

Journal of Nephropathology

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Comparison of clinical outcome of induction immunosuppressive therapy with thymoglobulin and standard therapy in kidney transplantation; a randomized double-blind clinical trial

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 7 August 2018
Accepted: 27 April 2019
Published online: 10 June 2019

Keywords:
Kidney transplantation
Induction therapy
Thymoglobulin
Acute allograft rejection
End-stage renal disease
Hemodialysis
Immunosuppression
Anti-thymocyte globulin

ABSTRACT

Introduction: Thymoglobulin is a lymphocyte-depleting polyclonal antibody, administered for induction therapy at the time of kidney transplantation to reduce the risk of acute allograft rejection. The appropriate dosage and duration of therapy is controversial. The higher dosages are associated with infection and malignancy.

Objectives: In this study efficacy and safety of lower dosage (in comparison with previous studies) of thymoglobulin in kidney transplant recipients was evaluated.

Patients and Methods: In this clinical trial, 106 adult kidney transplant recipients, were randomized before transplantation in two groups (case and control). The case group (53 patients) were received induction therapy with thymoglobulin (1.5 mg/kg/d for 3 days) and the control group (53 patients) were received non-induction regimen. Delayed graft function (DGF), glomerular filtration rate (GFR), acute allograft rejection and thymoglobulin complications were evaluated during the first post-transplantation year.

Results: Around 106 kidney transplant recipients were enrolled (71 or 66.98% deceased donor) to the study. No significant statistical differences were found in GFR at the time of discharge from hospital ($P=0.399$) and at 1 year ($P=0.851$) and acute allograft rejection ($P=0.304$) between two groups. Graft survival (73.5% in case group versus 81.1% in control group, $P=0.392$) at month 12th was similar among groups. Additionally, no significant differences of acute allograft rejection in recipient from deceased or living donor between two groups were detected. There was a higher incidence of DGF in the control group (26.4%) than the thymoglobulin group (5.8%) and the difference was statistically significant ($P=0.004$). Thrombocytopenia (17% versus 49.1%, $P<0.001$) and leukopenia (11.3% versus 50.9%, $P<0.001$) were also significantly higher in the case group.

Conclusion: While the incidence of DGF was reduced in thymoglobulin group, the short-term acute allograft rejection rate was not reduced compared to the control group. However, our results require further consideration with larger samples.

Trial Registration: Registration of trial protocol has been approved in Iranian registry of clinical trials (identifier: IRCT2017050933884N1; <http://irct.ir/trial/26025>, ethical code: IR.AJUMS.REC.1394.329).

Implication for health policy/practice/research/medical education:

In a randomized clinical trial on 106 kidney transplant recipients, we found that induction therapy with thymoglobulin did not associate with reduction in acute allograft rejection or improvement of graft survival.

Please cite this paper as: Shahbazian H, Ghorbani A, Hayati F, Beladi Mousavi SS, Sabetnia L, Ahmadi Halili S, et al. Comparison of clinical outcome of induction immunosuppressive therapy with thymoglobulin and standard therapy in kidney transplantation; a randomized double-blind clinical trial. J Nephropathol. 2020;9(1):e08. DOI: 10.15171/jnp.2020.08.

Introduction

Kidney transplantation is an effective treatment in patients with end-stage renal disease (ESRD) (1) and is the most cost-effective strategy in the treatment of patients with

kidney failure (2). Kidney transplantation is associated with improvement in quality of life and a significant reduction in mortality in comparison with hemodialysis (3). It should be considered that the success rate of the transplantation

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depends on the administration of appropriate immunosuppressive therapies (4). In recent years, induction therapy has been used extensively (2). Induction therapy is often used to prevent acute rejection of the allograft, which can lead to loss of the transplanted organ (5, 6). Induction therapy is an intensive immunosuppression in the early days after transplantation, when the immune system of the kidney recipient has the first contact with the antigens of the donor (6). Monoclonal and polyclonal antibodies are administered for induction therapy with different therapeutic protocols (7). Thymoglobulin is a lymphocyte depleting polyclonal antibody and is used as an induction therapy to reduce the acute rejection of allograft (8). There is no consensus on the appropriate dosage and duration of treatment. High doses of thymoglobulin can be associated with infection and malignancy and lower doses may be associated with increased risk of acute allograft rejection (9).

