Steroid-Avoidance Immunosuppression Regimen in Live-Donor Renal Allotransplant Recipients: a Prospective, Randomized, Controlled Study

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Objectives: **Steroids have occupied a major role in renal transplantation for more than 4 decades. However, chronic use of steroids is associated with numerous comorbidities. We sought to elucidate the safety and efficacy of a steroid-free immunosuppression regimen in live-donor renal transplant recipients.**

Patients and Methods: **One hundred patients were randomized to receive tacrolimus, mycophenolate mofetil, basiliximab induction, and steroids only for 3 days (experimental group, n=50 patients) or tacrolimus, mycophenolate mofetil, basiliximab induction, and steroid maintenance (control group, n=50 patients,). The median follow-up was 12 months.**

Results: **Patient and graft survival rates were 100% in both groups. The rate of biopsy-proven acute rejection was 16% in both groups. For patients in the control group, the mean serum creatinine level was 111.22 μmol /L compared with 110.39 μmol/L in patients in the experimental group. Post-transplant hypertension was encountered in 4% of the patients in the experimental group compared with 24% of the patients in the control group (*P* = .0009). Posttransplant diabetes mellitus was detected in 4% of the patients in the experimental group compared with 16% of the patients in the control group (*P* = .037). Posttransplant weight gain was reported in 6% of the patients in the experimental group compared with 15% of the patients in the control group (*P* = .001). The chronic allograft damage indexes of biopsy specimens at 1-year follow-up were comparable in both groups (2.48 vs 2.28, respectively) (*P* = .16).**

Conclusions: **In living-donor renal transplant recipients with low immunologic risk, steroid avoidance (using basiliximab induction, tacrolimus, mycophenolate mofetil maintenance, and 3 days' steroid treatment) is feasible, safe, and carries with it fewer morbidities compared with the same immunosuppressive protocol with steroid maintenance. Longer follow-ups are required to prove the safety of this regimen.**

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

Corticosteroids are widely used as part of the immunosuppressive regimen after transplant, but steroids have well-documented, multiple adverse effects on a patient's blood pressure, lipid profile, and glucose tolerance (1). Cardiovascular morbidity remains the most common cause of death in renal transplant recipients (2, 3). Because short-term renal graft survival rates at 1 year exceed 90%, clinicians have shifted their priorities so that long-term graft survival is maximized and quality of life for transplant recipients is improved. Steroid-avoidance protocols have been used successfully and are presently undergoing extensive evaluation. However, the literature is lacking large, prospective, randomized, controlled studies of steroid avoidance in live-donor renal transplantation.

We therefore aimed to assess the safety and efficacy of a steroid-free immunosuppression regimen in a prospective, randomized, controlled study among live-donor renal transplant recipients.

Patients and Methods

A total of 100 patients (mean age, 29.62 ± 10.79 years; range, 5-60 years) with end-stage renal disease who had undergone live-donor renal allotransplant, at the Urology and Nephrology Center of Mansoura University in Egypt between June 2004 and July 2005, from living donors aged 21

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and 60 years with compatible ABO blood groups were recruited into the study. Written informed consent was obtained from all patients and donors, and the study protocol, which was approved by the ethics committee of Mansoura University prior to the study's onset, conformed to the ethical guidelines of the 1975 Helsinki Declaration. We excluded recipients at high risk, defined as those patients that did not have a match at the HLA-DR locus, those with a positive crossmatch, or those patients who previously had received a transplanted kidney.

General design

This study was an open, one-to-one, prospective, randomized, parallel group, controlled, double-arm, comparative study. Patients were assigned either to stop steroids after 3 days (experimental group) or to continue steroids (control group).

Endpoints

The primary endpoint was the incidence of a first biopsy-proven acute rejection episode (Banff type 1 or higher) within 12 months of the transplant. Other endpoints included patient and graft survival rates, renal function, incidence of infections, incidence of new-onset diabetes mellitus, and blood pressure and lipid measurements at 12 months after transplant.

Immunosuppression

Patients from both groups received induction therapy in the form of anti-CD_{25} (basiliximab 20 mg) slowly administered intravenously 1 hour before transplant and at day 4 after transplant.

All patients received 500 mg of methyl-prednisolone just before transplant, and another dose of 500 mg was given to the study patients on the first day after surgery, 250 mg the second day, and 100 mg on the third day. Then, the steroids were stopped on the fourth day after transplant provided that an acceptable tacrolimus level had been achieved. The control patients received steroids according to the local standard protocol in the form of methylprednisolone (3.5 mg/kg/d) on days 1, 3, 7, and 14 followed by tapering the prednisolone dosage gradually to 0.15 mg/kg/day by the ninth month.

