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Review

Focal Segmental Glomerulosclerosis

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Introduction

Focal segmental glomerulosclerosis (FSGS) is a common type of glomerular disease that is responsible for 20-30% of cases with proteinuria in children and adults [1]. The etiology of idiopathic FSGS is unknown and it represents one of the leading causes of renal failure, with an increasing incidence over the last few years [2,3]. FSGS, minimal changes disease and mesangial proliferation are considered different histological patterns of idiopathic nephrotic syndrome [4]. The fact that FSGS was recognised in repeat biopsies of patients with minimal changes, 10 years after the original diagnosis and the presence of steroid-sensitivity in patients with FSGS, as well as steroid-resistance in patients with no sclerotic changes on adequate biopsies, suggest that FSGS and minimal changes disease might represent one disease [4]. However, the recent observation of parvovirus B19 and SV40 in the glomeruli of FSGS patients and the different patterns of cyclin-dependent kinase inhibitors expression, in minimal changes and FSGS, suggest that the latter represents a podocyte disease, totally different to minimal changes [4,5]. The disease is classified as primary, familial and secondary. Primary FSGS is the most common form, whereas, familial FSGS is also recognised in sporadic cases. FSGS is also observed secondary to reduction of renal mass or glomerular adaptation [reflux nephropathy and morbid obesity] as well as after HIV infection and heroin abuse (Table 1).

Table 1. Classification of FSGS

Primary (idiopathic)	
	Familial
	Secondary
A. Reduced renal mass / glomerular adaptation	
	reflux nephropathy
	renal dysplasia or unilateral renal agenesia
	oligomeganephronia
	morbid obesity
	sickle cell disease
	B. Secondary to hereditary nephropathies (s. Alport)
	C. HIV-associated nephropathy
	D. Heroin associated FSGS

Pathology and histological variants

The characteristic glomerular lesion is a focal segmental scar. The term focal means that only some glomeruli in the biopsy are involved, whereas, segmental refers to the involvement of only some lobules of any glomerulus [6]. The involved capillaries are obliterated and collapsed, whereas, in some cases, the scar contains areas of hyalinosis. However, serial three dimensional ultra thin sections showed more widely distributed disease than the observed in conventional light microscopy [7]. Chronic changes in the tubulointerstitial area are also common. IgM and C3 complement component are usually identified with immunofluoresence in the area of hyaline and scar whereas effacement of foot processes is recognised in the electron microscopy. Morphological variants of the disease; FSGS perihilar variant, FSGS not otherwise specified, cellular variant, tip lesion and collapsing FSGS have been described. Whether these variants represent differences in pathogenesis or severity of podocyte injury or tempos of histolopathologic evolution remains unclear [8].

Classic FSGS is characterized by the involvement of glomeruli, which are localized in the deeper cortex and juxtamedullary area, usually showing a perihilar scar. In many cases, the scar contains areas of hyalinosis that represent the remnants of subendothelial protein exudates in the obliterated capillaries [1].

Glomerular tip lesion is characterized by the presence of lesions (widening of capillary loops and foam cells) in the tubular pole of the glomerulus and lack of chronic tubulointerstitial disease. In repeat biopsies of patients with tip lesion, progression to other variants of FSGS has been described [9].

The cellular variant and its extreme form, the collapsing variant, are characterized by increased number of cells (podocytes) in Bowman's space. In collapsing glomerulopathy, severe collapses of the glomerular tuft that is surrounded by proliferating podocytes forming a 'pseudocrescent', is observed. Most of the proliferating cells overlie collapsed capillary loops, but in some cases, podocytes that have been detached from the basement membrane are found free in the Bowman's space [10,11]. Although the mature normal podocytes are not able to proliferate, podocytes in cellular and collapsing variant of FSGS regress to a fetal mesenchymal phenotype with proliferative capacity. The podocyte expression of proliferating cell nuclear antigen (PCNA), cyclin–dependent kinase inhibitor p21 and proliferation marker Ki-67, in cellular and collapsing variants, denotes a mitotic activity, which is not observed in mature podocytes or in cases with nephrotic syndrome due to minimal changes or membranous nephropathy [11]. This variant is more common in black and represents the main lesion of HIV associated nephropathy.

