Steroid Avoidance Reduce the Cost of Morbidities After Live-donor Renal Allotransplants: A Prospective, Randomized, Controlled Study

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Abstract

Objectives: **Steroids have had the main role in renal transplant for more than 4 decades. However, chronic use of steroids is associated with many comorbidities, owing to a lack of assessing cost-benefit of steroid avoidance in live-donor renal allotransplants. In this prospective, randomized, controlled study, we aimed to assess the cost-benefit of a steroid-free immunosuppression regimen among Egyptian live-donor renal transplants.**

Materials and Methods: **One hundred patients were randomly allocated to receive tacrolimus, mycophenolate mofetil, and steroids for only 3 days (n=50 patients; study group) or tacrolimus, mycophenolate mofetil, and steroids on a maintenance basis (n=50 patients; control group). All patients received basiliximab (Simulect) induction, with median follow-up of 12 months.**

Results: **Both groups showed comparable graft and patient survivals, rejection episodes, and graft functioning. Posttransplant comorbidities were significantly more prevalent in the steroid-maintenance group. Hypertension was detected in 4% of steroid-free group versus 24% in the steroid-maintenance group (P = .0009). Posttransplant diabetes mellitus, serious infections, and hyperlipidemia were significantly more prevalent in the steroid-maintenance group (P < .05). Associated hospitalization costs were 2.2-fold higher in the steroid-maintenance group than they were in the steroid-free group. One year after transplant, the cost of managing posttransplant comorbidities was significantly higher in steroid-maintenance group, despite comparable costs of immunosuppression.**

Conclusions: **In low, immunologic risk recipients of live-donor renal transplants, using basiliximab induction and maintenance with tacrolimus, mycophenolate mofetil, steroid avoidance was associated with lower first annual total costs despite comparable immunosuppression costs, which was attributed to lower costs of associated morbidities.**

Key words: *Steroid free, Kidney transplant, Comorbidity*

Kidney transplant remains the preferred treatment for end-stage renal disease and is associated with improved long-term mortality over dialysis.[1] Moreover, transplant is less costly than dialysis.[2]

Corticosteroids are widely used as part of the immunosuppressive regimen after transplant, but they have well-documented, multiple adverse effects on blood pressure, lipid profile, and glucose tolerance.[3] Cardiovascular mortality remains the most-common cause of death in renal transplant recipients and affects on graft survival due to death with a functioning graft.[4,5] With improved 1-year renal graft survival rates (more than 90%), clinical priorities have shifted toward maximizing long-term graft survival and the patient's quality of life. Steroid-avoidance protocols are presently undergoing extensive evaluation. In view of the lack of evaluating of the cost of steroid avoidance in live-donor renal transplants, we proceeded to study such costs. Therefore, we sought to assess the cost-benefit of a steroid-free immunosuppression regimen in a prospective, randomized, controlled study among live-donor renal transplants.

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Patients and Methods

One hundred patients with end-stage renal disease, who underwent live-donor renal allotransplant at the Urology and Nephrology Center, Mansoura University between June 2004 and July 2005, were enrolled into prospective, randomized, controlled study. Patients were assigned either to stop steroids after 3 days (study group) or to continue steroids (control group). Male or female recipients (age range, 22-56 years) with end-stage kidney disease were candidates for a first renal transplant from a living-donor, aged 21 to 60 years, with comparable ABO blood groups. We excluded recipients with high immunologic risk, defined as zero DR matching, positive crossmatch, or patients who previously had received a kidney transplant.

Patients and donors were fully informed and provided written consent. The study protocol was approved by the ethics committee of Mansoura University prior to its onset, and it conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Immunosuppression

Patients in both groups received induction therapy in the form of anti-CD25 (basiliximab) 20 mg, 1 hour before the operation and on the fourth day. All patients received 500 mg methylprednisolone just before the transplant, and another 500 mg the first day after surgery. In the steroid-free group, each patient received 250 mg methylprednisolone on the second day and 100 mg the third day after stopping methylprednisolone on the fourth day provided that acceptable tacrolimus levels were achieved.