Objectives

The aim of the present study was to determine the frequency distribution of effectiveness and outcome of induction therapy in kidney transplant patients, in lower dosage in comparison with previous studies. In this study, the lower dosage of thymoglobulin was administered as induction therapy to reduce the rate of thymoglobulin side effects.

Patients and Methods

Study design

This prospective randomized double-blind clinical trial in renal transplant recipients was designed to compare the clinical outcome of induction therapy with standard

immunosuppression. The study investigates the off-label use of thymoglobulin (anti-thymocyte globulin [rabbit]) for immunosuppression induction. The study design is shown in Figure 1.

Inclusion, exclusion and randomization

In this clinical trial, 106 kidney transplant recipients from living and deceased donor in Ahvaz Golestan hospital were included, if they were capable of giving written informed consent and were over 18 years of age. The study was conducted from June 2014 to December 2016.

Exclusion criteria were simultaneous transplantation of two organs and presence of contraindication for prescribing thymoglobulin (including thrombocytopenia, leukopenia, and malignancy within five years, hepatitis B or C viruses or HIV infection). Study participants were randomly allocated (1:1) by using random digits table.

Preparation of blinded induction therapy

Patients were randomly divided into two equal groups, including control (non-induction) and case (induction) group. Patients, assessors and those analyzing outcomes were reminded blind to the study group assignment. For case group induction therapy with thymoglobulin (1.5 mg/kg/d, for 3 days) was conducted. The first dosage was infused over 8 to 10 hours and subsequent infusions were administered over 4 to 6 hours. The control group received an equivalent placebo (normal saline) preparation. The first dose of thymoglobulin was given intra-operatively. Methylprednisolone, chlorpheniramine and acetaminophen administered as premedication for prevention of cytokine

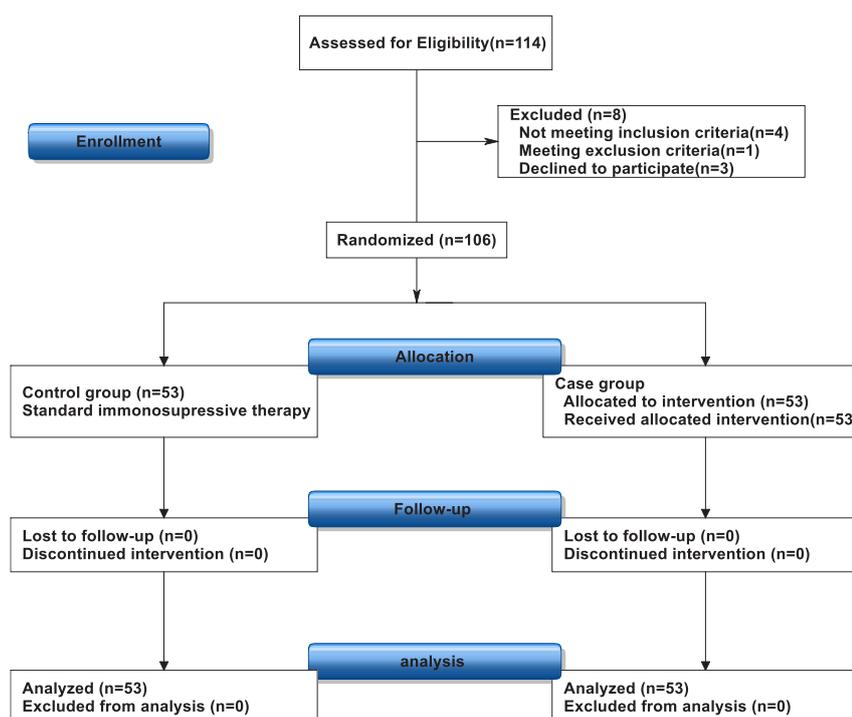


Figure 1. CONSORT flow diagram for the study.

