Steroid resistant focal segmental glomerulosclerosis: effect of arterial hyalinosis on outcome: single center study

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Background. Few data with adequate evidence exists as regards the effect of Cyclosporine (CsA) and mycophenolate mofetil (MMF) on pathological prognostic parameters in patients with steroid resistant focal segmental glomerulosclerosis (FSGS). The purpose of the present study is to compare the effect of cyclosporin and mycophenolate mofetil in addition to steroids on functional and histopathologic renal parameters in patients with steroid resistant FSGS one year after treatment.

Material and methods. Thirty-seven adults with primary FSGS patients resistant to steroid therapy consecutively randomized to treatment with either MMF or cyclosporine. Low dose prednisolone added to both groups. Glomerular filtration rate (GFR) and blood pressure (BP) were determined at all examinations and a second renal biopsy was taken 12 months after treatment with either of cyclosporin and mycophenolate mofetil.

Results. GFR significantly increased in MMF group $p < 0.01$ after 6 months and unchanged after 12 months. On the other hand, GFR significantly decrease in CsA group $p < 0.001$ after 6 months and reduced more after 12 months $p < 0.001$ compared to base line levels. There was a significant difference of GFR between the 2 groups at 6 months $p < 0.001$. The extent of proteinuria decreased significantly in CsA group after 12 months $p < 0.001$. The extent of arteriolar hyalinosis increased significantly in CsA group (0.78 to 1.81 score, $p < 0.001$) but was unchanged in MMF group (0.93 to 0.96 score), whereas interstitial fibrosis increased to same level in both groups (grade 3).

Conclusion. Conversion to MMF in those patients may be superior to CsA as regards GFR after 12 months after treatment in spite of the presence of greater level of protein excretion. The increased arteriolar hyalinosis during CsA treatment most likely results in higher BP compared to MMF treatment in patients with FSGS resistant to steroids.

Key words: cyclosporine, focal segmental glomerulosclerosis, steroid, fibrosis, proteinuria.

INTRODUCTION

Cyclosporine (CsA) is widely used as an effective immunosuppressive agent treatment in clinical transplantation and to some extent in cases with focal segmental glomerulosclerosis (FSGS) [1, 2]. The results of treatment of FSGS have improved since the introduction of CsA [3], but its nephrotoxicity remain a severe problem [4, 5].

Calcineurin inhibitors (CNI) nephrotoxicity can cause acute kidney injury (AKI), which is reversible usually after dose reduction, or can progress to chronic kidney disease, which is usually irreversible [6]. Other renal effects of the CNIs include tubular dysfunction and, rarely, a thrombotic microangiopathy (TMA) [7]. MMF as antiproliferative agent can be used instead of CsA when contraindicated or intolerated [8].

Despite recommendations for treatment of steroid-resistant, FSGS mainly based upon observational, uncontrolled studies. Only few numbers of randomized controlled trials discussed the benefits

of CsA against other immunosuppression or against placebo with contradictory results and even in the latest KIDGO FSGS guidelines, recommendations are not supported by enough evidence [9], most existing data support the use of cyclosporine specially after categorization of FSGS as Podocytopathy. Recent evidence indicates that podocytes are a direct CNI target. [10].

Dual effect of CNI on podocyte was found as it inhibit nuclear factor of activated T-cells (NFAT) [10] essential for IL2 transcription and T-cell activation. CNI block the calcineurin-mediated dephosphorylation of synaptopodin, a molecule essential for the integrity of the podocyte actin cytoskeleton and for the regulation of podocyte migration [11, 12].

Few data with adequate evidence exists regards the effect of CsA and MMF on pathological prognostic parameters in patients with steroid resistant FSGS. The purpose of the present study is to compare the effect of CsA and mycophenolate mofetil (MMF) in addition to steroids on functional and histopathologic renal parameters in patients with steroid resistant

primary FSGS one year after treatment in a prospective randomized study.

MATERIAL AND METHODS

This article is based on a prospective single-centre randomized controlled study conducted in the Nephrology department, Cairo University Hospitals from July 2016 to January 2020. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Primary FSGS patients resistant to steroid therapy were consecutively randomized to treatment after they signed a written consent with either MMF and prednisolone (MMF group) or CsA and prednisolone (CsA group). Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) and statins were used in both groups when indicated and as tolerated. Other antihypertensive agents were allowed in our protocol.

