One-Year Outcomes with Use of Anti-T-Lymphocyte Globulin in Patients Undergoing Kidney Transplantation: Results from a Prospective, Multicentric, Observational Study from India

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ABSTRACT

Introduction: Large-scale Indian data on the use of anti-T-lymphocyte globulin (ATLG) (Grafalon®) as induction therapy in kidney transplantation (KT) patients is lacking. The aim of this study was to determine the 1-year patient and graft survival outcomes with the use of ATLG as induction regimen in KT.

Methods: In a prospective, multicentric, observational study, adult patients who underwent ABO-compatible KT and had received ATLG as a part of induction were included in the study. The primary outcome measure was overall survival and death-censored graft survival at 12 months. The primary safety outcome was assessed by development of infectious complications and graft rejection.

Results: In total, 359 patients were included in this study. The mean age was

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42.77 ± 12.30 years and 83% were male. The average ATLG dose per patient was 6.2 ± 2.2 mg/kg whereas average cumulative dose per patient was 389.6 ± 149.8 mg. The rate of graft dysfunction was 13.4% of patients and 6.7% had biopsy-proven acute rejection (BPAR). There were a total of 12 (3.3%) deaths and one graft loss. Overall survival and death-censored graft survival at 12 months were 96.65% and 99.44%, respectively. The rate of infections was 13.6% with urinary tract infections being most common.

Conclusion: ATLG at an average dose of 6 mg/kg is an effective and safe induction regimen immunosuppressant for ABO-compatible KT with favourable impact on survival and graft function in Indian patients.

Keywords: Anti-T-lymphocyte globulin; Grafalon; Kidney transplant; Survival

Key Summary Points

Why carry out this study?

Anti-T-lymphocyte globulin (ATLG) (Grafalon®) has been approved in India for use in kidney transplantation. However, there has been no large-scale real-world studies from India

This multicentric study explored the 1-year outcomes of patient and graft survival as well as the rates of complications such as graft rejection and infections when ATLG was used as induction agent

What was learned from the study?

ATLG (Grafalon®) is associated with 1-year patient and graft survival comparable with the published literature from similar cohorts

The rate of biopsy-proven acute rejection with the use of ATLG (Grafalon®) remains acceptable compared to previous reports

We observed limited incidence of infective and other complications with the average mean ATLG (Grafalon®) dose of approx. 6 mg/kg body weight

INTRODUCTION

Chronic kidney disease (CKD) is a potentially life-threatening disease associated with significant morbidity and mortality and poor quality of life [1]. CKD ultimately results in end-stage kidney disease (ESKD). In India, the approximate prevalence of CKD and ESKD is 800 and 150–200 per million population [2]. The prevalence of CKD varies from 3% to 4% [3]. With increasing prevalence of risk factors such as diabetes and hypertension in India, the prevalence of CKD is expected to rise substantially [4]. This impacts the use of renal replacement therapy (RRT). Kidney transplantation (KT) is the ultimate modality of RRT that significantly improves the quality of life (QoL) [5]. The objective of immunosuppression in KT is to prevent acute graft rejection and improve overall graft survival [6–8]. A tailored induction regimen has been shown to be effective with good outcomes at 1 year [9].

In India, T-lymphocyte-depleting antibody—rabbit anti-thymocyte globulin (rATG) and interleukin-2 receptor antagonist (IL2RA) are commonly utilized induction agents [10]. The choice between these induction agents varies. Anti-T-lymphocyte globulin (ATLG) (Grafalon®, formerly ATG Fresenius) is produced differently than ATG (Thymoglobulin®). ATLG is prepared by immunizing rabbits with the T cell leukemia line Jurkat while ATG is

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produced by immunizing with the human thymocytes. ATLG has greater antigen specificity for activated T cells [11, 12] and it also depletes CD4$^+$CD28$^-$ T cells [13, 14]. ATLG is widely used in India as part of induction regimes for KT. Initial studies from India have shown equivalent patient survival and death-censored graft survival with ATLG and ATG [12]. Compared to basiliximab, ATLG has similar rates of biopsy-proven acute rejection (BPAR) and acute graft rejection [15]. However, rates of delayed graft function and need for dialysis were lower with ATLG than basiliximab [16]. In different studies from India, rates of BPAR varied from 13% to 32% [12, 17, 18]. As there is no multicentric, large-scale study from India assessing the utility of ATLG in KT, we conducted this study to determine the outcomes with use of ATLG and assess the impact of dose on the outcomes of KT.

METHODS

Design and Setting

This was a prospective, multicentric, observational study conducted across 11 centres in India. At each centre, an institutional ethical review board approved the study protocol. Informed consent was obtained from all the participants before enrolment into the study. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, good clinical practices and applicable local regulatory guidelines.

