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RESEARCH ARTICLE

Long term follow up of steroid-free immunosuppression in Egyptian living donor kidney transplant recipients

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Abstract

Background: Steroids have been a part of any immunosuppressive regimen since the beginning of kidney transplantation because of their anti-inflammatory and immunosuppressive property. Steroids have many adverse effects include worsening hypertension, worsening dyslipidemia, new-onset diabetes, osteoporosis, avascular necrosis and susceptibility to infection. With the availability of better immunosuppressive drugs, many centers have successfully performed corticosteroid free transplantation. The aim of this study was to compare the outcomes of steroid free regimen with steroid based regimen in Egyptian kidney transplant recipients, and their impact on both graft and patient survival.

Patients and methods: This retrospective case control study included 480 Egyptian kidney transplant recipients, who underwent transplantation at Urology and Nephrology Center, Mansoura University, Egypt, in the period between 2004 and 2013. They included 2 groups; group I: 240 kidney transplant recipients maintained on a steroid–free immunosuppression regimen [Tacrolimus (Tac)+ mycophenolate mofetil (MMF)], in whom steroids were removed after obtaining a satisfactory Tac trough level 5-10 ng/ml and group II: 240 kidney transplant recipients of matched age, sex and duration of follow up, maintained on a steroid containing immunosuppression regimen. Studied parameters for recipients included; age, sex, original kidney disease, pre-transplant data, immunosuppression, post-transplant complications, rejection episodes, patient and graft survival.

Results: The total dose of steroid in the first 3 months post-transplant was 2.55±1.39 gm in group I, vs 4.0±1.67 gm in group II, p<0.0001. There was no significant difference as regards the frequency of acute rejections; while acute humoral rejection was significantly higher in group II (7%), than in group I (1.7%), p=0.0004. Post-transplant viral infections, hypertension and diabetes mellitus were significantly higher in group II (11.6%, 29.6% and 6.6%), than in group I (5.8%, 19.2% and 2.5%), (p=0.026, p=0.009 and p=0.031). Patient and graft survivals were comparable in both groups; living with functioning graft (94.58% vs 91.66%), living on dialysis (5% vs 6.25%), died with functioning graft (0.42% vs 1.67%) or died with failed graft (none vs 0.42%). Also, serum creatinine and creatinine clearance levels were comparable in both groups (1.68±1.67 vs 1.64±1.51 mg/dl) and (83.1 ± 33.9 vs 77.5± 29.9 ml/min). The one year cost of steroid in group II was 1.6 folds that in group I, FK 0.9 folds and MMF 2 folds (total cost 1.15 folds).

Conclusion: Patient and graft survivals were comparable in steroid-free and steroid based renal transplantation groups, while post-transplant viral infections, hypertension and diabetes mellitus were higher in steroid-based regimen.

Introduction:

Steroids have been a part of any immunosuppressive regimen since the beginning of kidney transplantation because of their anti-inflammatory and immunosuppressive property, in addition to their ability to reverse acute rejection ***(1).*** Unfortunately steroids have many adverse effects include worsening hypertension, worsening dyslipidemia, new-onset diabetes, osteoporosis, avascular necrosis and susceptibility to infection. Many of these are responsible for a persistently elevated cardiovascular risk burden in kidney transplant patients, and therefore, excessive mortality ***(2).*** 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 post-transplant comorbidities was significantly higher in steroid-maintenance group, despite comparable costs of immunosuppression ***(3).*** Reduction or elimination of immunosuppression without affection of the graft function has long been a goal of the transplant profession. The point of such dose reduction is to induce a state of immune "hypo responsiveness," "acceptance," or "tolerance" to reduce complications of immunosuppression without increasing the risk of rejection ***(4).*** Steroid avoidance is now frequently attempted in de novo kidney transplant recipients at low immunological risk to prevent the long-term complications associated with maintenance steroid therapy ***(5).*** Immunosuppression protocols that completely avoid the use of steroids have been adopted in several studies in adult renal allograft recipients. These protocols appeared to be safe in terms of short-term renal allograft function and survival, with variable results for acute rejection incidence ***(6).*** The aim of this study was to compare the outcome of steroid free and steroid based regimens in Egyptian kidney transplant recipients, their cost, and graft and patient survival.