Drug doses:

Prednisolone dose 0.1 mg/kg per day (maximum dose 15 mg/day).

CsA dose 4 mg/kg BW day (given in two divided doses) adjusted to maintain a whole blood trough level between 100 and 175 mcg/L).

MMF dose 1 gm BID.

Definitions:

Steroid resistance refers to little or no reduction in proteinuria after 12 to 16 weeks of adequate prednisone therapy in an adult, or to patients who have some reduction in proteinuria with more prolonged therapy who do not meet the criteria for partial remission.

Inclusion criteria: Adults aged between 18 and 70 years with primary FSGS diagnosed 12 months previously treated with steroids with or without angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs). Those patients never received CsA or MMF. Moreover, their serum creatinine was less than 2.5 mg/dl and their GFR > 40 ml/min per 1.73 m².

100% of our patients presented with nephrotic syndrome and proteinuria > 3.5 gm at the presentation. All patients were subjected to detailed history and clinical examination to exclude secondary causes of FSGS. Genetic form are excluded also as it occurs early in life with aggressive course.

Due to limited resources and high costs, the electron microscopy examination is done only in some selected cases if there is doubt of diagnosis and in those patients podocyte effacement was > 80%, which is consistent with diagnosis of primary FSGS.

Exclusion criteria were unwillingness to participate, collapsing variant of FSGS, histologic evidence of extensive glomerulosclerosis and interstitial fibrosis in the first biopsy, heart failure, cancer and pregnancy.

End-points: the change in arteriolar hyalinosis and interstitial fibrosis and tubular atrophy (IFTA) scores from baseline to 12 months after receiving either CsA or MMF, mean change in the urinary protein from baseline to 6 months and from baseline to 12 months, and the change in eGFR from baseline to 6 months and from baseline to 12 months, mean change in blood pressure measurements from baseline to 12 months.

Study Mandated Stop Points: as exclusion criteria in addition to need for dialysis, death and side effects of the drugs used.

Follow up periods: one year.

Examinations intervals: during the follow up period, the patients examined twice at 6, and 12 months.

GFR, blood pressure (BP) and 24-hour urinary proteins were determined at all examinations and a second renal biopsy was taken 12 months after treatment with either CsA or MMF.

GFR determination: was determined as plasma clearance of ⁵¹Cr-EDTA corrected to a standard body surface of 1.73 m². The tracer was given intravenously at 9 a.m. and four blood samples were drawn at 30 minutes intervals from 4 to 4 hours after injection for determination of the disappearance rate.

Percutaneous renal biopsies: were performed with a True-cut needles using ultrasound guidance.

Arteriolar hyalinosis was semi quantitatively determined on PAS- stained sections using a scale of 0 to 3+.

The score 0 used for arterioles appearing normal and 3+ for arterioles with severe hyaline wall thickening. Score 1+ signified a slight but significantly abnormal hyalinosis and Score 2+ was used for a marked but not maximal hyalinosis.

Interstitial fibrosis and tubular atrophy were estimated were graded semi quantitatively by hematoxylin and eosin (H&E), periodic acid-Schiff silver (PAS) and Trichrome-Masson stained section using the following categorize:

Grade 0: < 5%

Grade 1: 5- < 25%

Grade 2: 25- < 50%

Grade 3: > 50%

These estimate were performed blindly without the investigator's knowledge of the time of biopsy or the clinical or laboratory data of the patients studied.

Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data were summarized using mean and standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while non-parametrical Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. For comparing categorical data, Chi-square (χ^2) test was performed. An exact test was used instead when the expected frequency is less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. P-values less than 0.05 were considered as statistically significant.

RESULTS

A total of 37 patients with primary FSGS resistant to steroids were enrolled to this study. 100% of our patients presented with nephrotic syndrome and proteinuria > 3.5 gm at the presentation. There were 19 patients in MMF group and 18 patients in

CsA group. Six patients were excluded in MMF group and 5 patients excluded in CsA group.

Demographic features, some laboratory data and subtypes of FSGS are summarized in Table (1).

Comparison between groups showed a significantly higher GFR in MMF group than in CsA group after 6 months **p < 0.001**, but no significant difference in GFR at the start of the study or after 12 months (Table 2).

