Use of Basiliximab with the Standard Immunosuppressive Protocol in Pediatric Renal Transplantation: A Double-Blind Randomized Clinical Trial

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ABSTRACT

Background: Several randomized clinical trials performed on adult renal transplant recipients have shown a significant reduction in the incidence of acute rejection by using basiliximab as induction therapy. However, few studies have been conducted on kidney graft survival following the use of the drug among pediatric transplant recipients.

Objective: To address the efficacy and safety of basiliximab in the improvement of the survival of children with kidney transplants.

Methods: This randomized, double-blind single-center clinical trial was conducted on 28 children (57% male) who underwent live-unrelated renal transplantation. They were randomly assigned into an intervention group receiving basiliximab (10 mg in patients weighing <40 kg or 20 mg in patients ≥40 kg) as induction therapy in combination with the standard immunosuppressive regimen (n=14), or to the control group (n=14) receiving only the standard immunosuppressive regimen (without basiliximab). The outcome was assessed by the measurement of serum creatinine level before transplantation, and 24, 48, and 72 hours as well as 3, 6, and 12 months post-transplantation. The estimated glomerular filtration rate at 12 months post-transplantation and graft survival were also measured. The number of acute rejection episodes in transplant recipients was also considered.

Results: The mean±SD age of participants was 12.3±4.2 years. No difference was observed between the two groups in terms of serum creatinine level before and after transplantation at various time points. The mean±SD eGFR at 12 months post-transplantation was 87.8±8.4 in the basiliximab and 85.2±5.8 in the control group (p=0.37). No significant difference was observed between the two groups in terms of acute rejection episodes (25% in basiliximab and 33% in the control group). The graft survival at 1-year post-transplantation was 93% in the basiliximab and 86% in the control group (p=0.54).

Conclusion: Adding basiliximab to the standard immunosuppressive regimen may not improve the graft survival.

KEYWORDS: Immunosuppressive agents; Basiliximab; Kidney transplantation; Living donors

INTRODUCTION

Following the first successful kidney transplantation in 1954, all efforts have focused on developing standard protocols for selecting the best immunosuppressive agents to achieve early and long-term graft survival [1]. The introduction and development of new immunosuppressive regimens have led to minimizing graft failure, particularly among children [2]. The recent studies report high kidney transplantation survival rates exceeding 90% within the first year of transplantation [3].

Basiliximab is a chimeric mouse-human monoclonal antibody against α-chain of the interleukin-2 (IL-2) receptor of T-lymphocytes that is used to prevent kidney graft re-

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jection [4]. This drug was first approved by the Food and Drug Administration (FDA) in 1998 and has widely been used since then [5]. The main mechanism of this agent is to compete with IL-2 to bind to the IL-2 receptors on activated T cells and to prevent T cells superficial receptors for signaling, which lead to the prevention of T cells replication and activation [6]. This process finally results in preventing the stimulation of an immune response against transplanted organs [7].

Some randomized clinical trials performed on pediatric renal transplant recipients show a significant reduction in the incidence of acute rejection by using basiliximab [8, 9]. However, the studies in this regard are scarce in children. This single-center clinical trial was conducted to evaluate the effect of adding basiliximab to the standard immunosuppressive regimen on the improvement of survival of kidney transplant among children in Iran.

MATERIALS AND METHODS

This single-center double-blind randomized clinical trial was conducted in Ali Asghar Children Hospital in Tehran in 2017. Using permuted block randomization, the patients were randomly assigned into two arms: 14 receiving the standard immunosuppressive regimen with basiliximab (Simulect, Novartis Pharma AG, Basel, Switzerland) (10 mg in patients weighing <40 kg or 20 mg in patients ≥40 kg), and 14 to a control group receiving the standard immunosuppressive regimen (without basiliximab). The first dose of basiliximab was administered on day 0 within 4 hours of reperfusion; patients received the same dose repeated on day 4. The standard immunosuppressive therapy consisted of prednisolone 250 mg for days 0–2 after transplantation and then reduced to 200 mg, 150 mg, 100 mg, and 60 mg during the next 4 days, followed by 40 mg/day for 3 days, 30 mg/day for 3 days, and 20 mg/day. The dosage was then reduced by 0.15 mg/kg every 15–25 days until 0.15 mg/kg/day six months after transplantation; then maintained at 0.15 mg/kg every other day. Cyclosporine was also administered at 10–12 mg/kg/day for the days 0–9, and was then reduced by 2 mg/kg every 10 days until a dosage of 4–6 mg/kg/day was achieved; the dosage was then adjusted to maintain a target of 100–150 ng/dL whole blood through level for the first 3 months, and 80–100 ng/dL thereafter. Mycophenolate mofetil (CellCept, Roche, Basel, Switzerland) was administered at 600 mg/m^2 every 12 hours instead of azathioprine after 1997. There was no place for IL-2 receptors antibodies (e.g., basiliximab) as induction therapy in this regimen [10–13]. The patients were followed for 12 months. In each visit, a checklist was completed by investigators to assess the patients' adherence to the immunosuppressive regimen. Patients' laboratory tests including CBC, WBC diff, biochemistry, urinalysis, and urine culture were also performed and examined to find out any adverse effects or infection episodes. An indication of thymoglobulin use was the presence of slow graft function and steroid-resistant acute rejection episodes.