Concomitant tacrolimus therapy (0.1 mg/kg/d po) was started 2 days before transplant, and the dosage was adjusted to achieve target whole-blood trough concentrations of 10 to 15 ng/mL during the first 2 weeks and 5 to 10 ng/mL thereafter. Tacrolimus concentrations in whole blood were measured with an IMx analyzer (Abbott Laboratories, Abbott Park, IL). Mycophenolate mofetil (1 g b.i.d.) was administered and decreased to 750 mg b.i.d. at 2 weeks after transplant until the end of the study. Dose reduction/interruption was allowed if mycophenolate-mofetil–related adverse effects occurred.

All episodes of rejection were verified by biopsy and graded using the Banff classification (4). Rejection episodes were primarily treated with methylprednisolone (500 mg) intravenously for 5 consecutive days. In cases of a steroid-resistant rejection, antithymocyte globulin was added. Maintenance steroids were allowed when the first episode of acute rejection was severe vascular rejection (Banff IIb or III); steroid-resistant rejection, or after treatment of the second episode of steroid-sensitive rejection. Also, prednisolone was administered at a dosage of 0.15 mg/kg/day if the mycophenolate mofetil dosage was less than 1000 mg/day, if the rejection episode was managed by antilymphocyte globulin therapy, or if there was an interruption in tacrolimus treatment.

Patient evaluations

At each follow-up visit, each patient underwent a thorough clinical examination with special emphases on blood pressure, organomegaly, and a neurologic evaluation. Laboratory investigations included evaluations of creatinine levels and creatinine clearance rates (using the Cockcroft and Gault formula), tacrolimus whole blood trough levels, liver functions, fasting and postprandial venous plasma glucose levels, serum cholesterol levels, low-density and high-density lipoprotein levels, triglyceride levels, urine, and 24-hour urinary protein level.

Histopathologic evaluations

In patients in the study group, histopathologic examinations of biopsy specimens of renal allograft tissue were performed in patients with delayed graft function, nephrotic-range proteinuria, renal dysfunction (defined as a 25% increase in the creatinine level from baseline) unexplained by prerenal or postrenal causes, or a high tacrolimus trough level. A routine protocol biopsy was performed at 1 year posttransplant. Histopathologic findings were graded using the Banff classification of 1997 (4).

Statistical analyses

The *t* test was used to compare continuous data, while noncontinuous data were compared using the

Mann-Whitney *U* test. The chi-square test and the chi-square test with Yates' correction were used to compare categorical variables. Graft survival was computed using the Kaplan-Meier technique; differences in survival were calculated with the log rank test. A *P* value < .05 was considered statistically significant.

Results

Table 1 gives the donors' and recipients' characteristics. The majority of recipients were men in their 20s, while more than half of the donors were women in their 30s. Also, the 2 groups were homogenous in terms of the donors' ages and sex, recipients' ages and sex, prior blood transfusions, hepatitis C virus status, urinary schistosomiasis, original kidney diseases, tissue matching, and pretransplant hypertension. In addition, no preformed antibodies against donor antigens were detected in the pretransplant crossmatch of any of the studied patients. The techniques employed for re-establishment of urinary continuity also were essentially similar.

Rejection episodes

Table 2 shows that the incidence of biopsy-proven acute rejection episodes was equal in both groups (16%). Similarly, the severity of the rejection episodes was comparable. The mean time to the first biopsy-proven acute rejection episode was significantly shorter in patients in the experimental group (1.88 vs 15 days, $P = .009$) than it was in patients in the control group. Among patients in the experimental group, acute tacrolimus nephrotoxicity was diagnosed in 1 patient, while acute tubular necrosis was diagnosed in 6 patients; conversely, in patients in the control group, 1 patient had both diagnoses. One-year protocol biopsies revealed higher chronic allograft damage index scores in the experimental group than in the control group; however, this result was not statistically significant ($P = .169$). Tubular atrophy and glomerular sclerosis were relatively higher among patients in the experimental group; increased mesangial matrix, interstitial inflammation, and vascular intimal proliferation were relatively higher in patients in the control group; these results were not statistically significant ($P > .05$). However, interstitial fibrosis was equal in both groups.

Outcome

The overall graft and patient survival rates were 100% in both groups at 1 year posttransplant.