Patients and methods:

This retrospective case control study included 480 Egyptian kidney transplant recipients, who underwent transplantation at Urology and Nephrology Center, Mansoura University, Egypt, in the period between 2004 and 2013. They included 2 groups; group I: 240 kidney transplant recipients maintained on a steroid–free immunosuppression regimen [Tacrolimus (Tac)+ mycophenolate mofetil (MMF)], in whom steroids were removed after obtaining a satisfactory Tac trough level 5-10 ng/ml and group II: 240 kidney transplant recipients of matched age, sex and duration of follow up, maintained on a steroid containing immunosuppression regimen. Studied parameters for recipients included; age, sex, original kidney disease, pre-transplant data, immunosuppression, post transplant complications, rejection episodes, patient and graft survival**.** Qualitative data were displayed in cross tabulations, and quantitative data were described in terms of arithmetic mean ± SD. Bivariate techniques were used for initial evaluation of contrasts. Thus, the chi-square and Fisher's exact tests were used for comparisons of frequencies of qualitative variables; the Mann-Whitney test and the unpaired t-test were used for comparisons of means of two quantitative variables. A p-value <0.05 was considered significant. Graft and patient survival rates were assessed using the Kaplan-Meier method. All analyses were carried out using the computer package SPSS for windows.

Results:

The total dose of steroid in the first 3 months post-transplant was 2.55±1.399 gm in group I, vs 4.00±1.67 gm in group II, P<0.0001. Resistant rejection occurred in 11.7% of cases in group I, vs 3.7% in group II, P<0.001**,** while liver impairment occurred in 2.55 of cases in group II, but did not occur in any case in group I. The number of cases which required a shift in their immunosuppressive regimen did not vary between the two groups (41 (17.1%) in group I, vs 36 (15%) in group II, P=0.4. There was no significant difference as regards the frequency of acute rejections; 168 (70%) in group I, vs 169 (70.5%) in group II, P=0.9, while acute humoral rejection was significantly higher in group II (7%), than in group I (1.7%), P=0.0004. Post-transplant viral infections, hypertension and diabetes mellitus were significantly higher in group II (11.6%, 29.6% and 6.6%), than in group I (5.8%, 19.2% and 2.5%), (p=0.026, p=0.009 and p=0.031). Patient and graft survival were comparable in both groups; living with functioning graft (94.58% vs 91.66%), living on dialysis (5% vs 6.25%), died with functioning graft (0.42% vs 1.67%) or died

with failed graft (none vs 0.42%). Also, serum creatinine and creatinine clearance were comparable in both groups (1.68±1.67 vs 1.64±1.51 mg/dl) and (83.1 ± 33.9 vs 77.5± 29.9 ml/min). The one year cost of steroid in group II was 1.6 folds that in group I, FK 0.9 folds and MMF 2 folds (total cost 1.15 folds).

Table (1): **Demographic data of the recipients and donors of both groups.**

Pretransplant characteristics	Group I (n=240)	Group II(n=240)	P-value
Recipient age (Mean ± SD) years	28.09 ± 11.83	30.31 ± 11.29	0.03 S
Recipient gender (M/F, frequency)	190 (79.17%)/ 50 (20.83%)	182 (75.83%)/ 58 (24.17%)	0.38 NS
Donor age (Mean ± SD) years	39.04 ± 9.926	38.86 ± 10.323	0.85 NS
Donor gender (Male/Female, frequency)	82 (34.17%)/ 158 (65.83%)	105 (43.75%)/ 135 (56.25%)	0.03 S
Related donor Unrelated donor	213 (88.75%) 27 (11.25%)	196 (81.67%) 44 (18.33%)	0.02 S
Original kidney disease:			
Mesangioproliferative glomerulonephritis	5 (2.1%)	6 (2.5%)	0.76 NS
Membranous nephritis	2 (0.8%)	2 (0.8%)	1.00 NS
Focal segmental glomerulosclerosis	2 (0.8%)	13 (5.4%)	0.004 HS
Membranoproliferative glomerulonephritis	6 (2.5%)	3 (1.2%)	0.31 NS
Crescentic glomerulonephritis	3 (1.2%)	3 (1.2%)	1.00 NS
Chronic Pyelonephritis	44 (18.33%)	52 (21.67%)	0.36 NS
Nephrosclerosis	5 (2.1%)	3 (1.2%)	0.47 NS
Congenital	4 (1.7%)	3 (1.2%)	0.70 NS
Obstructive uropathy	10 (4.2%)	15 (6.2%)	0.30 NS
Hereditary	4 (1.7%)	1 (0.4%)	0.17 NS
Amyloidosis	2 (0.8%)	4 (1.7%)	0.41 NS
Polycystic kidney disease	3 (1.2%)	6 (2.5%)	0.31 NS
Hypoplasia	1 (0.4%)	0 (0%)	0.31 NS
Others	33 (13.8%)	36 (15%)	0.69 NS
Unknown	116 (48.3%)	93 (38.8%)	0.03 S