The control patients received steroids according to the local standard protocol in the form of 3.5 mg/kg methylprednisolone on the first, third, and seventh days after transplant, tapered gradually to 0.15 mg/kg/d by the ninth month until the end of the first year. Concomitant tacrolimus therapy was started 2 days before transplant at a dosage of 0.1 mg/kg/d (orally), and it was adjusted to achieve target whole-blood trough levels of 10-15 ng/mL during the first 2 weeks and 5-10 ng/mL thereafter. Tacrolimus concentrations in whole blood were measured by an IMx analyzer (Abbott Laboratories, Abbott Park, IL, USA). Mycophenolate mofetil was administered to every patient at 1 g twice daily, and decreased to 750 mg twice daily after 2 weeks until the end of the study, guided by the white blood count.

All episodes of rejection were verified by biopsy and graded using the BANFF 97 working classification.[6] Rejection episodes were treated primarily with methylprednisolone 500 mg intravenously for 5 consecutive days. In case of a steroid-resistant rejection, antithymocyte globulin was added. Maintenance steroids were allowed if the first episode of acute rejection was severe vascular rejection (BANFF 2b or 3); steroid-resistant rejection, or after treatment of a second episode of steroid-sensitive rejection. Also, prednisolone was administered at a dosage of 0.15 mg/kg/d if the mycophenolate mofetil dosage was less than 1000 mg/d, if treatment was with antilymphocyte therapy, or if there was an interruption of tacrolimus.

Patient evaluations

In each follow-up, every patient was subjected to a clinical examination with special stress on blood pressure, organomegaly, and neurologic evaluation. Laboratory assessments included creatinine and creatinine clearance using the Cockcroft and Gault formula, tacrolimus whole blood trough levels, liver function tests, fasting and postprandial venous plasma glucose levels, serum cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, urinalysis, and 24-hour urinary protein.

Cost evaluation

The cost data from our hospital records and the costs were measured in US dollars. In a cost-effectiveness analyses, outcomes were measured in nonmonetary units (eg, number of rejection-free grafts, number of patients with a functioning graft, number of surviving patients). In this study, patient survival, graft survival, and the number of rejection-free patients were chosen as clinical outcome parameters. Direct costs associated with acquisition of immunosuppressive medications, diagnosing rejection, and hospitalization were included. For each type of rejection (steroid-responsive or resistant), the resources used were categories composed of hospitalization, diagnostic tests, and prescribed drugs used to treat the rejection episode. However, indirect costs, (eg, productivity loss or quality of life data) were not considered. Then, the total cost of this resource was calculated for each treatment group (total patient cost).

In the next step, total costs were divided by the number of patients who had used this resource in each treatment group (average cost per patient). Drugs used to treat adverse events also were included in the analysis, and their costs were based on the least-expensive brand or generic products available in Egypt. Hospitalization costs were calculated based on the daily cost according to the type of ward (ie, nonintensive care unit or intensive care unit). Hospital costs included the cost of health-related services (eg, pathology, surgery, and medical tests), blood transfusion center, hospital pharmacy, and nonhealth-related services (eg, meals, laundry, and special waste removal). Costs for the maintenance of tools and physician fees were included.

Statistical Analyses

The *t* test was used to compare the 2 groups for continuous data, while noncontinuous data were compared using the Mann-Whitney *U* test. The chi-square and chi-square with Yates correction were used to compare categoric variables. Survival of the grafts was computed using the Kaplan-Meier technique; differences in survival were calculated by the log-rank test. Values for $P < .05$ were considered significant.