Comparison within groups showed that GFR significantly increased in MMF group (41 to 49 ml/min, **p < 0.01**) after 6 months and GFR was unchanged after 12 months (40 ml/min) compared to baseline level, **p = 0.4**. On the other hand, GFR significantly decreased in CsA group (42 to 37 ml/min, **p < 0.001**) after 6 months and reduced more after 12 months (35 ml/min), **p < 0.001** (Table 2).

Blood pressure was decreased in MMF group compared to CsA group after 12 months, **p > 0.05**. The extent of proteinuria decreased significantly in CsA group (4.81 ± 2.2 to 1.49 ± 0.8 gm/d, **p < 0.001**) after 12 months but was unchanged in MMF group (4.96 ± 1.89 to 3.75 ± 1.57 gm/d, **p** value was non significant) (Table 2).

The extent of arteriolar hyalinosis increased significantly (Table 3) in CsA group (0.78 to 1.81 score, **p < 0.001**) after 12 months but was unchanged in MMF group (0.93 to 0.96 score), whereas interstitial fibrosis increased to same level in both groups (grade 3 = >50%) (Table 4).

Table 1

Demographic features of groups studied at baseline

	CsA group	MMF group
Patients enrolled	18	19
Patients excluded	5	6
Total numbers	13	13
Age (years)	36 ± 4.5 y	39 ± 3.7 y
Male sex (N/%)	(10) 77%	(10) 77%
Hypertension	69%	66%
Systolic blood pressure	130 ± 20.1	129 ± 18
Use of ACEI or ARBs	84.6%	77%
Baseline GFR ml/min per 1.73 m^2	42	41
Serum albumin (g/dl)	2.8	2.9
Total cholesterol (mg/dl)	291	280
24 hour urinary proteins gm/d	4.81 ± 2.2	4.96 ± 1.89
FSGS pathology in renal biopsy:		
Perihilar	15.4%	7.8 %
Cellular	7.8%	15.4%
Tip	7.8%	15.4%
NOS	69%	61.4%

CsA = cyclosporine

MMF = mycophenolate mofetil

ACEI = angiotensin-converting enzyme inhibitors

ARBs = angiotensin receptor blockers

GFR = Glomerular filtration rate

FSGS = focal segmental glomerulosclerosis

NOS = no otherwise specific

Table 2

Parameters of studied groups at 6 and 12 months after CsA or MMF treatment

	GFR at baseline	GFR at 6 months	P value
CsA group	42	37	< 0.001
MMF group	41	49	< 0.01
	GFR at baseline	GFR at 12 months	P value
CsA group	42	35	< 0.001
MMF group	41	40	0.4
	CsA group	MMF group	P value
GFR at 6 months	37	49	< 0.001
GFR at 12 months	35	40	0.2
	UP at baseline	UP at 6 months	P value
CsA group	4.81 ± 2.2	4.3 ± 2.1	0.6
MMF group	4.96 ± 1.89	4.8 ± 2	0.4
	UP at baseline	UP at 12 months	P value
CsA group	4.81 ± 2.2	1.49 ± 0.8	< 0.001
MMF group	4.96 ± 1.89	3.75 ± 1.57	0.4
	BP at baseline	BP at 12 months	P value
CsA group	130 ± 20.1	129 ± 18.2	0.6
MMF group	129 ± 18	120 ± 15	0.3

CsA = cyclosporine

MMF = mycophenolate mofetil

GFR = Glomerular filtration rate

UP = urinary proteins

BP = blood pressure

Table 3

Arteriolar hyalinosis Score in renal biopsy of groups studied at 12 months after CsA or MMF treatment

	Arteriolar hyalinosis score at base line	Arteriolar hyalinosis score after 12 months	P value
CsA group	0.78	1.81	< 0.001
MMF group	0.93	0.96	0.6

Table 4

Interstitial fibrosis and tubular atrophy (IFTA) in studied groups

	IFTA score at base line	IFTA score after 12 months	P value
CsA group	≤ 25%	> 50%	< 0.001
MMF group	≤ 25%	> 50%	< 0.001
	CsA group	MMF group	P value
IFTA score at base line	≤ 25%	≤ 25%	0.9
IFTA score after 12 months	> 50%	> 50%	0.9

DISCUSSION

Our study is different from other trials that studied the effect of CsA or MMF in steroid resistant FSGS patients in many aspects, as our study is a prospective randomized controlled one focused on clinical, laboratory, and histopathological parameters.