Pathogenesis

Although primary FSGS is considered a disease of podocytes, its pathogenesis remains largely unknown. Podocytes seem to have a unique response to injury, resulting in disruption of glomerular barrier and proteinuria. The early events of podocyte injury are characterized by

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alteration of molecular structutre at the slit diaphragm and effacement of foot processes, followed by re-organization of the actin cytoskeleton via induction of the podocyte α-actinin-4 molecule [11,12]. This results in perturbation of the attachment of podocytes onto the glomerular basement membrane by α3β1integrin, dystroglycan and podoplanin, leading to denudation of the basement membrane and collapse of the capillary loops. Finally, deposition of hyaline material and attachment of the parietal epithelial cells to the denuded glomerular basement membrane (GBM) occur with formation of synechiae and glomerular scar. These changes are irreversible and lead to the development of glomerulosclerosis and end-stage renal failure [12].

The recurrence of nephrotic syndrome in FSGS patients after renal transplantation and its remission after plasma exchange, the induction of proteinuria in rats with serum from patients with recurrent FSGS and the translocation of podocin and nephrin from the plasma membrane to the cytoplasm of human podocytes, cultured with plasma from nephrotic FSGS patients, suggest that glomerular permeability factors acting to podocytes are present in the plasma of nephrotic FSGS patients. Although the glomerular permeability factor(s) remain unkown, the induction of proteinuria in rats by elute from columns coated with staphylococcal protein A, used in plasma adsorption, suggests that a substance of molecular weight below 100,000 is involved [11,13].

Familial forms of FSGS are related to mutations of genes encoding nephrin, podocin, α-actinin-4, CD2AP, structural proteins of the slit diaphragm responsible for the integrity of glomerular barrier. Sporadic forms of the disease have been also identified. Nephrin mutations cause a severe form of nephrotic syndrome in newborns, known as 'Finnish type' nephrosis, because of its higher incidence (1 ever 8200 births) in Finland. Responsible gene is the NPHS1 gene, located on chromosome 19q13. Podocin mutations are responsible for the appearance of nephrotic syndrome in the early adulthood, inherited by autosomal recessive type and for sporadic forms of the disease. The responsible gene is the NPHS2 gene located on chromosome 1q25-31 and the most common mutation is the R138Q. Mutations of α-actinin-4 gene are located on chromosome 19q and result in the development of proteinuria in the adolescence or early adulthood, inherited by autosomal dominant type leading to chronic renal failure. Mutations of Wilms' tumor gene that is involved in activation of nephrin transcription have been also implicated in the development of FSGS in the spectrum of certain syndromes (Denys - Drash, Frasier syndrome). These familial forms of FSGS are steroid resistant and do not usually recur after renal transplantation [11,14].

Other causes of podocyte injury, responsible for secondary forms of the disease, are the presence of hyperfiltration and/or stretch in the glomeruli in remnant kidney model or in morbid obesity and reflux nephropathy, the presence of glomerular ischemia in ageing and hypertensive nephrosclerosis, the podocyte viral invasion in HIV associated nephropathy and the presence of toxic agents in heroin associated FSGS [11].

Clinical presentation

The presenting feature in all patients is proteinuria, which frequently results in nephrotic syndrome. Microscopic hematuria, arterial hypertension and renal insufficiency are other common manifestations [1,2]. Nephrotic syndrome is observed in about 75% of adult patients, microscopic hematuria in 40%, arterial hypertension in 43% and impaired renal function in 35% of patients, at presentation. Heavy proteinuria (>10 g/24h) is more frequently observed in patients with cellular or collapsing variant compared to classic FSGS [1,2]. Nephrotic syndrome of abrupt onset is a common manifestation of patients with glomerular tip lesion [90% of patients] and the remission rate after administration of corticosteroids is between that observed in minimal changes disease (80-90%) and classic FSGS (50-60%) [9].