Results

Donor and recipient characteristics are shown in Table 1.[1] The majority of recipients were men in their late twenties, while more than half of the donors were women in their midthirties. Also, the 2 groups were homogenous regarding donor age and sex, recipient age and sex, prior blood transfusion, hepatitis C virus status, original kidney diseases, tissue typing, and pretransplant hypertension. No preformed antibodies against donor antigens were detected in the pretransplant crossmatch of any of the studied patients. One year after the transplant, the cost of immunosuppression-induction, maintenance, and antirejection was comparable in both groups.

Rejection

The incidence and severity of biopsy-proven acute rejection episodes was comparable in both groups. The mean time to the first acute rejection episode was significantly shorter in the steroid-free group (10.88 days vs 15 days; $P = .009$; Table 2). We allowed maintenance steroids in 4 patients owing to severe rejection (2 patients) and repeated rejections (2 patients). The dosage of mycophenolate mofetil was reduced in 2 patients in the steroid-free group and in 4 patients in the control group. The total cost of antirejection therapy was comparable in both groups (USD $20,383.00 in the first group versus USD $21,107.00 in the second group ($P = .98$; Table 2).

Table 1. Demographic characteristics of the patients.

Patient characteristics	Group A (n=50) (steroid free)	Group B (n=50) (control)	*P* value
Recipient's age (y)	29.88 ± 11.36	29.36 ± 10.22	.868
Recipient's sex (male/female)	40 / 10	32 /18	.207
Recipient's body weight (kg)	61.72 ± 14.3	59.04 ± 11.32	.371
Original kidney disease			
Mesangiocapillary GN	-	4	
FSGS	2	–	
Chronic pyelonephritis	6	4	
Polycystic kidney	2	–	
Renal amyloidosis	–	4	
End-stage kidney (biopsy)	32	30	
Unknown	8	8	.350
Pretransplant hypertension	24	32	.528
Recipient HCV antibody - (Positive: negative)	10 : 40	14 : 36	.507
Donor's age (y)	36.76 ± 9.13	34.2 ± 11.22	.196
Consanguinity			
Related/unrelated	44/6	40/10	.478
Donor/recipient blood group			
Same/different	44/4	44/6	.637
Tissue typing:			
Number of HLA (A&B) matches:			
4 Mismatches	4	0	
3 Mismatches	1	7	
2 Mismatches	11	11	
1 Mismatch	4	4	
0 Mismatches	5	3	.603
Number of DR matches:			
1 Mismatch	17	21	
0 Mismatches	8	4	.185

Abbreviations: DR, Human leucocyte antigen –DR; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HCV, hepatitis C virus; HLA, Human leucocyte antigen

Table 2. Histopathologic examination of graft biopsies and cost of immunosuppression and cost of management of morbidities in both groups.

Rejection and costs	Group A (n=50) (steroid free)	Group B (n=50) (control)	*P* value
Acute rejection episodes:	8 (16%)	8 (16%)	
Steroid sensitive/resistant	6/2	6/2	.479
Acute tubular necrosis	6	1	
Acute FK nephrotoxicity	1	1	
Normal graft	5	1	
Total number of biopsies	20	11	.041
Cost of immunosuppression per patient			
Induction	USD $1000.00	USD $1000.00	
Antirejection	USD $20,383.00	USD $21,107.00	
Maintenance for 1 year	USD $8700.00	USD $8800.00	.98
Total cost of immunologic morbidities	USD $4127.23	USD $6097.44	.045
Cost per patient	USD $82.54	USD $121.96	.04

Outcome

Overall graft and patient survivals were 100% in both groups at 1 year after transplant. We observed better graft function as measured by serum creatinine and creatinine clearance among patients in the steroid-maintenance group at different intervals until the sixth month when the 2 groups were comparable regarding graft function (Table 3). Also, daily urinary protein excretion (g/d) was comparable in both groups (0.3 ± 0.1 g/d; $P = .12$).

Table 3. Laboratory evaluation of patient in both groups at different time intervals.