Participants

We enrolled adult patients aged 18 years or over, of either gender, with ESKD, undergoing KT and who had been prescribed ATLG as a part of induction. We excluded patients who had ABO-incompatible transplant, cadaveric donor transplant, patients who received ATG in the induction regime, pregnant and lactating women and patients with any other illness which in the opinion of the treating physician

was hazardous in terms of patient participation in the study.

Immunosuppressive Protocol

ATLG was administered on day 0 before transplant and day 1 and day 2 after transplant. ATLG was diluted in 0.9% normal saline (NS) at dilution ratio of 1:7. Over 4 h, ATLG was infused intravenously. First dose was given 6–8 h before the clamp release. Premedication with systemic antihistamine and steroid was done 1 h before ATLG administration. ATLG dose was decided by the treating physician. Mean ATLG dose was 6.2 ± 2.2 mg/kg and average cumulative dose per patient was 389.6 ± 149.8 mg. Cumulative dose varied from 100 to 900 mg. ATLG was administered either as a single dose or in divided doses. Standard regimens of prednisone (30 mg once daily), tacrolimus (0.1 mg/kg/day) and mycophenolate mofetil (500 mg thrice daily) were followed. Tacrolimus dose was adjusted on the basis of the trough levels with target levels of 8–12 ng/ml for first 3 months of transplant and 5–8 ng/ml after 3 months. All patients had received cytomegalovirus prophylaxis (valganciclovir 450 mg once a day for 3 months) and cotrimoxazole as prophylaxis for urinary infections and pneumocystis infection for 6 months.

Outcome Assessment

Patients were followed for 12 months posttransplant. The primary outcome measure was overall survival and death-censored graft survival. The primary safety outcome was assessed by development of infectious complications such as urinary tract infections (UTI), cytomegalovirus (CMV) infections, pneumonia; and development of graft rejection. Acute graft dysfunction was defined as rise of serum creatinine by 20–25% compared to baseline. In acute rejection cases, tissue biopsy from the transplanted graft was taken under standard procedures. Histological diagnosis was made as cell-mediated or antibody-mediated rejection. The diagnostic criteria for T cell-mediated rejection was based on finding of lymphocytic

infiltrate of tubules (tubulitis) and larger vessels (vasculitis). Severity of these lesions depends on the degree of lymphocytic infiltrate per high-powered field. Antibody-mediated rejection was diagnosed with Banff classification based on the findings of active tissue injury, immunohistologic evidence of peritubular capillary complement split-product C4d deposition, and circulating donor-specific antibodies (DSA).

Statistical Analysis

Data from all the centres was collated and entered in Microsoft Excel 2016. Data was analysed with SPSS version 15. Data were analysed with descriptive statistics. Continuous data were presented as mean values ± standard deviation for normally distributed variables and as median and interquartile range for non-normally distributed variables. Categorical data was described with frequency and percentages.

RESULTS

In this study, we included a total of 359 patients from different centres. Table 1 provides data on the baseline characteristics of the patients. The mean age was 42.77 ± 12.30 years and 83% of patients were male. In the native kidney disease, CKD of unknown etiology was most common (46.78%), followed by diabetes mellitus (20.8%) and chronic glomerulonephritis (11.9%). 47.6% patients had Human leucocyte antigen(HLA) mismatch greater than 3. Median dialysis vintage was 6 months (IQR_{25-75} 3–12). Transplant was pre-emptive in 7.2% of patients whereas 0.9% had prior transplantation. The donor mean age was 46.2 ± 11.4 years. Parents, spouse and sibling constituted 31.8%, 22.3% and 11.4% of total donors, respectively.

Table 2 shows the transplant outcomes. The graft function was well preserved over a 12-month period as indicated by serum creatinine levels (Fig. 1). Graft dysfunction was seen in 13.4% of patients whereas 6.7% had BPAR. Acute cellular rejection (ACR) and antibody-mediated rejection (ABMR) were noted in 5.3% and 1.1% of patients respectively whereas one patient had both ACR and ABMR. Calcineurin

Table 1 Baseline characteristics

Characteristics	Observation ($N = 359$)
Age (years) (range)	42.77 ± 12.30 (19–77)
Male sex	298 (83.0)
Mean ATLG dose (mg/kg)	6.2 ± 2.2
Mean cumulative dose per patient (mg)	389.6 ± 149.8
Total cumulative dose range (mg)	100 to 900
Native kidney disease	
CKD of unknown origin	182 (46.78%)
Diabetes mellitus	75 (20.8%)
Chronic glomerulonephritis	43 (11.9%)
Hereditary kidney disease	11 (3%)
Undetermined	23 (6.4%)
Others[a]	25 (7.0%)
HLA mismatch	
≤ 3	188 (52.3%)
> 3	171 (47.6%)
History of blood transfusion	85 (23.6%)
CDC	All negative
HBsAg(+) recipient	6 (1.7)
HIV(+) recipient	6 (1.7)
HCV(+) recipient	5 (1.4)
Dialysis vintage (months) ($n = 279$)	9.3 ± 10.5
Pre-emptive transplant	26 (7.2)
Prior kidney transplant	3 (0.9)
Donors' profile	
Age (range)	46.2 ± 11.4 (21–79)
Gender (M/F)	115:244
Parent	114 (31.8%)
Spouse	80 (22.3%)
Siblings	41 (11.4%)