Table 1. Demographic characteristics of the patients

	Experimental group (n=50)	Control group (n=50)	*P* value
Recipient age (year)	29.88±11.36	29.36±10.22	.868
Recipient sex (male/female)	40 / 10	32 /18	.207
Recipient body weight (kg)	61.72±14.3	59.04±11.32	.371
Original kidney disease			
Mesangiocapillary glomerulonephritis	–	4	
Focal segmental glomerulosclerosis	2	–	
Chronic pyelonephritis	6	4	
Polycystic kidney	2	–	
Renal amyloidosis	–	4	
End-stage kidney disease	32	30	
(Biopsy) unknown	8	8	.350
Pretransplant hypertension	24	32	.528
History of urinary bilharziasis	8	12	.637
Recipient anti-hepatitis C virus antibody: (Positive:negative)	10:40	14:36	.507
Donor age (year)	36.76±9.13	34.2±11.22	.196
Consanguinity (Related/unrelated)	44/6	40/10	.478
Donor/recipient blood group (Same/different)	46/4	44/6	.637

Table 2. Histopathologic examination of graft biopsies (event biopsy)

	Experimental group (n=50)	Control group (n=50)	*P* value
Acute rejection episodes			
Total number	8 (16%)	8 (16%)	
Banff grade			
Borderline	6	5	
Grade Ia	–	1	
Grade IIa	2	2	.479
Early/late	6/2	6/2	
Steroid sensitive/resistant	6/2	6/2	
Acute tubular necrosis	6	1	.041
Acute tacrolimus nephrotoxicity	1	1	
Normal	5	1	
Time to 1st rejection episode			
Range (days)	3-29	2-214	
Mean±SD (days)	1.88±5.85	15±51.57	.009

However, steroids were added to the immunosuppression protocol of 4 patients (8%); while mycophenolate mofetil was withdrawn owing to gastric upset in 2 patients (4%) in the experimental group and 4 patients (8%) in the control group. The mean tacrolimus dose required to achieve the target trough level between 5 and 8 ng/mL was significantly lower in the experimental group than it was in the control group over time until the end of the first year (Figure 1, $P = .049$).

Graft function

We observed better graft function, as measured by serum creatinine level and creatinine clearance,

among patients in the experimental group at different time points until the sixth month at which time the 2 groups were comparable (Table 3).

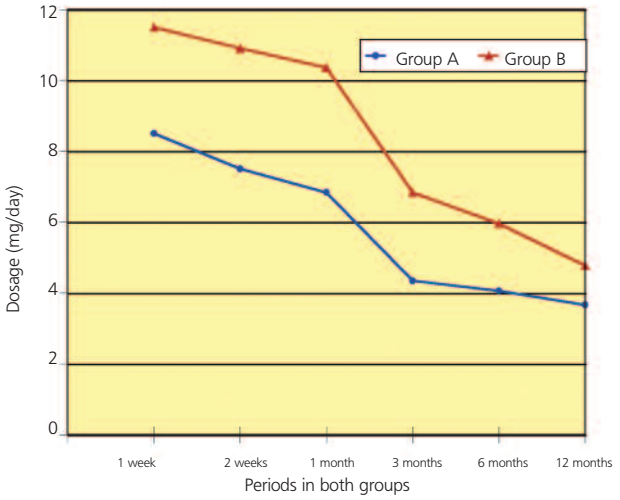

Figure 1. Mean tacrolimus dosage (mg/day) at different follow-up periods in both groups

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

	Experimental group (n=50)	Control group (n=50)	*P* value
Graft function follow-up	Mean±SD	Mean±SD	
Creatinine level (μmol/L) at the			
1st week	132±107	99.6±116	.12
1st month	132±66	91.3±24.3	.01
6th month	107.9±24.3	99.6±24.3	.51
12th month	107.9±45	107.9±0.44	.90
	Mean±SD	Mean±SD	
Creatinine clearance (mL/min) at the end of the			
1st week	77.3±18.1	80.9±13.7	.23
1st month	68.7±20.0	79.3±21.3	.38
6th month	76.4±18.1	73.4±14.4	.89
12th month	74.9±23.1	71.3±10.9	.86
Lipid profile	Mean±SD	Mean±SD	
High-density lipoprotein (mmol/L)			
Baseline	204±0.97	2.44±35	.71
At 12 months	3.36±0.77	4.07±0.56	.04
Cholesterol (mmol/L)			
Baseline	3.7±0.59	4.18±0.93	.72
At 12 months	4.1±0.81	5.76±1.35	.001
Triglyceride level (mmol/L)			
Baseline	1±0.41	098±0.17	.15
At 12 months	1.01±0.23	1.35±0.31	.001

