Original Article

Adding thymoglobuline to the conventional immunosuppressant regimen in kidney transplantation: A cost-benefit analysis

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Abstract

Background: Thymoglobuline (TG), is used for both induction and rejection therapy in kidney transplantation (TX). This study was conducted to compare between adding TG or not to the conventional drugs to evaluate the rate of rejections, infections and costs.

Methods: In two groups of patients, each of 45 cases; group A received conventional drugs (cyclosporine, mycophenolate and prednisolone) and in group B, TG was added; both groups were then compared. TG was administered for 5 doses (1.5 mg/kg/d for the first 3 days and 1 mg/kg/d for the last 2 days. Suspicious signs of rejection (fever, graft tenderness, graft enlargement and increase in length and depth), creatinine rise, diethylene triamine penta-acetic acid scan (DTPA) results and urinary tract infections (UTI) with counts > 10^5 CFU/ml were recorded. The duration of the first hospitalization, the CMV incidence of infection in the first 6 months and their costs were finally compared.

Results: There was no difference for age, duration of hospitalization and CMV infection between the two groups. UTI occurred more frequently in TG group ($p=0.049$). Creatinine rise, suspicious signs of rejection occurred more frequently in TG group ($p<0.05$). Creatinine rise and suspicious signs of rejection occurred more frequently in conventional group ($p=0.020$, $p<0.000$, respectively). The need for additional steroid pulses was more frequent in conventional group ($p<0.000$). The total costs of TG, ganciclovir, antibiotics and steroid pulses in both groups were similar.

Conclusion: The results show that the posttransplantation problems (signs of rejection, rise of creatinine, graft losses and delayed graft function) occurred rarely in TG group. The incidence of infection and the cost of both regimens were similar. We strongly recommend this protocol as induction therapy.

Keywords: Kidney transplantation, Anti rejection therapy, Immunosuppression, Cost & cost analysis

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Induction therapy, using potent immunosuppressive agents in the critical, early stage of organ transplantation with the goal of decreasing the risk of acute rejection and potentially allowing lower overall intensity of the maintenance immunosuppressive regimen, is a common therapy in kidney transplantation. The induction agent of choice, along with dose and duration of therapy is controversial, center-specific, and often based on limited clinical data (1). Rabbit antithymocyte globulin (rATG, Thymoglobulin, Genzyme, Cambridge, MA) is approved by FDA for the treatment of acute rejection at a dose of 1.5 mg/kg for 7–14 days based on the results of a multicenter, double-blind randomized trial .The role of Thymoglobuline in the prevention and treatment of allograft rejection, graft versus- host disease (GVHD), and treatment of aplastic anemia (AA) is well established. Recent investigations have shown that Thymoglobuline not only depletes T-cells, but modulates various lymphocyte surface antigens and interferes with the function of a number of different immune effector cells, including B cells, dendritic cells, natural killer (NK) cells, and regulatory T cells.

Although rATG is not currently approved by FDA as induction therapy in kidney transplantation, it is the most commonly administered agent for this purpose. In the US, antibody induction is used in the majority (>70%) of kidney and almost 50% of thoracic organ transplantations, and Thymoglobuline is the most frequently used induction agent (2). Over one-half of the 70% of patients that receive an induction agent at the time of kidney transplantation receive rATG. Induction doses have ranged from 1–6 mg/kg/dose over 1–10 days with a more typical regimen of 1.5 mg/kg for 3–5 days and a cumulative target of 4.5–10 mg/kg.

In animal models, higher initial doses of shorter durations approximating a human-equivalent dose of 6 mg/kg were associated with more peripheral and central lymphocyte depletion and better allograft survival. In human, the total doses of 5.7 mg/kg on average given as 1.5 mg/kg per day have been shown to produce similar outcomes in high risk recipients who received an average dose of 10.3 mg/kg. Based on these models, the optimal induction dose is felt to approximate 6 mg/kg.

Higher doses and prolonged duration of induction agents are thought to be associated with an increased risk of infection and the potential development of malignancy, while lower doses, <3 mg/kg, may not effectively prevent acute rejection. Thus, the optimal dose and duration of rATG have not been clearly defined (1). Therefore, the purpose of this study was to compare the adding of this agent or not to the conventional drugs to evaluate renal function, infections and costs.

Methods

In a retrospective cohort study, two groups (45 patients in each group) the first group on conventional induction therapy and the second one on Thymoglobuline (TG, Genzyme, Cambridge, MA) with conventional added drugs were enrolled. All patients had been transplanted between the years 2008-2009 and their files were selected randomly according to the table of random numbers. The patients in both groups were considered at low risk because they had negative panel reactivity assays (PRA). Regarding the CMV serostatus, all donors and recipients were positive (D+/R+). Conventional induction therapy includes cyclosporine (6 mg/kg), mycophenolate (2 g) and methyl prednisolone (pulses of 500 mg iv. daily for 3 days and afterwards 1mg/kg p.o). Pulse for any drug means a brief surge in dose which is much more than usual. TG (Thymoglobuline) was administered for 5 doses (1.5mg/kg/d for the first 3 days and 1 mg/kg/d for the last 2 days). Suspicious signs of rejection (fever, graft tenderness, enlargement and increase in length and depth, creatinine rise more than 25% of the base, DTPA isotope scan results), having at least 3 of them to urge administration of more steroid pulses (500 mg/d), nadir WBC counts, and urinary tract infections with counts $>10^5$ CFU/ml were recorded.