Table 1 continued

Characteristics	Observation (N = 359)
Others	124 (34.5%)

[a]Others—IgA nephropathy (n = 9), chronic interstitial nephritis (n = 6), focal segmental glomerulosclerosis (n = 5), reflux nephropathy (n = 3), lupus nephritis (n = 1) and haemolytic uremic syndrome (n = 1)

inhibitor toxicity was responsible for graft dysfunction in 1.4% of cases. Asymptomatic rise in creatinine was seen in 1.4% of patients and 13.6% of patients developed one or more infections. UTI was the most common infection that developed in 7% of patients followed by sepsis (3.3%). Cytomegalovirus (CMV) disease and varicella-zoster virus (VZV) disease were observed in one patient each. Only one patient had a graft loss, which was following ABMR. All-cause mortality was 3.3%. Case of death included acute coronary syndrome (n = 5), sepsis (n = 6) and fulminant hepatic failure (n = 1). Overall survival and death-censored graft survival at 12 months were 96.65% and 99.44% respectively.

DISCUSSION

In this large, prospective study with ATLG used as induction regimen, the achieved overall survival and the death-censored graft survival rate at 12 months post-transplant along with comparable rates of infections and graft rejection indicate that ATLG is useful for induction therapy in KT. Multiple studies reported similar rates of overall and death-censored graft survival at 1 year post-transplant [19, 20]. Even beyond 1 year (median 22 months), comparable patient survival and death-censored graft survival have been reported in India [12]. At 5 years post-transplant in patients who had steroid avoidance, the efficacy and safety of ATLG remained similar to those who received steroids for the initial 6 months [20]. These data indicate a substantial efficacy of ATLG in 'overall and

Table 2 Transplant outcomes

Parameters	Observations
Graft dysfunction	48 (13.4)
Biopsy-proven acute rejection	24 (6.7)
Acute cellular rejection (ACR)	19 (5.3)
Antibody-mediated rejection (ABMR)	4 (1.1)
ABMR + ACR	1 (0.3)
Calcineurin inhibitor toxicity	10 (2.8)
Graft dysfunction conservative management	5 (1.4)
Acute tubular necrosis with cortical necrosis	4 (1.1)
Asymptomatic rise in creatinine	5 (1.4)
Infective episodes	49 (13.6)
Urinary tract infection	25 (7.0)
Sepsis	12 (3.3)
Lower respiratory tract infection	4 (1.1)
Cytomegalovirus disease	1 (0.3)
Varicella-zoster virus disease	1 (0.3)
Others[a]	6 (1.7)
Deaths	12 (3.3)
Graft loss	1 (0.3)
Patient survival after 12 months	96.65%
Death-censored graft survival	99.44%

[a]Others—graft pyelonephritis (n = 1), perigraft collection (n = 1), gastroenteritis (n = 1), osteomyelitis (n = 1), right gluteal abscess (n = 1), perianal abscess (n = 1)

graft survival'. Adequate dose of ATLG is essential to induce better immunosuppression without increasing the risk of complications. Though the average ATLG dose in our study was 6.2 ± 2.2 mg/kg, it varied from 5.1 ± 2.7 mg/kg to 21 mg/kg in previous studies [19, 20]. A study from India using a relatively lower ATLG dose (4 mg/kg) had observed a comparatively lower rates of patient survival (91%) and graft survival (82%) at a median follow-up of 103 days [21].
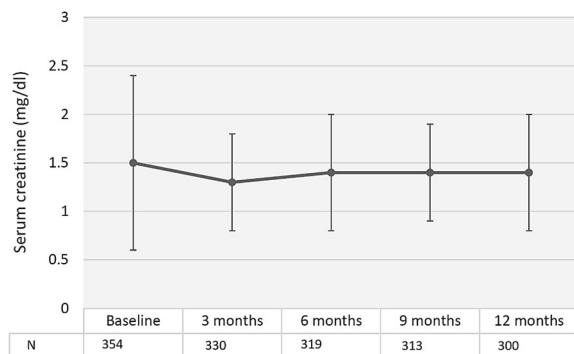
Fig. 1 Changes in serum creatinine over 12 months

However, contrasting these observations, another study from India reported comparable 12-month graft survival even with a low dose of ATLG (1.7 ± 0.15 mg/kg) [22]. Therefore, optimal dose that provides best outcomes still needs to be clearer. In our experience, an average ATLG dose of 6 mg/kg provides effective survival rates without affecting other complications and has been proved effective and safe in a previous similar study from India [12].