Study Population

In total, 28 children aged 18 years or younger with the first renal transplantation were found eligible for the study. Each patient who did not continue the follow-up was excluded. All patients had negative panel and crossmatch tests at the time of transplantation. Therefore, all patients were considered "low risk" for renal transplantation. All patients received the graft from living-unrelated donors. HLA assessment was not performed in our recipients and the unrelated donors. The study protocol was approved by the Research and Ethics Committee at Iran University of Medical Sciences. All participants or their legal guardians provided informed written consent to participate in the study (Fig 1).

Study Outcomes

The primary endpoint was the level of serum creatinine measured before as well as 24, 48, and 72 hours and also 3, 6, and 12 months post-transplantation to assess the trend of the changes in renal functional parameters. Secondary endpoint included acute rejection episodes.

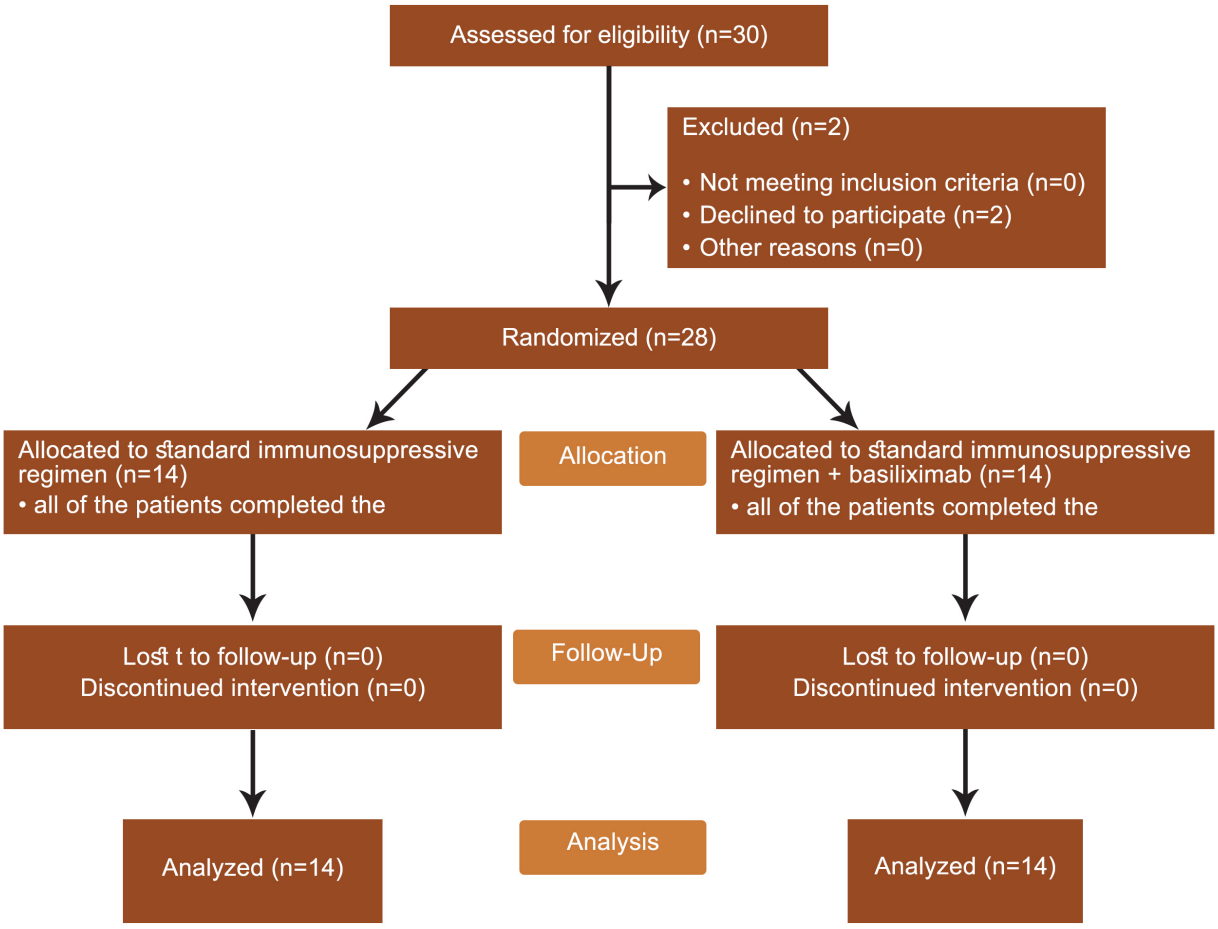

Figure 1: Study flow diagram

Clinical Definitions

If serum creatinine level increased, remained unchanged, or decreased by <10% per day immediately after transplantation for three consecutive days in the first week post-transplantation, "slow graft function" (SGF) was considered [13]. Acute rejection was considered when there was a persistent and rapid increase in serum creatinine (0.3–0.5 mg/dL/day) under the exclusion of other causes such as viral infection. The diagnosis of acute rejection was based on laboratory findings and response to high-dose steroid (5–10 mg/kg up to a total dose of 30 mg/kg). Resistant acute rejection episodes were indication for biopsy.

Statistical Analysis

SPSS® for Windows® ver 22.0 (SPSS Inc., Chicago, IL) was used for data analysis. Based on similar studies, a total of 28 children were calculated to show the differences between the two groups, with a two-tailed type I of 0.05 and a study power of 0.80. Quantitative variables presented as mean±SD, were compared with Student's t test or Mann-Whitney U test. The trend of the changes in serum creatinine levels in both groups was assessed using the repeated-measures ANOVA. A multivariate linear regression model was used to assess the difference during the 6-month period of creatinine level between the two groups with the presence of baseline parameters including primary etiology, transfusion, and use of ATG. The Wilcoxon-Gehan test was used to calculate differences in survival. A p value <0.05 was considered statistically significant.

RESULTS

Twenty-eight pediatric patients who received their first renal graft were included in this

Table 1: Demographic information of participants

Characteristics	Basiliximab group	Control group	Total
n	14	14	28
Mean±SD age (yrs)	11.2±3.8	13.4±3.8	12.3±4.2
