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Efficacy of losartan in patients with primary focal segmental glomerulosclerosis resistant to immunosuppressive treatment

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Abstract. Usta M, Ersoy A, Dilek K, Özdemir B, Yavuz M, Güllülü M, Yurtkuran M (Uludağ University Medical School, Bursa, Turkey). Efficacy of losartan in patients with primary focal segmental glomerulosclerosis resistant to immunosuppressive treatment. *J Intern Med* 2003; **253:** 329–334.

Objectives. Angiotensin II may play an important role in the progression of renal disease. Currently, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are commonly used for renoprotection. To our knowledge, there is no study investigating this effect of angiotensin II receptor antagonists in patients with primary focal segmental glomerulosclerosis (FSGS) in the literature. The aim of this study was to evaluate the effects of losartan on proteinuria and renal function in patients with FSGS refractory to immunosuppressive treatment.

Design. Twenty-three normotensive patients with FSGS proven through renal biopsy were included in the study. Thirteen of them, five men and eight women, were given losartan in a dose of 50 mg day^{-1} during 12 months, and 10, four men and six women, were in the control group. Mean arterial blood pressure (MAP), 24-h urine protein excretion, serum total protein and albumin levels were determined just before the start of treatment as well as after 1, 6 and 12 months of the study. In addition, serum creatinine, creatinine clearence (CrCl), cholesterol and triglyceride levels were determined at the beginning and end of the study.

Results. Age, gender and baseline levels of proteinuria, serum albumin, total protein, creatinine, CrCl and MAPs were similar in the two groups. Nephrotic range of proteinuria was present in five of 13 patients (38.4%) in the losartan group and in four of 10 patients (40%) in the control group. In the losartan group, 24-h proteinuria had decreased from 3.6 ± 0.5 g to 2.3 ± 0.5 g after 1 month, to 2.4 ± 0.7 g after 6 months and to 1.9 ± 0.7 g after 12 months. In the control group, a significant increase in proteinuria compared with the baseline value was noticed after 12 months. Proteinuria levels were significantly higher in the control group than in the losartan group after 6 and 12 months. Whilst total protein and albumin levels increased in the losartan group, they did not change significantly in the control group. The total protein levels after 6 and 12 months, and albumin levels after 6 months were significantly higher in the losartan group than in the control group. No significant change was observed between the baseline and the 12-month creatinine and CrCl levels of the groups when intra- and inter-group comparisons were made. Furthermore, serum cholesterol levels of the losartan group were reduced significantly. The changes in MAP values did not reach significant levels in either of the groups. There was no correlation between the percentage changes in MAP and in proteinuria of the losartan group after 12 months.

Conclusions. Angiotensin II receptor antagonists may be an alternative therapy in FSGS patients who are resistant to immunosuppressive therapy.

Keywords: angiotensin receptor blockade, focal segmental glomerulosclerosis, losartan, proteinuria, treatment resistant.

Introduction

Primary focal segmental glomerulosclerosis (FSGS) is a clinicopathological entity defined by the presence of proteinuria, commonly in nephrotic range, and by segmental glomerular scars involving some but not all glomeruli [1]. Proteinuria is associated with a progressive loss of renal function. The clinical feature most often used to distinguish the clinical course of FSGS is the degree of proteinuria at the presentation of the disease. The presence of nephrotic range of proteinuria has been associated consistently with a poor outcome in primary FSGS patients, with 50% reaching end-stage renal disease (ESRD) within 6–8 years [2–6]. The presence of massive proteinuria (>10 g 24 h^{-1}) portends an even more 'malignant' course, with ESRD occurring within 3 years in the majority of patients [7]. Hypoproteinaemia, oedema and hyperlipidaemia are all results of proteinuria that play important roles in the progression of renal diseases.

The renal protective properties of angiotensin converting enzyme inhibitors (ACEI) and angiotensin II type 1 receptor antagonists (AT1A) have been satisfactorily investigated in patients with diabetic or nondiabetic glomerulopathy. However, there is no study that investigated the effect of AT1As on proteinuria and renal function loss in FSGS patients in literature. Therefore, our aim was to evaluate the effect of long-term losartan administration on urine protein excretion and renal function in FSGS patients who are resistant to immunosuppressive treatment.