Clinical course

The clinical course of primary FSGS varies, but it is particularly poor in patients with persistent nephrotic syndrome, leading to end-stage renal failure (ESRF) more than 50% of them over 10 years [1,15,16]. Apart from heavy proteinuria, other parameters related to a poor clinical outcome, are the presence of impaired renal function and arterial hypertension at presentation and severe histopathological involvement with glomerulosclerosis and interstitial fibrosis in the renal biopsy [1,15]. FSGS usually follows an indolent clinical course, in patients with normal renal function and remission of nephrotic syndrome with immunosuppressive treatment [1,15,16]. In a large retrospective study, ESRF was observed in 6% and 18% of patients with complete and partial remission after administration of immunosuppressive drugs and in 45% of patients with persistent nephrotic syndrome, over a follow-up period of 5 years [17]. No difference in the 10-year renal survival rate has been observed among patients with FSGS variants, who showed remission of nephrotic syndrome (more than 80%). However, in patients who do not enter remission, a worse renal survival rate has been desribed for patients with collapsing variant and tip lesion in comparison to the classic form of FSGS (21 and 25% vs. 49% respectively) [2].

Treatment

Various therapeutic regimens, including corticosteroids, cytotoxic drus, cyclosporin, ACE ihibitors and mycophenolate mofetil (MMF), have been tried in nephrotic patients, in order to achieve remission and delay of FSGS progression.

The usual therapeutic approach includes a prolonged course of corticosteroids (more than 16 weeks), that is followed by partial or complete remission of nephrotic syndrome in about 50-60% of patients [1,18]. In this regimen prednisolone is given in high doses (1 mg/kg BW/day) for 3-4 months and then is gradually tapered to a lower dose. This regimen was followed by a higher remission rate, compared to that observed with shorter duration of treatment (61% vs. 15% respectively) and with long-term preservation of renal function in 70% of the patients [18]. Others suggest an alternate day prednisolone regimen (2 mg/kg, max 120 mg/d) that is followed by the same remission rate and less side-effects. Since the mean time to remission is 3 months, cases with persistent nephrotic syndrome after administration of 1 mg/kg BW/day of prednisolone for 4 months are considered as steroid resistant [19]. Patients with impaired renal function (serum creatinine >1.3mg/dl) and/or heavy

proteinuria (>10g/24h) at presentation, as well as patients with severe tubulo-interstitial injury and those with cellular variant of the disease and hypercellulatity in more than 20% of the glomeruli, show more frequently steroid resistance. Familial forms of the disease are also steroid resistant. Although no significant difference in the remission rate of the nephrotic syndrome has been described among cases with FSGS variants with administration of corticosteroids, a trend towards more frequent remission was observed in patients with glomerular tip lesion [2,9].

Cytotoxic drugs, such as cyclophosphamide (2mg/kg/day) or chlorambucil (0.1-0.2mg/kg/day) for 8-12 weeks, have been used as initial treatment with steroids in about 20% of patients but more commonly in steroid - dependent or frequently relapsing nephrotic syndrome, as well as, in cases resistant to corticosteroids. No additional benefit to that of corticosteroids has been observed with administration of cytotoxic drugs as initial treatment. Although most of the available studies with administration of cytotoxic drugs in FSGS patients are retrospective with short-term follow-ups, an analysis of these studies showed that more than 70% of steroid-dependent patients show persistent remission with cytotoxic drugs [1,18]. In steroid resistant cases, cytotoxics are not particularly effective (remission in <25%). No additional benefit to that of prednisolone and cyclosporin was proved with the administration of chlorambucil in steroid resistant cases, whereas conflicting results have been reported with azathioprine [20].