Male sex (%)	57	57	57
Etiology of ESRD (n)			
FSGS	3	3	6
Cystinosis	3	1	4
Hypodysplasia	2	3	5
Neurogenic bladder	5	4	9
Nephronophtisis	1	0	1
Unknown	0	3	3

study (Fig 1). All patients completed the trial. Sixteen (57%) patients were male. The mean±SD age of participants was 12.3±4.2 years (Table 1). Thymoglobulin was prescribed to 23% of patients in the basiliximab and 14% of the control group (p=0.65). There was no significant difference in the distribution of the primary causes of end-stage renal disease (ESRD) between the two groups (p=0.740). Pre-transplantation transfusion was reported in 8% of children in basiliximab and 7% in the control group (p=0.999). Delayed or slow graft function occurred in three patients in the basiliximab but none in the control group (p=0.098).

No difference was observed between the two groups in terms of serum creatinine level before and after kidney transplantation at different post-transplant time points (Table 2). In both groups, a substantial reduction in serum creatinine level occurred within 24 hours after transplantation. However, the trend of the serum creatinine level remained unchanged within 6–12 months later in both groups. The repeated-measures ANOVA revealed no difference in the 6- and 12-month trend of the changes in serum creatinine level between the two groups (p=0.977 and 0.06, respectively). Multivariable linear regression analysis could not show any difference in the 12-month change in serum creatinine level (compared to the baseline value) between the basiliximab and control groups (β=0.037, p=0.069, Table 3).

The mean±SD eGFR at 6 and 12 months post-transplantation were 107.8±8.8 and 87.8±8.4 mL/min/1.73 m^2, respectively in the basiliximab group; they were 102.7±6.4 and 85.2±5.8 in the control group. The mean eGFR did not differ significantly at 6 (p=0.112) and 12 months (p=0.373) post-transplantation between the two groups.

Acute rejection episodes occurred in 3 of 14 in the basiliximab and 2 of 14 in the control group (p=0.42). No adverse effects were seen

Table 2: The mean±SD serum creatinine level (mg/dL) at different post-transplantation time points in the basiliximab control group

Creatinine level	Basiliximab	Control	p value
Before	5.98±2.22	6.89±2.27	0.343
24 hrs	1.66±1.61	1.06±0.47	0.198
48 hrs	0.90±0.49	0.75±0.17	0.394
72 hrs	0.74±0.41	0.72±0.15	0.897
3 m	0.72±0.23	0.93±0.64	0.436
6 m	0.75±0.22	0.93±0.51	0.422
12 m	0.70±0.13	0.61±0.09	0.069

Table 3: Multivariate linear regression analysis to assess the difference in the 12-month change in serum creatinine level (compared to the baseline value) between the basiliximab and control groups

Variable	B	SE	p value
Constant	-5.258	2.288	0.042
Group	-0.091	0.048	0.069
Etiology	0.031	0.016	0.075
Transfusion	0.033	0.095	0.729

in those who received basiliximab.