Complications

At the start of the study, we observed no significant differences between the 2 groups regarding mean values for components of the lipid profile. However, 1 year later, compared with patients in the experimental group and compared with baseline values, patients in the control group had statistically significant elevations of mean cholesterol and low-density lipoprotein and triglyceride levels associated with a significant reduction of mean high-density lipoprotein levels (Table 3, $P < .05$). Also, at the end of the study, there was a statistically significant increase in mean body weight in patients in the control group compared with patients in the experimental group ($P < .0001$).

The percentage of patients with posttransplant diabetes mellitus was significantly higher in patients in the control group (16%) compared with patients in the experimental group (4%) ($P = .037$), and most were insulin dependent (Table 4).

Infections

Significant differences were seen regarding most types of infections (eg, urinary tract infections, chest infections, and herpes zoster) with the incidence being higher in patients in the control group than in patients in the experimental group ($P < .05$). On the other hand, incidences of skin abscesses, cytomegalovirus infection, and fungal infections were relatively higher in patients in the control group; however, this result was not statistically significant (Table 4, $P > .05$).

Bone aches and arthralgia were seen more frequently in patients in the control group ($P = .042$). Avascular bone necrosis was encountered in 1 patient in this group at 1-year follow-up.

The percentage of patients with hypertension controlled by 1 or more antihypertensive medications was significantly higher in the control group (Table 4, $P = .0009$). Surgical complications were more frequent in control group (10 cases); there were no surgical complications reported among any patients in the experimental group ($P = .001$).

Discussion

Corticosteroids have played a magic role in renal transplant surgery for more than 4 decades, being prescribed for every patient undergoing renal transplant to prevent or to treat episodes of acute rejection. Development of a steroid-related morbidity, however, is frequent in renal transplant recipients and may be responsible for poor quality of life, the need for frequent hospitalizations, increased costs of care, and esthetic disfiguration. Moreover, some complications caused by corticosteroids such as diabetes, hypertension, and hyperlipidemia can favor the development of cardiovascular diseases, which represent the leading cause of death in renal

Table 4. Posttransplant complications in both groups

	Experimental group (n=50)			Control group (n=50)			*P* value
Antihypertensive medications	1 drug	2 drugs	3 drugs	1 drug	2 drugs	3 drugs	
Baseline	24%	0%	0%	32%	0%	0%	.528
6 months	4%	0%	0%	12%	20%	0%	.0020
12 months	4%	0%	0%	12%	8%	24%	.0009
Mean body weight in kilograms							
At 2 weeks	61.72±14.30			59.04±11.32			
At 12 months	67.80±16.20			70.52± 14.51			< .0001
Diabetes mellitus	2			8			.037
Gastritis	9			12			.390
Bone and joint pain	2			8			.042
Acne	1			10			.001
Infections - bacterial							
Urinary tact infections	8			16			.029
Chest infections	6			16			.02
Infections - viral							
Cytomegalovirus	1			3			.297
Herpes zoster	–			4			.040
Infections - fungal	2			4			.395
Admissions	5/50			12/50			.03
Surgical complications	0			9			.001

transplant recipients. Withdrawal of corticosteroids after several months can trigger a late rejection by the up-regulation of T cells induced by long-term prednisone use (5). Complete avoidance of corticosteroids from the start, within the first posttransplant week, may overcome some of the problems encountered with late withdrawal. With the newer immunosuppressive agents, those created since 1999, use of steroids as maintenance therapy has gradually decreased. Several noncontrolled studies have used a combination of cyclosporine or tacrolimus with mycophenolate mofetil without induction (6) or with induction therapy with antithymocyte globulins (7) or anti-CD25 monoclonal antibodies (8).

This prospective, randomized, controlled study was undertaken at our center to assess the safety and efficacy of a steroid-free immunosuppression regimen in live-donor renal allotransplant recipients with planned follow-up of 1 year. All patients received basiliximab induction and were maintained on an immunosuppressive regimen consisting of tacrolimus and mycophenolate mofetil.