The term delayed graft function (DGF) was applied to a primary delay in graft function for at least 24 hours after transplantation. Graft loss means irreversible loss of function. Acute Tubular Necrosis (ATN) was diagnosed clinically by azotemia without graft enlargement and tenderness, fever and signs of cyclosporine toxicity. Cyclosporine level has been measured twice weekly as a routine, but after each creatinine rise, we have another measurement.

Measures above 350 ng/ml (through level) were considered toxic and if resolved during 1-2 days after dose reduction (1 mg/kg), toxicity would be confirmed. The duration of the first hospitalization and the rate of CMV infection (qualitative PCR) in the first 6 months and finally their costs were finally compared.

Statistical analysis: Data were analyzed using SPSS (version 18.0; SPSS Inc., Chicago, IL, USA). The student's t-test was used to compare the continuous variables and chi-square or Fisher's exact test was used to compare the categorical variables. A two-tailed p-value of < 0.05 was considered statistically significant.

Results

There were 23 males in group 1 (conventional) and 29 males in group 2 (TG). The median age was 37.9 and 39.9 years, respectively (p=0.87). In group 2, the median weight was 62 kg, so the cumulative dose of TG was 6.5 mg/kg. As shown in figure 1, creatinine rise, signs of rejection, and administration of more pulse doses had occurred more frequently in group 1 but the frequency of UTI was higher in group 2. CMV occurrence was equal in the two groups. In group 1, we had 27 additional steroid pulses (2-3 infusions of 500 mg methyl prednisolone), but in group 2, there were only 3 additional pulses for suspicious rejections (p>0.001). In the conventional group, 28 episodes of creatinine rise occurred, in which 27 cases were suspicious of rejection, but

there were 6 cases with creatinine rise in the TG group, 3 of them were attributed to ATN or cyclosporine toxicity (p>0.001). In group 1, TG was administered to 12 cases because of unresponsive rejections to initial pulses, ATN or DGF (147 days of additional TG). There were ATN and DGF, 3 cases of each and 2 cases of graft losses in group 1, whereas, no DGF or graft losses in the TG group. Leukopenia and UTI occurred more frequently in the TG group (p>0.001), (p=0.049), respectively. Median duration of the first hospitalization in the two groups were 17.24 and 15.46 days, respectively with no statistical significance (p=0.21).

During 6 months of follow up, CMV infection was seen in 15 and 14 cases in the two groups, respectively (p=0.82) and median duration of treatment was 24.2 and 28.7 days (p=0.449).

In both groups, most infections occurred during months 2 or 3 after transplantation, and in 2 cases in each group, CMV infection had occurred in the last week of the first month (table 1).

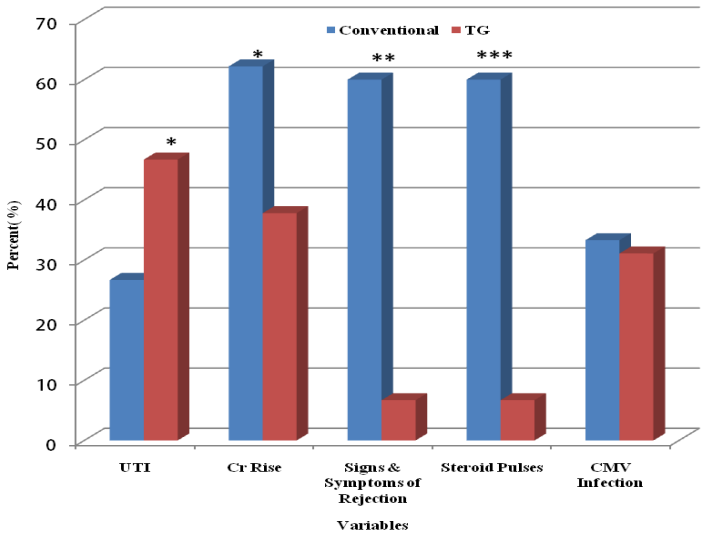

Figure 1: Percentage of urinary tract infection, creatinine rise, signs and symptoms of rejection, need for steroid pulses and CMV infection in the two groups. As shown in the figure, UTI has occurred more frequently in the conventional group, and rises of creatinine, signs of rejection and pulse therapy was more frequent in the TG group. CMV infection rate was relatively similar in the groups. (UTI: urinary tract infection, Cr: creatinine, CMV: cytomegalovirus, TG: thmoglobuline)

* Significant at α=0.05

** Significant at α=0.01

*** Significant at α=0.001

The cost of additional pulses, thymoglobuline therapy, antibiotics for UTI and ganciclovir for CMV infection were calculated in the two groups. However there was statistically significant difference only in steroids pulses. But there was no significant difference in cost between the two groups, either in other forms of therapy or in total costs (p=0.157) (table 2).

