Thymoglobulin single dose 1.5 mg/kg, Grafalon is not cost-effective. This analysis excludes cost required for diagnosis and treatment of acute rejection episodes.

Drug name	Content of vial	MRP of vial (INR)	Typical induction dose	No of vials used for average patient	Total cost of induction course for average patient (INR)
Grafalon	100 mg	33000	4-9 mg/kg	3-6	99000-198000
Thymoglobulin	25 mg	17400	1.5-3 mg/kg	4-8	69600-139200

[Table/Fig-5]: Cost comparison of grafalon and thymoglobulin.
For average patient with weight of 70 kg
Price shown is MRP in local market
INR: Indian rupee

DISCUSSION

Induction agents are routinely used in renal transplant but their role in tacrolimus and MPA era is not clear. Based on meta-analysis by Cochrane Collaboration, KDIGO 2009 guideline recommends use of induction agents in all kidney transplant recipients. As per KDIGO guideline, IL2 receptor antagonist is first line induction agent. Use of lymphocyte depleting agents is preferred in cases with high immunologic risk. Cases with high immunologic risk include those with HLA mismatch, ABO incompatibility, younger recipient, older donor, PRA >0%, presence of Donor Specific Antibody (DSA), increased cold ischaemic time [18,19]. Meta-analysis of randomised control trials published by Cochrane Collaboration in 2010 compared IL2RA induction with no induction and with Antithymocyteglobulins (ATG). The ATG was not superior than IL2RA in preventing acute rejections and safety profile favoured IL2RA. Biopsy proven acute rejections were 36% reduced by IL2RA when compared with placebo [19]. However, this meta-analysis included studies done in 1990s and early 2000s and since then, there has been major change in maintenance immunosuppression. Recent literature supports the fact that IL2RA may not be required for low risk patients in era of tacrolimus with MPA and depleting antibody induction reduces the risk of acute rejection in the setting of steroid withdrawal or high immunologic risk [5,20]. Several trials done in tacrolimus era have demonstrated superiority of ATG over IL2RA in standard risk renal transplant recipients [21,22]. To study efficacy of induction agent in tacrolimus and MPA era, Opelz analysed Collaborative Transplant Study (CTS) data from 38,311 first deceased-donor kidney transplants (2004-13). Transplants were classified as normal and increased risk as per current KDIGO guidelines. Both rATG and IL2RA induction were associated with reduced risk for graft loss versus no induction in increased-risk patients. In normal risk population, none of the two induction agent had any significant effect on risk of graft loss or treated rejection but hospitalisation for infection were increased by both [8]. To summarise in the era of tacrolimus based triple immunosuppression, IL2RA may no longer be beneficial in standard immunologic risk transplantation and is inferior to ATG in high immunologic risk transplantation [20]. Benefits of lymphocyte depleting induction have been demonstrated in recipients with high immunological risk [23,24]. However, in majority of studies, ATG used was Thymoglobulin.

The ATG are polyclonal IgG preparation, produced by immunising rabbits with either human thymocyte (Thymoglobulin-Sanofi Genzyme) or Jurkat human T-lymphoblastoid cell line (Grafalon© -Neovii Pharmaceuticals AG, Switzerland-formerly known as ATG-Fresenius or ATG-F). Mechanism of action of ATG involves depletion of T cells and other leukocytes through various mechanisms like complement-dependent and cell mediated cytotoxicity or via the induction of apoptosis. Manufacturing differences make the specificities of anti-HLA antibodies in Grafalon highly predictable (arising from a T cell line that has been HLA-typed), while the specificities in Thymoglobulin (arising from varying lots of human lymphocytes) are variable from lot to lot hence, usually unknown. Both types of ATG have different antigen specificities and respective antibody concentrations [25]. Grafalon shows a markedly narrower spectrum of activity against lymphocyte antigens than either Thymoglobulin or ATGAM, with no or weak reactivity against CD3, CD4, and CD44 [26].

Results of trials comparing Thymoglobulin and Grafalon are controversial. Incidence of acute rejection was either nondifferent or lower with Thymoglobulin when compared with Grafalon [27-32]. Several studies have shown higher CMV infection with Thymoglobulin when compared with Grafalon [28,31,32]. Retrospective analysis of CTS registry data of patients, who received deceased donor kidney transplant between 1985-2004, showed that Grafalon had lower incidence of lymphoma compared to Thymoglobulin (0.24% versus 1%). But it was inferior to thymoglobulin in term of graft and patient survival [33]. Docloux D et al., compared Grafalon with Thymoglobulin and reported higher malignancy incidence with thymoglobulin (12.3 versus 3.9% p=0.01) [28].

Optimal dose of Grafalon was not known and various dosing regimens of Grafalon were used with dose varying from 3 mg/kg to 21 mg/kg in different studies [28,34-40]. Most commonly used regimen was single intraoperative dose of 9 mg/kg [41-45]. Other regimens with lower doses include single dose 4-6 mg/kg intraoperatively and 2 mg/kg intraoperatively and repeated on day 1 and day 2 post renal transplant [29,46]. In our institute, commonly used induction agent is Thymoglobulin (rATG) at single dose of 1.5 mg/kg in high immunologic patients. Reason for using lower dose of rATG against recommended by western literature of 3-6 mg/kg is high rate of post-transplant infections as majority of our patients belong to low-medium socio-economic strata and have unhygienic living condition. In prior published study from Institute of Kidney Diseases and Research Centre, Ahmedabad, India, institute of 1523 living donor transplantation with single dose 1.5 mg/kg Thymoglobulin as induction agent had acceptable acute rejection rate, graft and patient survival [47]. So, considering cost and risk of infection, we decided to use Grafalon at lower dose of 4 mg/kg.

In the present study, rate of acute rejection was 36.3% with majority being ABMR which is more than expected. There was no significant difference in HLA-DR and HLA-ABDR match in those who got acute rejection and those who didn't. Out of four patients who got acute rejection, two had pre-transplant anti-HLA antibodies (though not DSA). In prior study of renal transplantation with single dose of 1.5 mg/kg Thymoglobulin from Institute of Kidney Diseases and Research Centre, Ahmedabad, India, center, rate of acute rejection was much lower than present study (7.5% vs 36.3%, p-value 0.0173, power 35% with two-sided α error of 0.05 to detect a significant difference of 5% in acute rejection rate) [47].

LIMITATION

Despite being the first prospective observational study of Grafalon safety and efficacy in Indian population, there were few limitations. The present study includes small sample size, short duration of follow up, use of lower dose of Grafalon than recommended by manufacturer, heterogenous study population and lack of monitoring of BK virus, CD 3, CD 4 and CD 8 counts. Protocol biopsy and DSA monitoring were not performed in absence of graft dysfunction. Prospective randomised double-blind study at different doses of Grafalon ideally in SCD transplantation and its comparison with Thymoglobulin is required to focus more light on safety, efficacy and cost benefit analysis of Grafalon.

CONCLUSION

Induction with Grafalon at 4 mg/kg dose is associated with high rate of acute rejection and so cannot be recommended in clinical practice at this dose.

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