Only adults were allowed to participate unlike other studies, which included both adults and children [13–18]. In addition, we included only steroid resistant primary FSGS cases unlike Choi MJ *et al.* [19], Day CJ *et al.* [20] who enrolled both steroid resistance and frequent relapsers.

The FSGS-Clinical trial (FSGS-CT) was a National Institutes of Health (NIH)-funded multicenter trial [13] and had several limitations, which make it underpowered to detect clinically significant benefits with cyclosporine. The overestimation of the benefit of immunosuppressive therapy is due to the wrong definition of steroid resistance as after only four weeks of glucocorticoid therapy with enrollment of patients with non-nephrotic proteinuria who generally have a good prognosis and are not considered for immunosuppressive treatment from the start. The number of enrolled subjects in their trial was smaller than anticipated; whereas the trial was designed to

include 500, only 138 patients were actually randomized. In addition, patients with secondary FSGS may be allowed to enrol due to lack of electron microscopy. This is potentially associated with lower overall response rate.

In this study, the two groups were comparable with regard to age, gender, serum creatinine, baseline GFR, BP, antihypertensive agents, steroids dose, and types of FSGS. Thus, the difference between the two groups studied must be attributed to the difference in immunosuppressive agent used i.e. CsA Vs MMF here.

Our study showed that continued CsA treatment (CsA group) for more than 12 months after steroid resistance resulted in a more marked arteriolar hyalinosis than if conversion to MMF had taken place (MMF group) with comparable interstitial fibrosis grade between the two groups. Comparison within groups between baseline level and after 12 months in our study showed a significant reduction in GFR in CsA group but unchanged in MMF group. However, comparison between groups showed a significant difference after 6 months as GFR increased in MMF group and decreased in CsA group.

Obliterative arteriolopathy and striped fibrosis are seen with both low-dose and higher-dose cyclosporine therapy. Despite this risk, patients with steroid-resistant focal segmental glomerulosclerosis (FSGS) may benefit from treatment with calcineurin inhibitors [10, 11, 12&21]. The reported response rates with cyclosporine therapy in steroid-resistant disease range from 20 to 70 percent. Low remission rate in some patients may be due to the fact that patients treated with cyclosporine have often already failed glucocorticoid therapy and may therefore have more severe disease [22].

Up-regulation of transforming growth factor beta (TGF- β) with release of aldosterone, activation of the renin-angiotensin-aldosterone system (RAAS), imbalance between vasoconstrictive and vasodilator factors and formation of free radicals play a significant role in acute CyA related arteriolopathy [7].

Low the intraglomerular pressure and the GFR caused by CsA due to afferent and efferent vasoconstriction may explain the significant improvement of protein excretion and the significant drop of proteinuria in CsA group in our study compared to MMF group [23].

Blood pressure decreased in MMF group compared to CsA group after 12 months. This is logic enough as the imbalance between vasoconstrictor and vasodilator cause an increase in vascular resistance which reflected clinically by an elevated plasma creatinine concentration and hypertension [24].

Some patients were excluded from our study due to loss of follow up after randomization or death of the patient. The collapsing variant was also excluded from our study because it is particularly associated with a worse prognosis, often considered a unique variant and usually related to HIV [25].

Most of our patients received ACEI or ARBs to reduce proteinuria, secondary hemodynamic damage and to slow progression of kidney diseases [26] and when indicated our patients received statins to decrease hyperlipidemia related to nephrotic syndrome or related to hyperlipidemia caused by cyclosporine itself as a side effect of the drug.

Iranian study reviewed the pathology of 50 patients with primary FSGS and found no significant association between the presence of interstitial fibrosis and the rate of renal impairment in those cases. In this study, the presence of mesangial hypercellularity and hyalinosis were prognostic factors for lower remission rate [27] but this study is different from our study. It enrolled all FSGS patients not only steroid resistant cases as our study. In addition, they did not mention the effect of drugs.