release syndrome due to thymoglobulin infusion. Thymoglobulin withheld if the platelet count dropped below 50000/mL or white blood cell (WBC) count dropped below 2000/mL. If the platelet count was between 50000 and 75000/mL or the WBC count was between 2000 and 3500/mL, the thymoglobulin dose was halved. All patients (case and control groups) were received methylprednisolone 1 g/d IV infusion for three days and the first dose was administered intra-operatively.

Maintenance immunosuppression

In all patients methylprednisolone IV infusion followed by prednisolone tablet 1 mg/kg and in case group tapered to 10 mg/d after 5 weeks and in control group tapered 5 mg at the end of each week. Mycophenolate mofetil was given 1 g pre-transplantation in both groups and then restarted with 1 g twice daily after 3 days for 5 days and then continued with 500 mg three times a day in case group. In control group, mycophenolate mofetil was continued with 1 g twice daily from the 1st day of transplantation. In both groups when the serum creatinine level became below 2 mg/dL, calcineurin inhibitor was added to immunosuppressive regiment (cyclosporine 5 mg/kg or tacrolimus 0.15 mg/kg). The dose of calcineurin inhibitor was adjusted according to the blood level.

Prophylaxis against infection

All transplant candidate received prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX), for *Pneumocystis jiroveci* pneumonia and clotrimazole for oropharyngeal candidiasis for 6 months and valganciclovir for cytomegalovirus for three months after transplantation.

Patients follow-up

Patients were assessed and data were collected daily during the hospital admission after transplantation and at regularly clinic visits weekly in the first month and then monthly during the first post-transplant year. During the hospital admission, patients were evaluated for delayed graft function (DGF) which was defined as requiring hemodialysis in the first week after transplantation. Glomerular filtration rate (GFR) was estimated by modification of diet in renal disease (MDRD) equation and chronic kidney disease epidemiology collaboration (CKD-EPI) equation at the time of discharge from hospital and after one year (10). All patients with clinical suspicion of acute rejection (if the serum creatinine increased more than 25% from the baseline), underwent allograft biopsy and the result were reported according to Banff 2013 criteria. Additionally, allograft and patient survival, complications of immunosuppressive agent (infections, cytopenia, and malignancy) were evaluated during the first post-transplantation year and the case and control group were compared.

Sample size

The sample size was determined with NCSS software, based

on Cronbach's alpha of 0.05 and a power of 0.08.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consents were obtained from all patients. The study was approved by the ethical committee of Ahvaz Jundishapur University of Medical Sciences (ethical code; IR.AJUMS.REC.1394.329). This paper is a part of nephrology fellowship thesis of Leila Sabetnia, in department of nephrology of Ahavaz Jundishapur University of Medical Sciences. Moreover, the study protocol was registered in the Iranian registry of clinical trials website (identifier: IRCT2017050933884N1; <http://irct.ir/trial/26025>).

Statistical analysis

To analyze the data, descriptive statistics including frequency distribution tables, charts and central indices and dispersion variables of the study were first described. All data were analyzed using SPSS version 23 (SPSS Inc, Chicago, IL, USA). The quantitative variables were compared by *t* test or U-test and Fisher's exact test for categorical variables. Log-rank tests were used to calculate and compare patients and graft survival, while *P* values less than 0.05 were considered statistically significant.