Cyclosporin (CsA) has been used in steroid resistant cases and is followed by remission of nephrotic syndrome in 50-70% of patients [21,22]. CsA has a direct antiproteinuric effect, which is independent of changes of plasma factors, that increase glomerular permeability acting probably via increasing the negative charge content of glomerular basement membrane [23,24]. The major problems, with the administration of cyclosporin, are its potential nephrotoxicity and the large possibility of relapse of the nephrotic syndrome with discontinuation of the drug. CsA should not be used in patients with creatinine clearance below 60 ml/min and presence of chronic tubulointerstitial injury of moderate severity as well as at a dose higher than 5.5 mg/kgBW/day in order to avoid nephrotoxicity [19]. However, it shoud be given for at least 12 months after remission of nephrotic syndrome, followed by gradual tapering of the dose, in order to avoid relapses [25]. In a prospective study by Ponticelli *et al*., 45 patients (adults and children), with nephrotic syndrome resistant to treatment with steroids for 6 weeks, were randomised to either cyclosporin 5-6 mg/kg/day for 6 months followed by a gradual tapering of the dose for further 6 months or to supportive therapy [21]. A significantly higher percentage of CsA treated patients showed remission (59% vs. 16%), whereas about 40% of patients remained in remission one year after discontinuation of CsA [24]. In a prospective randomised trial by Cattran *et al*., 49 patients with steroid resistant nephrotic syndrome (mean duration of treatment 13-14 weeks) and well preserved renal function, were treated by prednisone 0.15 mg/kg/day and CsA 3.5 mg/kg/day or prednisone and placebo for 6 months. The administration of CsA was followed by remission of nephrotic syndrome, in most patients (70% vs. 4% in the controls) and better preservation of renal function, over a follow-up period of 4 years, as a decrease of 50% in baseline creatinine clearance was observed in 25% of treated patients and in 52% of the controls [22]. The median time to remission was 7 weeks. However, relapses of the nephrotic syndrome were observed in 40% of patients within the first year of follow-up [22]. It should be noted that some patients included in the first study might not be steroid-resistant, since prednisolone (1 mg/kg BW/day) was given for less than 16 weeks (only 6 weeks) before the initiation of cyclosporin. The mean time to remission of nephrotic syndrome with corticosteroids was 3 months and the majority of patients reached remission at 9 months from the beginning of treatment. Thus, at least 16 weeks of treatment with prednisolone >1 mg/kg BW/day is necessary in order to characterize the situation as steroid resistant [18,19].

Others have used CsA in combination to low prednisolone dose as initial treatment, in patients with borderline diabetes, obesity or osteoporosis, in order to avoid high doses of corticosteroids [26]. However, not many randomized prospective trials are available for the treatment of idiopathic FSGS. In our recent retrospective analysis, the effect of immunosuppressive treatment with prednisolone alone (1 mg/kg BW/day) or combination of lower prednisolone dose (0.5 mg/kg BW/day) with azathioprine (2 mg/kg BW/day) or CsA (3 mg/kg BW/day, in gradually reduced dose), was compared to that of conservative management [27]. The regimens with lower prednisolone dose were used in obese and borderline diabetic patients and in patients with bone disease. Deterioration of renal function was observed more frequently (35% vs. 8%) among patients treated conservatively whereas the administration of immunosuppressive drugs was followed by more frequent remissions of the nephrotic syndrome (75 vs. 30.7% of patients). Corticosteroids alone were followed by remission in 63% of patients, whereas, combination of lower dose of prednisolone with azathioprine and cyclosporin were followed by remission in 80 and 87% of patients, respectively [27]. Although the number of treated patients in each subgroup was small, the results of this study show that low-dose of prednisolone and cyclosporin might be a good choice as initial therapeutic approach, since it is followed by frequent remission of nephrotic syndrome and no serious side-effects. Relapses of the nephrotic syndome after discontinuation of CsA were observed in 20% of patients, with the gradual tapering of CsA [27]. Tacrolimus and sirolimus have been used in a small number of patients with steroid and/or cyclosporin dependent or resistant nephrotic syndrome with good results [28, 29]. However, the experien-ce is very limited and further research is required in particular for sirolimus that showed nephrotoxicity in some FSGS patients.

Mycophenolate mofetil has been used in some patients with frequently relapsing or resistant to corticosteroids, cytotoxic drugs and cyclosporin nephrotic syndrome. A reduction of proteinuria by 50% was observed in more than 40% of patients with resistant nephrotic syndrome, along with the preservation of renal function in patients with progressive renal insufficiency and a lack of serious side-effects [30,31]. In a recent prospective trial, MMF was not effective in children with steroid – resistant nephrotic syndrome, but in steroid-dependent cases it was equally effective to cyclosporin with less adverse reactions [32].

ACE inhibitors and angiotensin II receptor blockers have been given in FSGS patients for blood pressure control and reduction of proteinuria. The experience with these drugs is limited since long-term protection is not necessary in patients who go into remission with immunosuppressive drugs. However, administration of losartan (50 mg/day), in patients with nephrotic syndrome resistant to cortico-steroids and cytotoxic drugs, was followed by remission of proteinuria in some of them [33].