After 1 year of follow-up, the percentage of rejection-free patients was 84% in both groups. Eight episodes of acute rejection were reported in the experimental group (1 episode per patient) (16%), 6 of them (12%) were graded as borderline acute rejection, and all were steroid sensitive. The remaining 2 episodes (4%) were grade 2 and both required antithymocyte globulin therapy. Similar results were reported among patients in the control group. Two episodes were grade-2 acute rejection (4%) and necessitated antithymocyte globulin therapy. The remaining episodes were steroid sensitive.

Vitko and associates (9) reported a higher incidence of acute rejection in the experimental group using tacrolimus and mycophenolate mofetil as maintenance immunosuppression; this could be attributed to the absence of induction therapy. In spite of using basiliximab induction, they reported a decreased incidence of acute rejection to 26.1%; however, this is still higher than our incidence (16%).

Mean time to acute rejection was significantly lower in patients in the experimental group compared with those in the control group (1.88 vs 15 days, respectively, $P = .009$). The majority of acute rejection episodes in patients in the experimental group were diagnosed early, before we stopped administering steroids, a fact demonstrating that steroid stoppage was not responsible for these episodes.

Other studies have shown excellent patient and graft survival rates (100%) (10), with an absence of episodes of clinical acute rejection in steroid-free patients after a mean follow-up of 9 months. However, the main limitations of these studies are short follow-ups, small numbers of patients (n=10), and no control groups. Also, these studies demonstrated that even without corticosteroids, the

risk of acute rejection during the postoperative period can be minimized by the current immunosuppression (10, 11).

Our study differs from other large, prospective, randomized, controlled studies in that our renal transplant recipients were given tacrolimus in place of cyclosporine as a primary immunosuppressant agent. We withdrew steroids after a shorter time after transplant compared with other studies (3 days vs 90 days). Moreover, we used induction therapy for all patients (100% vs 16%-33%), and we used a longer follow-up than did the other study (1 year vs 6 months) (12).

Interestingly, steroids decrease the bioavailability of mycophenolate mofetil by increasing hepatic uridine diphosphate glucuronyl transferase activity. One study showed that when steroids were tapered or withdrawn, mycophenolate mofetil area under plasma concentration curves increased; that is when steroids were eliminated, there was more mycophenolate mofetil exposure, possibly resulting in fewer episodes of acute rejection (13). Another study showed that tacrolimus exposure also increased by 11% after withdrawal of 5 mg of steroid and by 36% after withdrawal of 10 mg of steroid. The significant increase in tacrolimus exposure after steroid withdrawal may, on one hand, counteract the reduction in immunosuppression intended by steroid withdrawal, and on the other hand, may result in an increase of serum creatinine, which could be misinterpreted as rejection (14). In our study, this was represented by a significant reduction of the mean tacrolimus dosage after steroid withdrawal in patients who were steroid free at all times during follow-up ranging from 51% in the first month to 30% at the end of 1 year, with lower mean tacrolimus dosages at the end of 1 year (0.053 mg/kg/d) in patients in the experimental group versus 0.068 mg/kg/day in patients in the control group.

Assessing the safety and efficacy of steroid-free immunosuppression treatment in live-donor renal allotransplant recipients was considered incomplete except after histologic evaluation of renal allograft tissue at the end of the study. In our study, estimating mean chronic allograft damage index scores at 1 year revealed comparable results in both groups.

Sarwal and associates (10) performed protocol biopsies for only 4 patients; 3 of whom had chronic tacrolimus toxicity that 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 and then 4 to 8 ng/mL thereafter. In our study, most patients in the experimental group stopped antihypertensive medications shortly after transplant, while 75% of hypertensive patients taking 1 drug before transplant in the control group required 3 drugs to control their hypertension by the end of the first year. A statistically significant between-group difference was found regarding the use of antihypertensive agents (Table 4, $P = .009$).

Our study showed a statistically significantly higher frequency of posttransplant diabetes mellitus among patients in the control group compared with patients in the experimental group (16% vs 4%). Our findings are in accord with the results of a study by Vitko and associates in 2005 (9) that found a 7% incidence of diabetes mellitus among steroid-free kidney transplant recipients treated with mycophenolate mofetil and tacrolimus; this incidence increased to 12% in the steroid-maintenance group.

We found that mean values for total serum cholesterol, triglyceride, and low-density lipoprotein levels were significantly higher among patients in the control group than they were in patients in the experimental group at 1 month and throughout the follow-up; this is attributed to steroid withdrawal. This is in agreement with other studies that show that a steroid-free immunosuppression regimen lowers blood lipid levels (9, 15). Our results are in agreement with those of other studies regarding improvements in cardiovascular risk factors such as that global cardiovascular risk factors decrease by 10% at 1 year posttransplant in renal transplant recipients who undergo early corticosteroid withdrawal (16).