Materials and methods

This study was conducted on normotensive patients with primary FSGS, refractory to immunosuppressive therapy, that were followed up by our nephrology outpatient clinic between January 1999 and March 2001. Patients receiving calcium channel blockers, ACEIs, diuretics, nonsteroid anti-inflammatory agents and albumin; patients with infections, hypotension, dehydration, hyperpotassaemia and thromboembolic complications, and those having a serum creatinine value higher than 3.5 mg dL^{-1} and CrCl <30 mL min^{-1} were excluded from the study. Informed consent was obtained from all patients before entry into the study.

Twenty-three FSGS patients were included in the study. The histopathological diagnoses of all patients were confirmed through renal biopsy. The immunosuppressive therapies consisted of corticosteroids (CS) alone or CS plus azathioprine or cyclophosphamide. The patients were followed and treated for 19.8 ± 11.3 months (range: 11–48); the immunosuppressive treatments of 21 patients were discontinued because of unresponsiveness to the therapy for at least 6 months. Of those who continued taking the drug, one was given a low dose of CS plus azathioprine, 50 mg day^{-1} and one cyclophosphamide, 100 mg day^{-1}, plus a low dose of CS.

The patients were divided into two groups using a table with randomized numbers. The factors of age, gender and proteinuria level were similar in the two groups. During 12 months, 13 patients received a daily dose of 50 mg losartan (losartan group) and 10 patients did not (control group). All patients had a standardized diet providing protein of approximately 1.5 g kg^{-1} day^{-1}. We did not change their dietary salt habits. In both groups, blood pressure, proteinuria, serum total protein and albumin were measured at the start of the study, and after 1, 6 and 12 months, and serum cholesterol, triglyceride, creatinine and CrCl values at the start and after 12 months.

The characteristics and pathological features of the groups were similar ($P > 0.05$, Table 1). At the initiation of the study, 24-h urine protein excretion ranged between 1.2 and 9 g day^{-1} in all patients. The outcome was defined as follows: complete remission when a stable reduction in urinary protein excretion

Table 1 Patient characteristics and renal biopsy features of the groups

	Losartan group ($n = 13$)	Control group ($n = 10$)
Patient characteristics		
Sex (M/F)	8/5	6/4
Mean age (years)	32 ± 10	32 ± 13
Scar location (%)		
Tip lesion	23	20
Hilar lesion	61.5	50
Intermediate lesion	46.1	30
Histopathologic findings (%)		
Hyalinosis	53.8	50
Cellular lesion	30.7	20
Mesangial IgM (diffuse)	7.7	–
Mesangial hypercellularity	61.5	50
Interstitial fibrosis	38.4	40

to ≤ 0.25 g 24 h^{-1} was observed, and partial remission when proteinuria ranged between 0.26 and <3 g 24 h^{-1} in the presence of stable renal function. Any side-effect of losartan was carefully recorded.

After the patients were allowed rest for 15 min, blood pressure (BP) measurements were made twice in supine position with a 5 min interval and their average was calculated. Mean arterial blood pressures (MAP) were calculated according to the formula diastolic [BP + (systolic BP−diastolic BP)/3)]. Proteinuria was evaluated in 24-h urine collection. Biochemical parameters (serum urea, creatinine, total protein, albumin, cholesterol and triglyceride) were measured with autoanalyser (Technicon autoanalyser, Technicon Instruments Corp., Tarrytown, NY, USA). The CrCl was studied in 24-h urine collection and calculated according to the following classical formula [urine creatinine (mg/dL) × 24-h urine volume (mL)]/[1440 (min) × serum creatinine (mg/dL)] and corrected according to body surface area (mL min^{-1}× 1.73 m^2).

Statistical analysis of the numerical variables was performed using Mann–Whitney *U*-test and Wilcoxon signed rank test. Pearson's *r*-test was used for the correlation analysis and Fisher's exact test for the comparison of the ratios. All numerical variables were given as mean ± standard error (SEM) and *P*-values <0.05 were considered significant.