Acute rejections are associated with significant impact on graft survival [8]. ATLG is used as induction regime primarily to prevent the graft dysfunction and graft rejection. BPAR was relatively lower (6.7%) when compared to the rates of 12.8–36.3% among other studies from India [12, 21]. Using a regimen of 9 mg/kg prior to reperfusion of the allograft, followed by 3 mg/kg/day on day 1 to 4, a randomized study from Switzerland reported ABMR and ACR rate of 35% and 11% within 1 year of transplantation [23]. With similar dosing regime, Kamar et al. observed BPAR and graft loss rate of 3.6% and 9.6% at 1 year [15]. These data indicate that ATLG is effective in reducing acute rejection and improving graft survival. Avoiding the graft rejection is the primary objective of immunosuppression in KT. We observed well-maintained graft function over the 12 months. Persistently good graft function can be seen even after 1 year of transplant [23]. Thus, the use of ATLG in KT patients can effectively prevent rejection and help in maintaining good graft function in the post-transplant period.

Infections are common with immunosuppressive treatments. Infection rate was 13.6% in our study which is comparable to previous studies (approx. 13%) [12, 17]. Compared to ATLG, a North Indian study reported higher rates of infections with ATG [12]. That result was further substantiated by a metanalysis reporting that the rate of bacterial and viral infections is usually lower with ATLG compared to ATG (odds ratio 1.49, 95% confidence interval 0.43–5.23) [24]. Among the infective complications, reactivation of viral disease, especially CMV, is worrisome. We had very limited viral disease reactivation with once case each of CMV and VZV. Yilmaz et al. [19] observed 12.7% of patients diagnosed with CMV. A study from Thailand reported 43% incidence of CMV reactivation with use of ATG as induction regime [25]. A comparable rate of infections and lower viral disease reactivation in our study perhaps suggests that ATLG is a safe induction agent for KT in the Indian setting.

Though we did not compare the ATLG with other induction therapies, it is essential to understand the differences in the outcomes. A systematic review of randomized controlled trials (RCTs) identified no significant differences in 1-year patient survival or graft loss or BPAR when basiliximab was compared to ATG or OKT3 (eight RCTs) [26]. At 6-year follow-up, Ulrich et al. did not observe significant difference between basiliximab and ATG in the patient and graft survival outcomes, nor in the incidence of BPAR. Rates of CMV infection and haematological complications with ATG were higher than those with basiliximab [27]. Another study comparing daclizumab and ATG did not find significant difference in 1-year patient and graft survival rates. Rates of BPAR and steroid-resistant rejection were significantly lower with ATG than daclizumab [28]. However, comparing the use of single bolus dose of basiliximab or ATLG, Yang et al. [29] reported significantly higher acute rejection rates with basiliximab (35.7% vs. 15%, $p = 0.032$). The 1-year patient and graft survival did not differ between the two groups. Thus, the optimal induction regimen for KT that is effective and safe needs to be established in future comparative studies.

Limitations

Though the observations from this study show promising efficacy and safety of ATLG in KT recipients, the study has limitations. The proportion of male patients was substantially greater. CKD seems to be slightly more prevalent in men than women in India [30]. Previous studies have also reported gender disparity in KT with male recipient of transplants being significantly greater in number than female recipients [31]. We did not assess the outcomes based on HLA mismatch. Furthermore, our study had a shorter follow-up duration of only 1 year. Studies with longer follow-up are necessary in the Indian setting.

CONCLUSION

In this first large-scale Indian study of ATLG in KT, we observed better patient survival and death-censored graft survival at 12 months that were comparable to those in previous reports. With a mean dose of 6 mg/kg, we can achieve better outcomes with lower rates of infection, graft dysfunction and rejection. Thus, ATLG at median optimal dose of 6 mg/kg can be effectively and safely used in Indian patients undergoing KT.

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Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the participants for participation in the study with all the rights to withdraw anytime during the entire duration. Ethics committee approvals were obtained from individual

institutional and an independent ethics committee. Ethics committee for research, Fortis Hospital (ECR/57/DL/2013/RR-2016), Ethics committee for Manipal Hospital, Bangalore Ethics committee, Sir Gangaram Hospital (EC/01/18/1313), Ethics Committee PSRI, Ethics committee, MPUH (EC/506/2018), NHRTIICS Ethics committee, Ethics Committee, Medanta Hospital and Sangini Hospital Ethics Committee (ECR/147/Inst/GJ/2013).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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