The incidence of infectious complications from immunosuppression was significantly lower in patients in the experimental group. The incidence of hepatitis was relatively lower in patients in the experimental group; however, this result did not reach statistical significance. This could be explained by the role played by steroids in activating dormant viral hepatitis (16, 17).

Conclusions

In living-donor renal transplant recipients with low immunologic risk, steroid avoidance (ie, using basiliximab induction, tacrolimus, and mycophenolate mofetil maintenance) is feasible, safe, and provides fewer incidences of morbidity than does a standard immunosuppression regimen. Long-term follow-up is required to further prove the safety of this regimen.

References

1. Lemieux I, Houde I, Pascot A, et al. Effects of prednisone withdrawal on the new metabolic triad in cyclosporine-treated kidney transplant patients. Kidney Int. 2002;62(5):1839-1847.
2. Kasiske BL, Ramos EL, Gaston RS, et al. The evaluation of renal transplant candidates: clinical practice guidelines. Patient Care and Education Committee of the American Society of Transplant Physicians. J Am Soc Nephrol. 1995;6(1):1-34.
3. Matas AJ, Humar A, Gillingham KJ. Five preventable causes of kidney graft loss in the 1990s: a single-center analysis. Kidney Int. 2002;62(2):704-714.
4. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int. 1999;55(2):713-723.
5. Almawi WY, Melemedjian OK, Rieder MJ. An alternate mechanism of glucocorticoid anti-proliferative effect: promotion of a Th2 cytokine-secreting profile. Clin Transplant. 1999;13(5):365-374.
6. Miller J, Mendez R, Pirsch JD, Jensik SC. Safety and efficacy of tacrolimus in combination with mycophenolate mofetil (MMF) in cadaveric renal transplant recipients. FK506/MMF Dose-Ranging Kidney Transplant Study Group. Transplantation. 2000;69(5):875-880.
7. Birkeland SA, Larsen KE, Rohr N. Pediatric renal transplantation without steroids. Pediatr Nephrol. 1998;12(2):87-92.
8. Matas AJ, Kandaswamy R, Humar A, et al. Long-term immunosuppression, without maintenance prednisone, after kidney transplantation. Ann Surg. 2004;240(3):510-516; discussion 516-517.
9. Vítko S, Klinger M, Salmela K, et al. 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. 2005;80(12):1734-1741.
10. Sarwal MM, Yorgin PD, Alexander S, et al. Promising early outcomes with a novel, complete steroid avoidance immunosuppression protocol in pediatric renal transplantation. Transplantation. 2001;72(1):13-21.
11. Opelz G, Döhler B, Laux G; Collaborative Transplant Study. Long-term prospective study of steroid withdrawal in kidney and heart transplant recipients. Am J Transplant. 2005;5(4 Pt 1):720-728.
12. Vanrenterghem Y, Lebranchu Y, Hené R, Oppenheimer F, Ekberg H. Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. Transplantation. 2000;70(9):1352-1359.
13. Cattaneo D, Perico N, Gaspari F, Gotti E, Remuzzi G. Glucocorticoids interfere with mycophenolate mofetil bioavailability in kidney transplantation. Kidney Int. 2002;62(3):1060-1067.
14. van Duijnhoven EM, Boots JM, Christiaans MH, Stolk LM, Undre NA, van Hooff JP. Increase in tacrolimus trough levels after steroid withdrawal. Transpl Int. 2003;16(10):721-725.
15. Rogers CC, Alloway RR, Hanaway M, et al. Body weight alterations under early corticosteroid withdrawal and chronic corticosteroid therapy with modern immunosuppression. Transplant Proc. 2005;37(2):800-801.
16. Bahra M, Neumann UI, Jacob D, et al. MMF and calcineurin taper in recurrent hepatitis C after liver transplantation: impact on histological course. Am J Transplant. 2005;5(2):406-411.
17. Zekry A, Gleeson M, Guney S, McCaughan GW. A prospective cross-over study comparing the effect of mycophenolate versus azathioprine on allograft function and viral load in liver transplant recipients with recurrent chronic HCV infection. Liver Transpl. 2004;10(1):52-57.
18. Citterio F, Rigotti P, Scatà MC, et al. Steroid withdrawal from tacrolimus-based therapy in renal transplant patients. Transplant Proc. 2002;34(5):1707-1708.