Table (2)**: Steroid use, induction and shift in immunosuppression regimens in both groups.**

Total dose of steroid in the first three months post-transplantation in both groups	Group I (n=240)	Group II (n=240)	P-value
Total dose of steroid in grams (M ± SD)	2.55±1.399	4.001±1.671	<0.0001 VHS
Total dose of steroid in grams by group			
<5 gm	228 (95%)	189 (78.8%)	<0.0001 VHS
5-10 gm	12 (5%)	48 (20%)	<0.0001 VHS
>10 gm	0 (0%)	3 (1.2%)	0.08 NS
Adjuvant therapy	240 (100%)	240 (100%)	1.00 S
ATG*	17 (7.1%)	17 (7.1%)	1.00 S
Basiliximab (Simulect)	216 (90%)	218 (90.8%)	0.75 S

Alemtuzumab (campath 1-H)	**7 (2.9%)**	**5 (2.1%)**	**0.55 S**
No shift in immunosuppression regimen **Shift in immunosuppression regimen**	**1 99 (82.9%)** **41 (17.1%)**	**204 (85%)** **36 (15%)**	**0.47** **NS**
Creatinine at the day of shift (Mean ± SD) mg/dl	**2.30 ± 1.56**	**2.88 ± 2.70**	**0.28 NS**
Indication of shift: **Elective:** **Infection:** **Resistant rejection:** **Drug toxicity:** **GIT upset:** **Cosmotic:** **Liver impairment**	 **5 (2.1%)** **2 (0.8%)** **28 (11.7%)** **1 (0.4%)** **5 (2.1%)** **0 (0%)** **0 (0%)**	 **6 (2.5%)** **4 (1.7%)** **9 (3.7%)** **5 (2.1%)** **5 (2.1%)** **1 (0.4%)** **6 (2.5%)**	 **0.76** **0.41 (NS)** **0.001 (HS)** **0.10 (NS)** **1.00 (NS)** **0.31 (NS)** **0.01 (S)**
Immunosuppression regimen shift: **Imuran+high dose steroid:** **St+FK+AZA:** **St+FK+MMF:** **St.+CSA+MMF:** **FK+Steroid:** **Steroid+ MMF:** **ST.+FK+rapamycin:** **St.+MMF+rapamycin:** **FK+MMF:**	 **0 (0%)** **1 (0.4%)** **33 (13.7%)** **1 (0.4%)** **1 (0.4%)** **4 (1.7%)** **0 (0%)** **1 (0.4%)** **0 (0%)**	 **2 (0.8%)** **8 (3.3%)** **0 (0%)** **6 (2.5%)** **2 (0.8%)** **10 (4.2%)** **2 (0.8%)** **4 (1.7%)** **2 (0.8%)**	 **0.15 (NS)** **0.01 (S)** **< 0.0001(VHS** **0.05 (NS)** **0.56 (NS)** **0.10 (NS)** **0.15 (NS)** **0.17 (NS)** **0.15 (NS)**

Table (3): **Frequency, type and management of acute rejection episodes of both groups.**