Patient characteristics	Group A (n=50) (steroid free) Mean ± SD	Group B (n=50) (control) Mean ± SD	*P* value
Creatinine (mg/dL)1st month	132 ± 66	91 ± 24	.01
6 Months	107.9 ± 33	99.6 ± 24	.51
12 Months	107.9 ± 41	107.9 ± 28.2	.90
Creatinine clearance (mL/min)			
First month	68.7 ± 20.0	79.3 ± 21.3	.38
Sixth month	76.4 ± 18.1	73.4 ± 14.4	.89
12th Month	74.9 ± 23.1	71.3 ± 10.9	.86
Lipogram			
HDL (mg/dL)			
Basal	0.74 ± 0.12	0.76 ± 0.10	.81
At 12 months	1.20 ± 0.22	0.88 ± 0.26	.04
LDL (mg/dL)			
Basal	1.98 ± 0.62	1.96 ± 0.70	.71
At 12 months	2.60 ± 0.59	3.14 ± 0.42	.04
Cholesterol (mg/dL)			
Basal	2.86± 0.68	3.22 ± 0.71	.72
At 12 months	3.16 ± 0.62	4.44 ± 1.04	.001
Triglycerides (mg/dL)			
Basal	0.89 ± 0.36	0.86 ± 0.15	.15
At 12 months	0.89 ± 0.20	1.19 ± 0.27	.001

Abbreviations: HDL, High density lipoprotein; LDL, low density lipoprotein

Morbidities

Initially, we found no significant difference between the 2 groups regarding mean components of the lipid profile. But after 1 year, we observed a significant elevation in mean cholesterol, low-density lipoproteins, and low-density lipoproteins associated with significant reduction of mean high-density lipoproteins among patients in the steroid-maintenance group compared with patients in the steroid-free group with baseline values (Table 3; $P \leq .05$). Therefore, management of daily costs was elevated by USD $1 per patient.

The prevalence of posttransplant diabetes mellitus was significantly higher in steroid-maintenance group (16%) versus the steroid-free group (4%; $P = .037$), and most of patients were insulin-dependent (Table 3). This was associated with a 3.6-fold increase in the cost needed to control diabetes mellitus. Serious infections like urinary tract infections, chest infections, *cytomegalovirus*, and herpes zoster were more frequent in steroid-maintenance group than they were in the steroid-free group (Table 4; $P < .05$). This was associated with a 2.9-fold increase in management costs and 2.2-fold increase in hospitalization costs for these serious infections in the same group.

The cost of controlling hypertension among steroid-maintenance group was 13 times higher than that needed for the steroid-free group. Patients with hypertension controlled by 1 or more

Table 4. Posttransplant complications and their costs in both groups.

Complications	Group A (n=50) (steroid free)			Group B (n=50) (control)			*P* value
Antihypertensives	1 Drug	2 Drugs	3 Drugs	1 Drug	2 Drugs	3 Drugs	
Basal	24%	0%	0%	32%	0%	0%	.528
6 Months	4%	0%	0%	12%	20%	0%	.0020
2 Months	4%	0%	0%	12%	8%	24%	.0009
Total cost							
1 Drug	USD $500.00			USD $1243.60			.04
≥ 2 Drugs	USD $0.00			USD $5349.00			.02
Diabetes mellitus	2			8			.037
Cost of therapy	USD $75.00			USD $272.70			.04
Gastritis	9			12			.390
Cost of therapy	USD $200.00			USD $261.00			.23
Infections - Bacterial							
UTI	8			16			.029
Chest infections	6			16			.02
Cost of therapy	USD $109.00			USD $272.00			.045
Infections - Viral							
CMV infection:	1			3			.297
Herpes zoster	–			4			.040
Cost of therapy	USD $1000.00			USD $3018.00			.35
Infections - fungal	2			4			.395
Cost of therapy	USD $36.30			USD $72.7			.05
-Admission (d)	94			213			.03
Cost of hospitalization	USD $8545.00			USD $19,363.00			.04
t-Total cost of nonimmunologic morbidities	USD $10,495.30			USD $29,952.00			.025

Abbreviations: CMV, *cytomegalovirus*; UTI, urinary tract infection

antihypertensives were significantly higher in the steroid-maintenance group than they were in the steroid-free group (Table 3; $P = .0009$).