Results

Patient enrollment

Around 114 patients were enrolled initially, who had undergone kidney transplantation from June 2014 to December 2016. Eight patients were excluded because of age < 18 years (n=4), positive HBsAg (n=1), dissatisfaction (n=3). We have used intention-to-treat protocol for handling the recipients who did not receive induction therapy in our analysis. Around 106 adult recipients were randomized to receive induction with thymoglobulin (1.5 mg/kg/d for 3 days) and standard immunosuppression therapy without induction. All patients were followed for 12 months.

Recipient and donor characteristics

The patients were 58 men and 48 women. The mean age was 38.74±12.33 years. There were no differences in baseline demographic or patients' characteristics between two groups, except donor type (living or deceased), as shown in Table 1. Panel reactive antibody (PRA) titer of all recipients was lower than 20%. Cold ischemia time for kidney was 2 to 6 hours in both groups. All donors and recipients were ABO (A, B or O blood type) – compatible.

Delayed graft function

DGF defined as requirement hemodialysis during the first week after transplantation. DGF occurred in 14 recipients (26.4%) of the control group and 3 recipients (5.8%) of case group. The difference was statistically significant (*P*= 0.004).

Table 1. Donor and recipient characteristics

Variable ^a	Control (n= 53)	Case (n=53)
Donor age (mean± SD)	33.62±11.26	36.45±18.6
Recipient age (mean± SD)	37.85 ±13.69	39.58±12.43
Gender (male/Female)	27/26	31/22
Body weight (mean± SD)	64.28±16.68	67.96±18.21
Preemptive transplantation (%)	0	0
Previous transplantation (%)	0	0
PRA positive patients (%)	52	41
Deceased donor (%)	54.7	79.2

^a All continuous variables are presented as a mean ± standard of deviation and qualitative variables as a sum number of patients.

Graft function

At the time of discharge from the hospital, after transplantation, there was no significant difference in serum creatinine and estimated GFR (eGFR) as calculated by MDRD and CKD-EPI equations. Additionally at the end of first post-transplant year, serum creatinine and eGFR were similar (Table 2).

Acute allograft rejection

During follow-up, any patient with rising serum creatinine more than 25% from baseline, was underwent kidney biopsy. Around 19 patients were diagnosed with biopsy-proven acute allograft rejection (8 patients in the case and 11 patients in the control group). The rate of acute allograft rejection was similar. Additionally, there was no statistically significant difference in the rate of acute rejection on the basis of donor's type (living vs deceased) between two groups (Table 3).

Infection

The one-year incidence of infection which required hospitalization is shown in Table 4. In 28 patients in the control and case groups, bacterial infection occurred. There was no significant difference between groups regarding the proportion of patients with bacterial infection. The study also showed that, at least in one patient of each group, an episode of viral infection has been reported, indicating a non-significant difference between groups (one case of

Table 2. Graft function

Variable		Control	Case	P value
Serum creatinine (mg/dL)	Time of discharge	1.16±0.24	1.44±1.41	0.190
	At 1 year	1.25±0.45	1.22±0.37	0.771
GFR (MDRD) (cc/min)	Time of discharge	65.93±19.08	61.82±18.47	0.399
	At 1 year	63.24±17.77	63.97±17.58	0.851
GFR (CKD-EPI) (cc/min)	Time of discharge	73.08±20.97	69.07±20.64	0.496
	At 1 year	71.35±21.32	71.24±19.63	0.981

Abbreviations: GFR, Glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration.

Table 3. Acute rejection episodes

Variables	Control	Case	P value
T Cell	10 (20.8%)	6 (12%)	0.304
Antibody	1 (2.10%)	2 (4.10%)	
Deceased donor			
T Cell	3 (12.5%)	6 (14.6%)	1.00
Antibody	1 (4.2%)	1 (2.4%)	
Living donor			
T Cell	7 (29.20%)	0 (0 %)	0.044
Antibody	0 (0%)	1 (12.5%)	

parvovirus B₁₉ with bone marrow involvement in induction group and one case of BK virus nephropathy in the control group). The incidence of CMV infection was the same in both groups.