Number of rejections	**Group I (n=240)**	**Group II (n=240)**	**P-value**
No rejection	**168 (70%)**	**169 (70.5%)**	**0.921 NS**
Rejection	**72 (30%)**	**71 (29.5%)**	**0.921 NS**
One rejection	**53 (22.1%)**	**60 (25%)**	**0.451 NS**
Two rejections	**19 (7.9%)**	**6 (2.5%)**	**0.007 NS**
Three rejections	**0 (0%)**	**3 (1.2%)**	**0.082 NS**
More than three	**0 (0%)**	**2(0.8%)**	**0.151 NS**
Hyperacute	**6 (2.5%)**	**2 (0.8%)**	**0.154 NS**
Acute cellular	**62 (25.8%)**	**52 (21.7%)**	**0.283 NS**
Acute humoral	**4 (1.7%)**	**17 (7%)**	**0.004 NS**
Management of rejection			
Steroid	**58 (24.167%)**	**45 (18.75%)**	**0.148 NS**
ATG (anti-thymocyte globulin)	**3 (1.25%)**	**4 (1.67%)**	**0.703 NS**
Plasma exchange & steroids	**6 (2.5%)**	**14 (5.84%)**	**0.068 NS**
Plasma exchange & ATG	**4 (1.67%)**	**4 (1.67%)**	**1.000 NS**
Rituximab	**1 (0.42%)**	**4 (1.67%)**	**0.177 NS**

Table (4): **Post-transplant complications, graft and patient survival, serum creatinine in mg/dl and creatinine clearance in ml/minute in both groups.**

ransplant complications	Group I (n=240)	Group II (n=240)	P-value
Acute tubular necrosis	14 (5.8%	24 (10%)	0.09 NS
Chronic rejection	14 (5.8%)	8 (3.3%)	0.17 NS
Bacterial infection	35 14.5%)	41 (17.1%)	0.48 NS
Viral infection	14 (5.8%)	28 (11.6%)	0.02 S
Hepatic impairment	26 (10.8%)	18 (7.5%)	0.18 NS
Post transplant hypertension	46 (19.2%)	71 (29.6%)	0.009 VHS
Post transplant diabetes mellitus	6 (2.5%)	16 (6.6%)	0.03 S
GIT troubles	8 (3.3%)	8 (3.3%)	0.96 NS
Malignancy	0 (0%)	1 (0.4%)	0.32 NS
Condition of patient and graft			
Living with functioning graft	227 (94.58%)	220 (91.66%)	0.20 NS
Living on dialysis	12 (5%)	15 (6.25%)	0.55 NS
Died with functioning graft	1 (0.42%)	4 (1.67%)	0.17 NS
Died with failed graft	0 (0%)	1 (0.42%)	0.31 NS
S creatinine in mg/dl (Mean ± SD)			
At one year	1.23 ± 0.53	1.23 ± 0.41	0.96 NS
At two years	1.34± 0.60	1.31± 0.64	0.72 NS
At three years	1.38 ± 0.62	1.14 ± 0.79	0.84 NS
At four years	1.44 ± 0.88	1.39 ± 0.76	0.70 NS
At five years	1.39± 0.71	1.35± 0.93	0.80 NS
At the last follow up	1.68±1.67	1.64±1.51	0.81 NS
Creatinine clearance in ml/minute at last follow up (Mean ± SD)	83.1 ± 33.9	77.5 ± 29.9	0.11 NS