Table 1. The studied variables in these two groups

Variable	Mean±SD	Pvalue
Age (year)		
TG	39.96±13.426	0.473
Conventional	37.91±13.492	
Duration of hospitalization (day)		
TG	15.47±4.693	0.210
Conventional	17.76±11.225	
WBC count		
TG	3955.56±1362.410	0.000
Conventional	6808.89±2617.669	
Anti-CMV therapy (day)		
TG	28.79±19.120	0.449
Conventional	24.20±12.554	
Variable	**Number**	**pvalue**
UTI cases		
TG	21	0.049
Conventional	12	
Signs & Symptoms Cases		
TG	3	0.000
Conventional	27	
CMV infection cases		
TG	14	0.822
Conventional	15	
n. of additional pulses		
TG	3	0.000
Conventional	27	
n. of cr. Rise		
TG	17	0.020
Conventional	27	

Table 2: Cost in the two arms of therapy in different parts of the study (No=45).

Group	Mean (Rial)±SD	pvalue
Ganciclovir		
Conventional	7999990.5667±200127.13999	0.721
TG	9173350.4667±259868.96943	
Antibiotics		
Conventional	586660.6667±98386.99101	0.050
TG	1026660.6667±110995.49540	
Steroid pulse		
Conventional	109200.0000±9016.89324	0.000
TG	12130.3333±4591.17731	
TG		
Conventional	34035560.3333±6060660	0.140
TG	47600000.0000±0	
Total cost		
Conventional	42731420.5667±6875340	0.160
TG	57812150.4667±1747620	

Discussion

Polyclonal antibodies or depleting agents including ATG and TG have been used as induction for many years, but in most studies, dosage of these drugs or duration of induction have not been included and some authors have reported that although the rejection rate has been decreased, the risk of infection is more than conventional therapies (3-6). In this retrospective cohort and cost-benefit analysis, it is shown that the use of a certain dose and duration of TG in low risk patients can significantly decrease the rejection episodes without adding to the risk of viral infections (CMV) and costs.

Increase in frequency of UTI in our study is similar to some other studies (4). Clesna, et al. reported an increase in incidence of UTI with cumulative doses more than 7 mg/kg that is similar to our results (6.5 mg/kg). According to Langone et al. induction has a dosage lower than treatment so the incidence of CMV infection is lower. In the current study, similar rates of CMV infection are compatible with Langone's results (7).

Leukopenia, a usual complication of polyclonal antibodies, occurred in almost all patients even in group 2 with low dose of TG. But, it may not have resulted in later infections such as CMV infection. Charpenlier et al. and Mourad et al. in two RCTs, demonstrated that the induction had resulted in significant increase in leukopenia, thrombocytopenia, fever and CMV infection in comparison to control groups (8, 9). In Mourad et al.'s study, was a tacrolimus- based one, whereas, we used cyclosporine in all patients. The relative incidence of CMV infection in our study was higher than the Mourad et al.'s study, (about 30% in two groups) that might be due to high seropositivity in our patients but opposite to Mourad et al.'s study, the infection occurred equally in the two arms.

On the other hand, Hardinger et al.'s prospective study on live donors (like ours) the recommended TG is a good induction agent due to less infection rate (10). Buchler et al. reported that TG for induction could lead to less maintenance drug doses, but this study had no control group. Using the clinical and paraclinical tools (not biopsy), there was rejection in 27% of cases. CMV infections had occurred in 33% of patients. Cumulative dose in this study was relatively high (8.8 mg/kg) (11).

Mehrabi et al. reported the reduction in the risk of ischemia reperfusion injury (IRI) by TG. IRI represented as DGF and in our study, there was no DGF in the TG group, but we had 3 cases of DGF in the opposite arm. Although the difference was not significant, these events could have a profound effect on the graft outcome (12).

Buchler et al. demonstrated that induction with TG would give a chance to reduce or even discontinue the steroids (13). With regard to the benefits of early discontinuation of steroids after transplantation, it seems that TG use as induction can be quite rational.

Finally, Ram Peddi et al. reported that the cost of 100 mg TG in one center was 2165 $ (14). This amount in Iran equals to about 47,630,000 rials. So, TG is an expensive drug and using it for a long period is only justified when it diminishes the complications of transplantation to the point that almost balances the costs and the benefits. In the current study, more episodes of rejection in the conventional group mandated us to use TG for a longer course to treat rejection. So, the total costs in the two groups became equal. But due to the risk of worse outcomes after rejection, a mild induction with TG is recommended. Our limitations in this study were: first, its designation as a retrospective one and secondly, none of the suspicious rejection cases had a biopsy to be confirmed.

In conclusion, induction with a protocol consisting of a few days of TG plus usual drugs is superior to conventional protocol. Many variables are similar, but rejection, DGF and ATN occur more frequently with conventional induction. TG administration permits us to have a somewhat safe and uneventful course of transplantation with similar costs. Consequently, we strongly recommend this protocol.

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