The 1-year graft survival rate was 93% in the basiliximab and 86% in the control group (p=0.54).

DISCUSSION

Our study found that adding basiliximab to the standard immunosuppressive regimen could not improve its efficacy and change the drug adverse effects among pediatric renal transplant recipients in a developing country. On the other hand, basiliximab plus the standard regimen was not superior to the standard regimen alone in terms of graft survival and function as well as the rate of acute rejection episodes. Because of the high reported efficacy of basiliximab, some studies have attempted to compare its benefits, especially in controlled trials, but most of them conducted in high socioeconomic and developed countries. In a similar study conducted by Offner, *et al.* [14], the 6-month biopsy-proven acute rejection episode, or treatment failure in basiliximab and placebo-treatment groups was 16.7% and 21.7%, respectively with no significant difference. Moreover, graft function was similar in both treatment arms, and there were no significant between-treatment differences in the incidence of adverse events or infections. The authors concluded that considering a regimen of cyclosporine, mycophenolate mofetil, and steroids with and without basiliximab would lead to similar clinical outcome. Furthermore, they have shown a higher rate and severity of subclinical rejections in basiliximab group (Table 4). In another randomized clinical trial conducted by Grenda, *et al.* [15], the pediatric patients received tacrolimus/azathioprine/steroids with and without basiliximab. The study could similarly show comparable consequences in the two groups concerning biopsy-proven acute rejection rates, steroid-resistant acute rejection rates, graft survival rates, and also the nature and incidence of adverse events. Thus, they showed that although adding basiliximab to a tacrolimus-based regimen was safe in pediatric patients, it did not improve the clinical efficacy of immunosuppressive regimen (Table 4). Contrarily, Duzova, *et al.* [16], found that basiliximab significantly reduces the rate of acute rejection 3–6 months after renal transplantation with good tolerability and without significant side effects in pediatrics (Table 4). Pape, *et al.* [9], also showed that although 1-year graft survival in the basiliximab group

Table 4: Comparison of the results of our study with those found in previous studies. Values represent comparison of basiliximab *vs.* control group.

Study	n	Design	Immunosuppression	Follow up	Acute rejection rate	Mean eGFR (mL/min per 1.73 m^2)	Graft survival
Pape, *et al*	77	Observ.	CsA, MMF, CS	12 m	14% *vs* 34%	58 *vs* 52	95% *vs* 93%
Duzova, *et al*	43	Observ.	CsA/TC, MMF/AZA, CS	12 m	0% *vs* 17.4% at 3 m; 0% *vs* 26% at 1 m; 7.1 *vs* 26.1% at 12 m	98 *vs* 75	—
Grenda, *et al*	112	RCT	TAC/AZA/CS	6 m	19.2% *vs* 20.4%	77.6 *vs* 79.4	95% *vs* 95%
Offner, *et al*	192	RCT	CsA, MMF, CS	12 m	16.7% *vs* 21.7%	—	99% *vs* 99%
Our study	28	RCT	CsA, MMF, CS	12 m	21% *vs* 14%	87.7 *vs* 85.1	93% *vs* 86%

(95%) was similar to that in the comparison group (93%), children receiving basiliximab show a lower incidence of acute rejection compared with the control group (14% vs. 34%) (Table 4). A comprehensive review of the literature indicates conflicting results regarding the efficacy of basiliximab when added to the immunosuppressive regimen. In fact, it seems that basiliximab may reduce acute rejection compared with placebo in renal transplant recipients receiving dual (cyclosporine microemulsion and corticosteroids) or triple immunotherapy (azathioprine- or mycophenolate mofetil-based); however, graft and patient survival rates at 12 months were similar to each other [17]. The incidence of adverse events was also similar in basiliximab and placebo recipients with no increase in the incidence of common infections [17].

We concluded that adding basiliximab to common immunosuppressive regimens may not improve graft survival and function; nor does it reduce acute rejection episodes in pediatric renal recipients. The use of new immunosuppressive triple regimens in pediatric renal transplantation including cyclosporine, mycophenolate mofetil, and prednisolone may be an important factor to reduce the need for induction therapy with basiliximab.

The most important limitation of this study was the small sample size; some patients did not want to participate in the study. Further studies should be performed to examine these results especially in the long term.

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CONFLICTS OF INTEREST: None declared.

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