Figure (1): **Graft survival in months in both groups.**

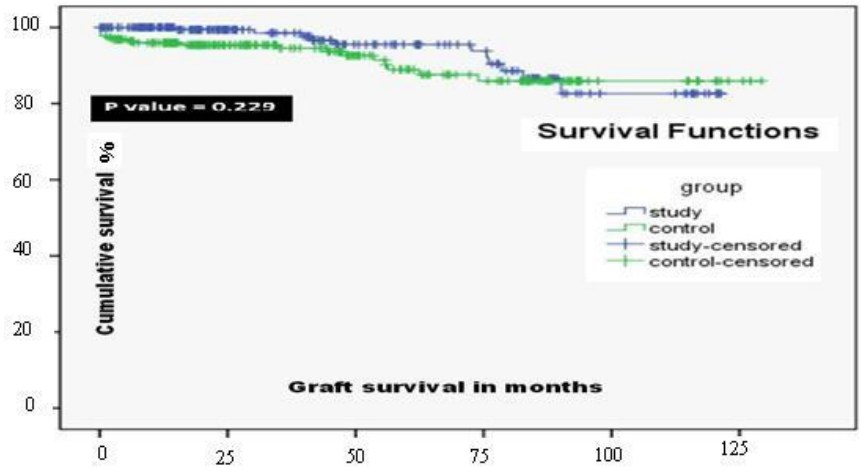

Figure (2): **Patient survival in months in both groups.**

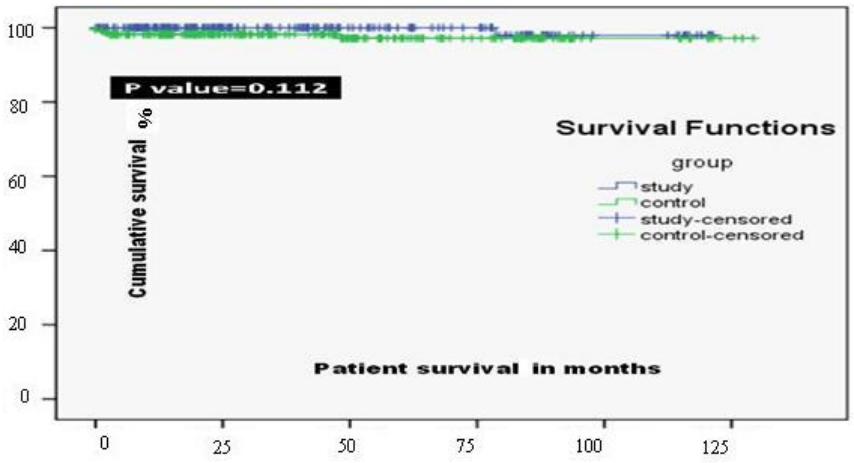

Table (5): **Cost (LE) of induction therapy, management of rejection episodes and immunosuppression regimens in both groups.**

Cost in LE	Group I (n=240)	Group I (n=240)	P-value
Induction	**n=240**	**n=240**	
<5000	**7 (2.9%)**	**5 (2.1%)**	**0.55 NS**
5000- 10000	**216 (90%)**	**218 (90.8%)**	**0.75 NS**
>10000	**17 (7.1%)**	**17 (7.1%)**	**1.00 NS**
Rejection episodes	**n=72**	**n=71**	
<10000	**56 (23.33%)**	**51 (21.25%)**	**0.58 NS**
10000- 40000	**5 (2.08%)**	**10 (4.17%)**	**0.18 NS**
>40000	**11 (4.58%)**	**10 (4.17**	**0.82 NS**
Immunosuppression	**For 1 male patient 53 year old**	**For 1 male patient 54 year old**	**Group II/ Group I**
Total in one year	**32862 LE**	**37923 LE**	**1.15 Folds**
Steroid in one year	**639 LE**	**1004 LE**	**1.5 Folds**
FK in one year	**24193 LE**	**20859 LE**	**0.86 Folds**
MMF in one year	**8030 LE**	**16060 LE**	**2.0 Folds**
FK in 5 years	**99097 LE**	**83439 LE**	**0.84 Folds**
MMF in 5 years	**40150 LE**	**80300 LE**	**2.0 Folds**

Discussion:

Corticosteroids are widely used as a part of the immunosuppressive regimen after transplantation, but steroids have well documented multiple adverse effects involving many body systems, including effects on blood pressure, lipid profile and glucose tolerance ***(7)***. Minimizing glucocorticoid use in the setting of organ transplantation has therefore been a goal for many years ***(8).*** Our retrospective analysis of a large cohort of Egyptian kidney transplant recipients (480 patients) compared the outcomes of steroid free and steroid based regimens and their impact on both graft and patient survival in the Urology and Nephrology Center, Mansoura University, Egypt between 2004 and 2013. Patients in our study were divided into two groups; Group I (240 patients on steroid–free regimen), which included