Discussion

Kidney transplant, like all treatments for end-stage renal disease, is costly. Therefore, it would be wise to think of ways to reduce the rate of end-stage renal disease in the community. Prevention and early referral of cases with hypertension, diabetes mellitus, and glomerulonephritis (which account for > 53% of all causes of end-stage renal disease[7]) could prevent or at least decrease the rate of morbidity.

Development of a steroid-related morbidity is frequent in renal-transplant recipients and may be responsible for a poor quality of life. Complete avoidance of corticosteroids from the start may overcome some of the problems encountered with late withdrawal. Several noncontrolled studies have used a combination of cyclosporine or tacrolimus with mycophenolate mofetil without induction[7] or with induction therapy as antithymocyte globulins[8] or anti-CD25 monoclonal antibodies.[8] This increased interest in steroid-free immunosuppression is fueled by recognition that half of all transplant loss is related to patient death due to cardiovascular disease and/or infectious complications, and that long-term use of steroids contributes to such elevated cardiovascular morbidity and mortality.[10]

One year after transplant, we found that the percentage of rejection-free patients was 84% in both groups. Eight rejection episodes were reported in the steroid-free group (16%); 6 of them (12%) were graded as borderline acute rejection, and all were steroid sensitive. The remaining 2 episodes were grade 2 and required antithymocyte globulin therapy. Similar results were reported among the steroid-maintenance group. The total cost of antirejection therapy was comparable in both groups (USD $203.83 in the study group vs USD $211.07 in the control group). The total cost per patient was USD $811.56 in steroid-free group and USD $1215.18 in the steroid maintenance group.

Short-time and long-time patient and graft survival rates were comparable to international standards.[11] These facts could explain why the kidney transplant rate increased in Egypt and why it was one of the active countries in the field of kidney transplant in the Middle East Society for Organ Transplantation (MESOT) region. There also were some factors that might entice foreigners to undergo kidney transplant in Egypt. Based on current regulations, candidates from foreign countries were allowed to undergo transplant if the donor and the recipient were of the same nationality. The price of a kidney transplant for such patients was near the mentioned costs. A similar policy is allowed in Iran and is increasing.[12]

Vitko and associates[13] reported a higher incidence of acute rejection episodes (30.5%) in the steroid-free group using tacrolimus and mycophenolate mofetil as maintenance immunosuppression, which could be attributed to an absence of induction therapy in their cohort. Despite using basiliximab induction in another group, they reported a decreased incidence of acute rejection (26.1%), which is still higher than our cohort (16%).

In comparison to the FREEDOM[14] trial, steroid-free immunosuppression was consumed in 338 kidney transplant recipients who were randomly assigned to maintenance-steroid therapy, early steroid withdrawal after 7 days, or true steroid avoidance together with basiliximab, cyclosporine, and enteric-coated mycophenolic acid. Preliminary results from this open-label, multicenter trial after 3 months of follow-up indicate the lowest incidence of acute rejection in patients who were maintained on steroids (5.9%), the highest incidence in patients who were treated with steroid avoidance (20.9%), and intermediate rates in patients who underwent early steroid withdrawal (15.6%). Our study differed in that our patients consumed tacrolimus in place of cyclosporine as a primary immunosuppressant agent with shorter steroid duration (3 days vs 7 days). Moreover, we used induction therapy for all patients with a longer follow-up (1 year vs 3 months in other studies).[14] However, we reported a similar acute rejection rate.