When they compared cyclosporine Vs mycophenolate mofetil in steroid resistant FSGS patients, Gipson DS *et al.* found no difference in rates of proteinuria remission between the studied groups [13], while Hogg RJ *et al.* [14] found improvement of proteinuria in both groups with reversible reduction in GFR in CsA group.

Choi MJ *et al.*, Cattran DC *et al.* and Montané B *et al.* [19, 28 & 15] had the same conclusion: MMF lowered proteinuria with stabilized renal function.

Study limitations

The limitations of this study are the small sample size, therefore, future studies are needed.

CONCLUSION

The increased arteriolar hyalinosis during CsA treatment most likely results in higher BP compared to MMF treatment in patients with FSGS resistant to steroids. Conversion to MMF in those patients may be superior to CsA as regard GFR after 12 months after treatment in spite of the presence of greater level of protein excretion.

Introducere. Există puține date despre efectul ciclosporinei (CsA) și al micofenolatului mofetil (MMF) asupra markerilor morfologici de prognostic la pacienții cu FSGS. Scopul studiului a fost de a compara efectul CsA și al MMF pe lângă terapia cu cortizon asupra parametrilor renali morfologici la pacienții cu FSGS, la un an după tratament.

Metode. 37 de pacienți adulți cu FSGS primară rezistentă la corticoterapie au fost randomizați la tratament cu MMF sau CsA. Doze mici de prednisolon au fost adăugate la ambele grupuri. GFR și tensiunea arterială au fost determinate la fiecare examinare și o biopsie renală a fost din nou prelevată la 12 luni de la tratament.

Rezultate. GFR a crescut la MMF după 6 luni și a rămas neschimbat după 12 luni. GFR a scăzut la grupul cu CsA după 6 luni comparativ cu nivelurile bazale. Proteinuria a scăzut semnificativ după 12 luni. Hialinoza arterială a crescut semnificativ la grupul cu CsA după 12 luni ($0,78-1,81$, $p < 0,001$), dar a rămas neschimbată în grupul MMF.

Concluzii. La pacienții ce au primit MMF, GFR pare să îmbunătățească la 12 luni după tratamentul cu CsA, deși nivelul proteinuriei a fost mai mare. Gradul mai mare de hialinoză în timpul tratamentului cu CsA pare să fie datorat nivelurilor mai mari ale TA comparativ cu pacienții tratați cu MMF.

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REFERENCES

- ADRIANA MUNTEAN AND MIHAI LUCAN. Immunosuppression in kidney transplantation. *Clujul Med.* 2013; 86(3): 177–180.
- KORBET SM. Treatment of primary FSGS in adults. *J Am Soc Nephrol.* 2012 Nov. 23(11):1769–76.
- LAURIN LP, GASIM AM, POULTON CJ, HOGAN SL, JENNETTE JC, FALK RJ, *et al.* Treatment with Glucocorticoids or Calcineurin Inhibitors in Primary FSGS. *Clin J Am Soc Nephrol.* 2016; 11(3):386.
- BURDMANN EA, ANDOH TF, YU L, BENNETT WM. Cyclosporine nephrotoxicity. *Semin Nephrol.* 2003; 23(5):465.
- NAIMISSA, ALEKSANDRA KUKLA AND HASSAN N. IBRAHIM. The over-exaggerated chronic nephrotoxicity of calcineurin inhibitors. *Arab Journal of Urology* (2012) 10, 169–174.
- WILLIAMS D, HARAGSIM L. Calcineurin nephrotoxicity. *Adv Chronic Kidney Dis.* 2006; 13(1):47.
- NAESENS M, KUYPERS DR AND SARWAL M. Calcineurin Inhibitor Nephrotoxicity. *Clin J Am Soc Nephrol.* 2009; 4:481–508.
- EKBERG H, TEDESCO-SILVA H, DEMIRBAS A, VÍTKO S, NASHAN B, GÜRKAN A, *et al.* Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med.* 2007; 357(25):2562.
- [GUIDELINE] Kidney Disease/Improving Global Outcomes. KDIGO Clinical Practice Guideline for Glomerulonephritis (GN). *Kidney Int.* June 2012. 2 suppl 2.
- SCHÖNENBERGER E, EHRICH JH, HALLER H, SCHIFFER M. The podocyte as a direct target of immunosuppressive agents. *Nephrol Dial Transplant* 2011; 26(1):18–24.
- FAUL C, DONNELLY M, MERSCHER-GOMEZ S, CHANG YH, FRANZ S, DELFGAAUW J, *et al.* The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008; 14(9):931–938.
- ASANUMA K, YANAGIDA-ASANUMA E, FAUL C, TOMINO Y, KIM K, MUNDEL P. Synaptopodin orchestrates actin organization and cell motility via regulation of RhoA signalling. *Nat Cell Biol* 2006; 8(5):485–491.
- GIPSON DS, TRACHTMAN H, KASKEL FJ, GREENE TH, RADEVA MK, GASSMAN JJ, *et al.* Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int.* 2011; 80(8):868.
- HOGG RJ, FRIEDMAN A, GREENE T, RADEVA M, BUDISAVLJEVIC MN, GASSMAN J, *et al.* Renal function and proteinuria after successful immunosuppressive therapies in patients with FSGS. *Clin J Am Soc Nephrol.* 2013 Feb; 8(2):211–8.
- MONTANÉ B, ABITBOL C, CHANDAR J, JOSÉ STRAUSS, GASTÓN ZILLERUELO. Novel therapy of focal glomerulosclerosis with mycophenolate and angiotensin blockade. *Pediatr Nephrol* 2003; 18:772.
- PONTICELLI C, RIZZONI G, EDEFONTI A, ALTIERI P, RIVOLTA E, RINALDI S, *et al.* A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. *Kidney Int.* 1993; 43(6):1377.
- NIAUDET P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French Society of Pediatric Nephrology. *J Pediatr.* 1994; 125(6 Pt 1):981.