patients maintained on steroid–free regimen [Tacrolimus (Tac) + mycophenolatemofetil (MMF)], as a primary immuno-suppression level and Group II (240 patients maintained on steroid containing regimen post-transplantation). In our work, we observed that patients in steroid free group were younger (28.09 ± 11.83 years) than patients on steroid based group (30.31 ± 11.29), (p=0.036). This is in agreement with ***(9),*** who reported that minimizing steroid exposure in pediatric renal transplant recipients can improve linear growth and reduce metabolic disorders. We also noticed that the there was no statistically significant difference regarding the original kidney disease between the two groups except focal segmental glomerulosclerosis (FSGS) (p= 0.004), being higher in steroid-based group and unknown original kidney disease (p= 0.034), being higher in steroid-free group. This may be explained by the high risk of recurrence of FSGS in grafts which is approximately 30% and recurrence occurs in renal grafts in early post-transplant period ***(10),*** so patients with FSGS as original kidney disease preferably to be maintained on steroid based immunosuppression after renal transplantation, if there is no contraindication. In addition, we found that the total dose of steroid in the first three months was more in the steroid based group (4.001±1.67 gms), than in steroid free group (2.55±1.39 gms) (p <0.0001), as this group was maintained on steroid, while steroid free group stopped steroid at the fourth day post transplantation provided by satisfactory FK level, but we noticed that acute rejection rates in steroid free group did not significantly differ when compared to steroid based group (p= 0.921). This agrees with ***(11)***, who observed that there was no significant difference in acute rejection when calcineurin inhibitors were used in combination with mycophenolatemofetil and antibody induction with or without steroids. However ***(9)*** found that acute rejection rates in living donor kidney transplantation with early corticosteroids withdrawal regimen of basiliximab/TAC/MMF were significantly higher as compared to similar regimen with corticosteroids. This may be explained by smaller number of patients in that study (140 patients) compared to our study (480 patients).While in another trial ***(12),*** which compared TAC-MMF-prednisolone with TAC-MMF and basiliximab-TAC, they reported a higher incidence of acute rejection episodes in steroid free group using Tacrolimus and MMF as a mainterance immunosuppression, which could be attributed to the absence of induction therapy in their study which has improved our results in comparison to their results. In the other steroid free arm in the same study ***(12),*** using Basiliximab induction and Tacrolimus, had decreased the incidence of acute rejection. They suggested that induction plus double therapy is probably required for success of steroid free regimen. In our study, we found that there was an effect on the type of rejection, with higher acute humoral rejection in steroid-based group (p= 0.004). This may be explained by glucocorticoid action in T cells and the crucial role for glucocorticoids in regulating T cell number, repertoire and function, but an antibody-mediated rejection is defined by histological changes caused by a circulating, anti-HLA, donor-specific antibody ***(13).*** Therapeutic strategies that include combinations of plasma exchange to remove donor-specific antibody, and/or intravenous immunoglobulins and anti-CD20+ monoclonal antibody (rituximab) to suppress donor-specific antibody production have been used to successfully treat acute humoral rejection ***(14).*** Shift in immunosuppression regimen was indicated in 17.1% of patients in steroid-free group, which was comparable to that in steroid-based group (15%), (p=0.47). Indications for this shift were similar in both groups, but resistant rejection was higher in steroid-free group (11.7%) than in steroid-based group (3.7%), (p=0.001), while liver impairment occurred in 2.5% of steroid-based group, but not in any of steroid-free group, (p=0.01). In our study, the prevalence of post-transplant hypertension was higher in steroid based group (29.6%) than in steroid-free group (19.2%), (p= 0.009). This can be explained by higher dose of steroid given which promote fluid retention and elevated blood pressure as all corticosteroid drugs, including prednisone, can cause sodium retention, resulting in fluid retention ***(15).*** We also observed higher post-transplantation diabetes mellitus (PTDM) (6.6%) in steroid based group than in steroid free group (2.5%) (p= 0.031). This concurs with ***(1)***, who demonstrated that steroid-free immunosuppression was associated with a significant reduction in the likelihood of developing new onset diabetes, compared with steroid-containing regimens**.** Our results also showed higher prevalence of viral infection among recipients with steroid based regimen (11.6%) than in steroid-free group (5.8%), (p= 0.026). This is in agreement with ***(16),*** who demonstrated that steroid therapy makes patients prone to infections. This could be explained by minimization of immunosuppression, as the steroid could have a significant role in activation of viral infection. However ***(9)*** observed that the incidence of infections was significantly higher in steroid free group, in which 20.5% had some infection and in steroid based group, 7.5% had infections (p = 0.02). This may be explained by higher number of rejections in steroid free group leading to more use of steroid pulses and higher immunosuppression. In our study, we observed that there was no significant difference in gastro-intestinal (GIT) troubles between the two groups. This may be explained by the usage of proton pump inhibitors in steroid based group, which are used to protect against peptic ulcer caused by corticosteroids. In addition, we noticed that follow up serial serum creatinine values post-transplantation revealed that there was no statistically significant difference between the two groups. We also observed that creatinine clearance at the last follow up showed no difference between the two groups. Regarding the cost, a little difference was found in the total cost of immunosuppression therapy in one year, being more in the steroid based group. The cost was calculated for one