Plasma excange and plasma adsorption have been applied in patients with recurrence of the disease after transplantation and they are followed by remission of proteinuria, via removal of permeability factors [13]. In primary FSGS, plasma exchange has been tried in a limited number of patients with nephrotic syndrome resistant to immunosuppressive drugs with rather favorable results in remission of proteinuria [33].

In summary, patients with primary FSGS and proteinuria 0.5-2 g/24h, who have a favorable outcome, are usually treated only by ACE inhibitors. In patients with proteinuria of nephrotic range and reasonable renal function (serum creatinine <3 mg/dl) the initial treatment of choice is prednisolone (1 mg/kg BW/day for 4 months followed by gradual tapering of the dose for further 4 months). In patients with higher risk from increased steroid dose (obese, elderly, borderline diabetics etc.) cyclosporine (3 mg/kg BW/day) with or without a lower dose of corticosteroids can be used as initial treatment. In cases with frequently relapsing or steroid dependent nephrotic syndrome, a 2-3 month course of cytotoxic drugs is indicated, in order to obtain a more sustained remission, whereas, in steroid resistant cases, cyclosporin is effective in a large percentage of patients. ACE inhibitors can be used in cases with resistance to immunosuppressive drugs and MMF in cases resistant to other regimens.

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References

1. Korbet SM. Treatment of primary focal segmental glomerulosclerosis. *Kidney Int* 2002; 62: 2301-2310.
2. Chun MJ, Korbet SM, Scwartz M, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: Presentation, prognosis and response to therapy of the histologic variants. *J Am Soc Nephrol* 2004; 15: 2169-2177.
3. Kitiyakara C, Eggers P, Kopp JB. Twenty-one year trend in ESRD due to focal segmental glomerulosclerosis in the United States. *Am J Kidney Dis* 2004; 44: 815-25.
4. Meyrier A and Niaudet P. Minimal change and focal segmental glomerular sclerosis. In Oxford Text book of Clinical Nephrology (ed. A M Davison), pp 439-467. Oxford University Press 2005.
5. Li RM, Branton M, Tanawattanacharoen S, Falk R, Jennette JE, Kopp JB. Molecular identification of SV 40 infection in subjects and possible association with kidney disease. *J Am Soc Nephrol* 2002; 13: 2320-2330.
6. D' Agati VD. The many masks of focal segmental glomerulosclerosis. *Kidney Int* 1994; 46: 1223-1241.
7. Fogo A, Glick AD, Horn SL, Horn RG. Is focal segmental glomerulosclerosis really focal? Distribution of lesions in adults and children. *Kidney Int* 1995; 47: 1690-1695.
8. D'Agati VD, Fogo AB, Bruijn JA, Jennette JE. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004; 43: 368-382.
9. Stokes BM, Markowitz GS, Lin J, Valeri AM, D'Agati VD. Glomerular tip lesion: A distinct entity within the minimal change disease / focal segmental glomerulosclerosis spectrum. *Kidney Int* 2004; 65: 1690-1702.
10. Korbet SM and Schwartz MM. Primary focal segmental glomerulosclerosis: a treatable lesion with various outcomes. *Nephrology* 2001; 6: 47-56.
11. Meyrier A. Mechanisms of disease: Focal segmental glomerulosclerosis. *Nature Clin Pract Nephrol* 2005; 1: 44-54.
12. Asanuma K and Mundel P. The role of podocytes in glomerular pathobiology. *Clin Exp Nephrol* 2003; 7: 255-259.
13. Dantal J, Bigot E, Bogers W, Testa A, Kriaa F, Jaques Y, Hurault De Ligny B, Niaudet P, Charpentier B, Soulillou JP. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with reccurent nephrotic syndrome. *N Engl J Med* 1994; 33: 7- 14.
14. Tryggvason K, Patrakka J, Wartiovaara J. Hereditary proteinuria syndromes and mechanisms of proteinuria. *New Engl J Med* 2006; 354: 1387-1401.
15. Burgess E. Management of focal segmental glomerulosclerosis: Evidence - based recommend-ations. *Kidney Int* 1999; 55(Suppl. 70): S26-S32.
16. Cameron JS. Focal segmental glomerulosclerosis in adults. *Nephrol Dial Transplant* 2003; 18(Suppl 6):45-51.
17. Troyanov S, Wall C, Miller J, Scholey J, Cattran DC. Focal segmental glomerulosclerosis: Definition and relevance of a partial remission. *J Am Soc Nephrol* 2004; 16: 1061-1068.
18. Ponticelli C, Villa M, Banfi G, Cesana B, Pozzi C, Pani A, Passerini P, Farina, Grassi C, Baroli A. Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? *Am J Kidney Dis* 1999; 34: 618-625.
19. Meyrier A, Noel LH, Auriche P, Callard P, Collaborative Groups of the Societe de Nephrologie: Long-term renal tolerance of cyclosporin A treatment in adult idiopathic nephrotic syndrome. *Kidney Int* 1994; 45: 1446-1456.
20. Heering P, Braun N, Mullejans R, Ivens K, Zauner I, Funfstuck R, Keller F, Kramer BK, Schollmeyer P, Risler T, Grabensee B; German Collaborative Glomerulonephritis Study Group: Cyclosporine A and chlorambucil in the treatment of idiopathic focal segmental glomerulosclerosis. *Am J Kidney Dis* 2004; 43: 10-18.
21. Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, Ghio L, Lusvarghi E, Gusmano R, Locatelli F, Pascuali S, Castelani A, Della Casa-Alberighi O. A randomized trial of cyclosporin in