The frequency of fungal infection was 2 episodes of fungal infection in 2 patients in control group and, 5 episodes of fungal infection in case group patients. In addition, one case of scabies was observed in the case group.

Hematologic complications

While, there was no significant difference of hematological profile before transplantation between two groups, however, a significant leukopenia (50.9%) and thrombocytopenia (49.1%) in the case group, after transplantation was detected. No case of malignancy or post-transplant lymphoproliferative disorder was reported in any of two groups during the first year (Table 4).

Survival

In the survival analysis, 9 people in each group died during one year after transplantation. Hence, the patients' survival did not statistically differ between treatment and control groups after transplantation (83% in both groups, $P=1$).

One year survival of allograft was 73.5% in the case and 81.1% in the control group (the difference was not significant; $P=0.392$).

Non-inferiority of treatments

The difference between treatments was -0.55 (95% CI - 4.26 to 3.15). It can be concluded that induction therapy is not inferior in effectiveness to the standard immunosuppressive therapy.

Table 4. Frequency of infectious and hematologic complications

	Control	Case	P value
Infection (number of patients)			
Viral	1	1	1.00
Fungal	2	5	< 0.001
Bacterial	28	28	1.00
Site (episodes of infections)			
Blood	7	6	
Urine	13	23	
Skin and soft tissue	0	3	
Lung	3	4	
Gastrointestinal	7	4	
Others/unknown	1	6	
CMV infection	2	2	
PLT (cells/mL)			
≤100 000	9	26	
>100 000	44	27	<0.001
WBC (cells/mL)			
≤3500	6	27	
>3500	47	26	<0.001

Discussion

Until 2014, more than 32 000 kidney transplants have been performed and added 2500-2700 cases annually (10-13). One of the important issues is that the success rate of the transplant depends entirely on receiving immunosuppressive therapies. In recent years, an induction immunosuppressive regimen has been administered extensively in many transplantation centers (8). Thymoglobulin has not been approved by the Food and Drug Administration (FDA) for kidney transplantation yet. However, due to fewer complications and possibly better efficacy than other antibodies, it is widely used for induction therapy (14). Despite the widespread administration of thymoglobulin, no consensus on the ideal dosage and duration of treatment was existed, while it is experimental in many centers. There are various protocols and there is an overwhelming concern about immunosuppression. Various studies have shown that it can be safe for transplanted patients to administer thymoglobulin at appropriate doses and in controlled conditions. Higher doses and longer duration of using induction therapy can be associated with increased risk of infection and potential malignancy. Furthermore, lower doses may not effectively reduce the rate of allograft rejection (10). The dose of thymoglobulin is determined according to the weight of the patient and is administered at a dose of 1.5 mg to a maximum of 5 mg/g body weight for 3 to 10 days (15-17). The results of various studies are different on the rate of acute rejection of allograft, survival of patients and the transplanted kidney, and also the side effects of thymoglobulin.

In this study, no significant difference in acute allograft rejection between the groups receiving induction therapy with thymoglobulin (16.1%) compared to the standard treatment (22.9%) was detected ($P=0.304$).

In previous studies (12 studies were included) the total dosage of thymoglobulin as induction therapy was 2.5 (18) to 15 (19) mg/kg and the rate of acute allograft rejection was 4% (20) to 29.1% (21). The rate of acute allograft rejection was significantly reduced with induction therapy in these studies. Only in one study (18) the dosage of thymoglobulin was lower than our study, which was non-randomized and retrospective. In our study, no reduction in the rate of acute allograft rejection in induction group can be due to low and inadequate doses of thymoglobulin.

In our study also, no significant difference in one-year patients' survival in both groups was detected (83%). Similar results in other studies were seen, while the range of one-year patients survival was 88% (22) to 98.3% (21) in thymoglobulin group. In other studies, the graft survival at the end of 1 year after transplantation was 85.3% (23) to 97.6% (21) after induction therapy, which were similar to our study (73.5%).