patient in each group, with comparable age, and sex, but the cost for complications treatment, rejection management and hospitalization was not calculated for registry data shortage. Using one patient model from each group as an example, we found that the one year cost of steroid in group II was 1.6 folds that in group I, FK 0.9 folds and MMF 2 folds (total cost 1.15 folds). Similarly, ***(3)*** noticed that associated hospitalization costs were 2.2-fold higher in the steroid-maintenance group than they were in the steroid-free group and that one year after transplant, the cost of managing posttransplant comorbidities was significantly higher in steroid-maintenance group. Our results showed that 10 years graft and patient survival were comparable between the recipients in both groups (p= 0.229) and (p= 0.112) respectively, which was also observed by ***(17).*** The advantage of this study is that it clearly documented several benefits of steroid free regimen such as significant lower incidence of hypertension, diabetes and viral infection without increasing the rate of acute rejection. The shortcomings of this study included the failure to estimate the overall cost differences between steroid-free and steroid-based regimens. Further studies should try to use more registry data as regards cost and centers should keep these data available for further studies.

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References:

1- Luan FL, Steffick DE and Ojo AO (2009). Steroid-free maintenance immunosuppression in kidney transplantation. Kidney In. 76: 825-830.

2- Ojo AO (2006). Cardiovascular complications after renal transplantation and their prevention.Transplantation. 82 (5): 603-611.

3- Gheith OA, AH, Bakr MA, et al. (2011). Steroid avoidance reduces the cost of morbidities after live-donor renal allotransplants: a prospective, randomized, controlled study. Exp Clin Transplant. 9 (2): 121-127.

4- Kirk AD (2003). Less is more: maintenance minimization as a step toward tolerance. Am J Transplant. 3 (6): 643-645.

5- Thierry A, Mourad G, Büchler M, et al. (2014). Three-year outcomes in kidney transplant patients randomized to steroid-free immunosuppression or steroid withdrawal. J Transplant. 171898.

6- Naesens M, Salvatierra O, Benfield M, et al. (2012). Subclinical inflammation and chronic renal allograft injury in a randomized trial on steroid avoidance in pediatric kidney transplantation.Am J Transplant. 12 (10): 2730-2743.

7- Lemieux I, Houde I and Pascot A (2002). Effects of prednisone withdrawal on the new metabolic triad in cyclosporine-treated kidney transplant patients. Kidney Int. 62 (5): 1839-1847.

8- Bodziak, K. and Hricik, D (2003): Minimizing the side effects of immunosuppression in kidney transplant recipients. Transplantation. 8: 160-165.

9- Bansal SB, Sethi S, Sharma R, et al., (2014). Early corticosteroid withdrawal regimen in a living donor kidney transplantation program. Indian J Nephrol. 24 (4): 232-238.

10- Radha S, Afroz T, Prasad Ch r et al. (2015). Focal segmental glomerulosclerosis in renal allografts: Is it possible to diagnose the etiology? Indian J Nephrol. 25 (2): 82–85.

11- Rostaing L, Cantarovich D, Mourad G, et al. (2005). Corticosteroid-free immunosuppression with tacrolimus, mycophenolatemofetil, and daclizumab induction in renal transplantation. Transplantation. 79 (7): 807- 814.

12- Vítko S, Klinger M, Salmela K, et al. (2005). Two corticosteroid-free regimens-tacrolimus monotherapy after basiliximab administration and tacrolimus/ mycophenolate mofetil-in comparison with a standard triple regimen in renal transplantation: Results of the Atlas study. Transplantation. 80 (12): 1734–41.

13- Herold MJ, McPherson KG, and Reichardt HM (2006). Glucocorticoids in T cell apoptosis and function. Cell Mol Life Sci. 63(1): 60–72.

14- Salvadori M and Bertoni E (2014). Impact of donor-specific antibodies on the outcomes of kidney graft: Pathophysiology, clinical, therapy. World J Transplant. 4 (1): 1–17.

15- Hulisz D and Lagzdins M (2008). Drug-Induced Hypertension**.** US Pharmacist. 33 (9): HS11-HS20.

***16- Sureshkumar KK, Marcus RJ, and Chopra B, (2015*)**. Role of steroid maintenance in sensitized kidney transplant recipients. World J Transplant.5 (3): 102- 109.

17- Vincenti F, Schena FP, Paraskevas S, et al. (2008). A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant. 8 (2): 307-316.