18. LIEBERMAN KV, TEJANI A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *J Am Soc Nephrol*. 1996; 7(1):56.
19. CHOI MJ, EUSTACE JA, GIMENEZ LF, ATTA MG, SCHEEL PJ, SOTHINATHAN R, *et al*. Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int*. 2002; 61(3):1098.
20. DAY CJ, COCKWELL P, LIPKIN GW, SAVAGE CO, HOWIE AJ, ADU D. Mycophenolate mofetil in the treatment of resistant idiopathic nephrotic syndrome. *Nephrol Dial Transplant*. 2002; 17(11):2011.
21. DEEGENS JK, ASSMANN KJ, STEENBERGEN EJ, HILBRANDS LB, GERLAG PGG, JANSEN JLJ, *et al*. Idiopathic focal segmental glomerulosclerosis: a favourable prognosis in untreated patients? *Neth J Med* 2005; 63:393.
22. BANFI G, MORIGGI M, SABADINI E, FELLIN G, D'AMICO G, PONTICELLI C. The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. *Clin Nephrol* 1991; 36:53.
23. Ruggenti P, Perico N, Mosconi L, Gaspari F, Benigni A, Amuchastegui CS, Bruzzi I, Remuzzi G. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. *Kidney Int*. 1993; 43(3):706.
24. Scherrer U, Vissing SF, Morgan BJ, Rollins JA, Tindall RS, Ring S, Hanson P, Mohanty PK, Victor RG. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med*. 1990; 323(11):693.
25. LAURIN LP, GASIM AM, DEREBAIL VK, MCGREGOR JG, KIDD JM, HOGAN SL, *et al*. Renal Survival in Patients with Collapsing Compared with Not Otherwise Specified FSGS. *Clin J Am Soc Nephrol* 2016; 11:1752.
26. KORBET SM. Angiotensin antagonists and steroids in the treatment of focal segmental glomerulosclerosis. *Semin Nephrol* 2003; 23:219.
27. DIANA TAHERI, ALI CHEHREI, PARGOL SAMANIANPOUR, SHOHREH SADRARHAMI, AMMAR HASSANZADEH KESHTALI AND SHAHRZAD SHAHIDIE. The predictive role of histopathological findings in renal insufficiency and complete remission in a sample of Iranian adults with primary focal segmental glomerulosclerosis. *J Res Med Sci*. 2010 Jan-Feb; 15(1): 14–19.
28. CATTRAN DC, WANG MM, APPEL G, MATALON A, BRIGGS W. Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis. *Clin Nephrol*. 2004; 62(6):405.

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