steroid-resistant idiopathic nephrotic syndrome. *Kidney Int* 1993; 43: 1377-1384.
22. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, Maxwell DR, Kunis CL. A randomized trial of cyclosporin in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. *Kidney Int* 1999; 56: 2220-2226.
23. Zietse R, Wenting GJ, Kramer P, Schalekamp MA, Weimar W. Effects of cyclosporin A on glomerular barrier function in the nephrotic syndrome. *Clin Science* 1992; 82: 641-650.
24. Cattran D, Neogi T, Sharma R, McCaRTHY E, Savin V for the North American Nehrotic Syndrome Group. Serial estimates of serum permeability activity and clinical correlates in patients with native kidney focal segmental glomerulosclerosis. *J Am Soc Nephrol* 2003; 14: 448-453.
25. Ponticelli C and Passerini P. The place of cyclosporin in the management of primary nephrotic syndrome. *Biodrugs* 1999; 12: 327-341.
26. Cattran DC. Cyclosporine in the treatment of idiopathic focal segmental glomerulosclerosis. *Semin Nephrol* 2003; 23: 234-241.
27. Goumenos D, Tsagalis G, El Nahas AM, Shortland JR, Davlouros P, Vlachojannis JG, Brown CB. The immunosuppressive treatment of focal segmental glomerulosclerosis: A five-year follow-up study. *Nephron Clin Pract* 2006; 104: c75-c82.
28. Duncan N, Dhaygude A, Owen J, Cairns TH, Griffith M, McLean AG, Palmer A, Taube D. Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. *Nephrol Dial Transplant* 2004; 19: 3062-3067.
29. Tumlin JA, Miller D, Near M, Selvaraj S, Hennigar R, Guasch A. A prospective open – label trial of sirolimus in the treatment of focal segmental glomerulosclerosis. *J Am Soc Nephrol* 2006; 1: 109-116.
30. Choi MJ, Eustace JA, Gimenez LF, Atta MG, Scheel PJ, Sothinathan R, Briggs WA. Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int* 2002; 61: 1098-1114.
31. Cattran DC, Wang MM, Appel G, Matalon A, Briggs W. Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis. *Clin Nephrol* 2004; 62: 405-411.
32. Mendizabal S, Zamora I, Berbel O, Sanahuja M, Fuentes J, Simon J. Mycophenolate mofetil in steroid/cyclosporine-dependent/resistant nephrotic syndrome. *Pediatr Nephrol* 2005; 20: 914-919.
33. Usta M, Ersoy A, Dilek K, Ozdemir B, Yavuz M, Gullulu M, Yurtkuran M. Efficacy of losartan in patients with primary focal segmental glomerulosclerosis resistant to immunosuppressive treatment. *J Int Med* 2003; 253: 329-334.
34. Feld SM, Figueroa P, Savin V, Nast CC, Sharma R, Sharma M, Hirschberg R, Adler SG. Plasmapheresis in the treatment of steroid-resistant focal segmental glomerulosclerosis in native kidneys. *Am J Kidney Dis* 1998; 13: 524.