Infectious complications after transplantation are associated with significant morbidity and mortality and are the most common causes of death in the early stages of transplantation. In the current study, no significant difference in the incidence of CMV infection between induction therapy with thymoglobulin and standard immunosuppressive treatment (2 cases in each group) was detected. Yang et al (24) and Hardinger et al (25) reported no significant difference in CMV infection in comparison of two doses thymoglobulin. In contrast to these studies, Castro et al (19) and Nafar et al (10), who compared two dosages of thymoglobulin, were reported a higher incidence of CMV infection in higher dosage while the rate of this infection was 33% in these two studies. However, the study by Mourad et al, detected induction with thymoglobulin was associated with 35.5% CMV infection, which had a significant difference with standard treatment (26). Several studies have reported that the administration of thymoglobulin is associated with an increased incidence of cytomegalovirus disease, rather than cytomegalovirus infection (27). The low rate of CMV infection in comparison with other studies can be due to the administration of lower dosage of thymoglobulin. In fact, this infection was evaluated, only if the patient had clinical or laboratory symptoms in favor of CMV infection. Same as current results in our study, a significant difference was observed in Mourad et al for the presence of leukopenia and thrombocytopenia, which was significantly higher in patients with thymoglobulin induction therapy (26). Cytopenia was expected in induction group due to the thymoglobulin's effect on blood cells. However, none of the patients showed infection or hemorrhage as a result of cytopenia. We think special attention should be paid to the dosage and duration of induction therapy in clinical practice when leukopenia and thrombocytopenia or other complications develop.

The incidence of DGF depends on several factors such

as obesity, high creatinine levels of donor, expanded criteria donor, race, donor age, and the cold ischemia time (28). DGF is associated with increased risk of acute allograft rejection and a risk factor for graft survival (28). In the present study, DGF was observed in 5.8% of the induction treatment and in 26.4% of the standard treatment, which had a significant difference between the two groups. While Martinez-Mier et al, in a retrospective descriptive study reported DGF in 19% of patients treated with thymoglobulin at a mean dose of 4.4 mg/kg (23). In randomized clinical trial by Mourad et al (26), induction therapy with 12.5 mg/kg thymoglobulin was compared with standard treatment. They found that DGF was reported in 17.9% of induction group and 24.1% in non-induction patients while the difference was not significant.

This significant reduction in DGF was seen in thymoglobulin group in our study. Despite the significant reduction in DGF, acute allograft rejection was not different between the two groups. This conflict can be due to lack of performing protocol biopsy of transplanted kidney and may some cases of subclinical rejection were not diagnosed.

Conclusion

In this randomized clinical trial, which was a non-inferiority trial, induction therapy with 4.5 mg/kg thymoglobulin was done. It is important to point out although induction therapy with thymoglobulin did not reduce the risk of acute rejection in this study, but, due to reduced DGF, it could be effective in tracking patients for more than one year in reducing acute rejection. Also, the fixed dose of thymoglobulin may not have the same efficacy for all patients and it is necessary to determine the dose of thymoglobulin based on the response of different patients and the appropriate dosage could be determined based on the count of T cell subtypes (CD₃⁺) or absolute lymphocyte count. Authors believed due to the limitations of the present study, the justification of these results requires more extensive research and studies.

Study limitations

An important limitation and weakness of the study was lack of protocol biopsy due to economic issues and patients' refusal to consent to repeated kidney biopsies. Additionally, failure to perform a periodic monitoring of patients for CMV infection and not tracking patients for more than one year were other limitations of our study.

Authors' contribution

HS and FH designed the study, observed accuracy and validity of the study. LS collected the data and follow the study. HS, SSB, SS, SA and IR supervised the project. LS and A-GH wrote the paper. All authors edited and revised the final manuscript and accepted its publication.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Funding/Support

We declare no source of funding on this project.

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