Roistang and associates[15] published the preliminary results of the CARMEN study concerning early steroid withdrawal in patients who were receiving tacrolimus/mycophenolate mofetil and either a single preoperative dose of methylprednisolone (n=260) or standard dosages of steroids without daclizumab induction (n=278). The incidence of acute rejection was 16.5% in each group, but duration of follow-up was only 6 months. The reported benefits included a significantly reduced incidence of new-onset diabetes in the steroid-free

group (0.4 vs 5.4%; P = .003) and lower mean cholesterol levels at last follow-up. In our study, we used steroids only for 3 days, with basiliximab for all patients and again, we followed them for a longer time. We reported a comparable estimated mean chronic allograft damage index score at 1 year in both groups. Sarwal and associates[16] performed a protocol biopsy for only 4 patients; 3 of them had chronic tacrolimus toxicity, which could be attributed to higher tacrolimus trough levels (15-20 ng/mL) until the end of the second month, while our accepted levels ranged from 5 to 10 ng/mL until the end of the first 2 weeks then 4 to 8 ng/mL thereafter.

We found a significant difference between the 2 groups regarding antihypertensive agents (Table 3; P = .009). Most patients in the steroid-free group stopped antihypertensive medications shortly after transplant, while 75% of hypertensive patients on 1 drug before transplant in the control group required 3 drugs to control their hypertension by the end of the first year. The cost of controlling hypertension among the control group was 13 times higher than in the study group.

Posttransplant diabetes mellitus was significantly higher in the steroid-maintenance group in comparison to the steroid-free group (16% vs 4%). Subsequently, this was associated with a 3.6-fold increase in the cost needed for its management. Our findings are in accord with those reported by Vitko and associates 2005[12] that diabetes mellitus was more prevalent in the steroid group (12%) versus the steroid-free group (7%). Moreover, this was matched with that found by Roistang and associates,[15] who reported a significantly reduced incidence of new-onset diabetes in the steroid-free group (0.4% vs 5.4%; P = .003) and lower mean cholesterol levels at last follow-up.

We found that the mean values of total serum cholesterol, triglycerides, and low-density lipoproteins were significantly higher among steroid-maintenance patients than were the steroid-free patients at 1 month and throughout the posttransplant follow-ups, which was attributed to steroid withdrawal. This was associated by elevation of daily cost by USD $1 per day per patient. This was matched with that reported in almost all recent clinical trials using a steroid-free regimen with observable lower blood lipids.[13, 17] These could favor improvement in cardiovascular risk factors, as previously reported, that global cardiovascular risk decreased by 10% at 1 year after transplant in renal transplant recipients who undergo early corticosteroid withdrawal.[18] However, the mean plasma concentration of total cholesterol and triglycerides did not improve in some studies, possibly owing to the choice of maintenance regimens other than steroids.[10]

Serious infections were associated with a 2.9-fold increase in the cost of management and a 2.2-fold increase of the cost of hospitalization in steroid-free patients. This was matched with the results reported by Tan and associates[19] who observed an increased risk of rejection and reduction of infections in the steroid-free group. However, in a meta-analysis by Simon and Morris,[20] they reported that the risk of infection and malignancy are unaffected, although the risk of leucopenia was significantly increased (fixed effects, RR 1.66; CI: 1.42-1.93; P = .0001). This debate might be due to differences in the immunosuppression protocols.

So, in an optimal kidney transplant population (young recipients; nondiabetics; and live, well-matched donors), important outcome differences exist with and without steroid exposure. These are predominantly differences in hypertension, posttransplant diabetes mellitus, and cholesterol.

Conclusions

Among low-immunologic risk recipients of live-donor renal transplants, steroid avoidance was feasible, safe, and had fewer morbidities, using basiliximab induction, and maintenance by tacrolimus and mycophenolate mofetil. Steroid avoidance was associated with lower total cost despite comparable immunosuppression cost, which was attributed to a lower cost of associated morbidities.

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