Results

There were no significant differences between the two groups in baseline 24-h urine protein excretion, serum total protein, albumin, creatinine or MAP values (Table 2) ($P > 0.05$). As for proteinuria, nephrotic range was present in five of the 13 patients (38.4%) in the losartan group and in four of the 10 patients (40%) in the control group. All of them had oedema and hypoalbuminaemia. In the losartan group, we noticed a significant decrease in proteinuria level after 1, 6 and 12 months compared with the baseline values (Table 2, Fig. 1). Four of 13 patients achieved remission and five showed marked reduction in proteinuria. In two patients, proteinuria levels were below nephrotic range and in the other two they did not change. In the losartan group, a comparison of five cases with nephrotic range of proteinuria with eight cases who had nephritic range of proteinuria at the start revealed no significant difference in terms of complete and partial remission ($P > 0.05$). A significant increment in proteinuria levels was seen after 12 months in the control group and the percentage of patients with nephrotic range of proteinuria rose up to 60% (6/10). The proteinuria levels after 6 and 12 months were significantly higher in the control group than in the losartan group (Table 2, Fig. 1).

There was an increase in total protein and albumin levels in the losartan group. These changes were significant except for serum albumin levels after 1 month. In patients showing reduction in proteinuria with therapy, significant improvement in oedema was also noticed. The total protein and albumin levels after 6 months and total protein levels after 12 months were significantly higher in the losartan group than in the control group.

Table 2 The changes in mean arterial pressure (MAP), serum and urinary findings of both groups

	Baseline		After 1 month		After 6 months		After 12 months	
	Losartan	Control	Losartan	Control	Losartan	Control	Losartan	Control
MAP (mmHg)	91 ± 3.2	92 ± 3.7	86 ± 3.2	93 ± 3.3	92 ± 2.2	91 ± 3.3	94 ± 2.4	90 ± 4.0
Proteinuria (g day^{-1})	3.6 ± 0.5	3.4 ± 0.4	2.3 ± 0.5[a]	3.3 ± 0.6	2.4 ± 0.7[a]	4.6 ± 1.0[b]	1.9 ± 0.7[c]	6.6 ± 1.7[d,e]
CrCl (mL min^{-1})	68 ± 7	70 ± 4	–	–	–	–	65 ± 8	68 ± 5
Creatinine (mg dL^{-1})	1.33 ± 0.6	1.01 ± 0.1	–	–	–	–	1.4 ± 0.2	1.11 ± 0.2
T.Protein (g dL^{-1})	6.2 ± 0.2	5.6 ± 0.3	6.4 ± 0.2[d]	5.5 ± 0.3	6.5 ± 0.3[d]	5.6 ± 0.3[b]	6.7 ± 0.3[d]	5.5 ± 0.3[b]
Albumin (g dL^{-1})	3.3 ± 0.2	2.9 ± 0.2	3.4 ± 0.2	2.9 ± 0.3	3.7 ± 0.2[a]	2.7 ± 0.2[b]	3.7 ± 0.2[d]	2.8 ± 0.3
Cholesterol (mg dL^{-1})	233 ± 14	237 ± 20					171 ± 11[d]	249 ± 21[e]
Triglyceride (mg dL^{-1})	145 ± 15	178 ± 14					150 ± 24	187 ± 17

[a]$P < 0.01$, compared with baseline value. [b]$P < 0.05$, compared with same month value of other group. [c]$P < 0.001$, compared with baseline value. [d]$P < 0.05$, compared with baseline value. [e]$P < 0.01$, compared with same month value of other group.

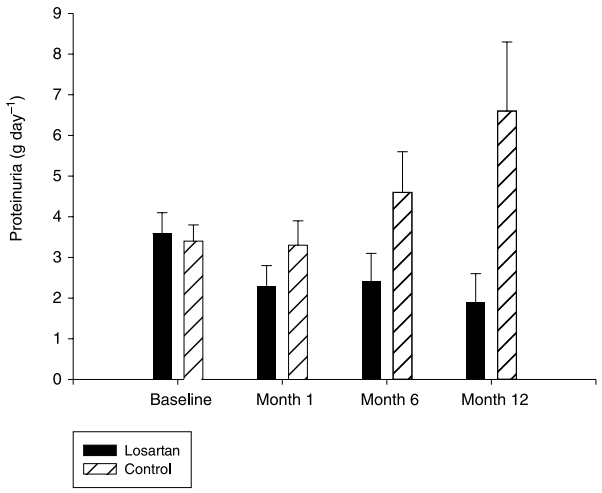

Fig. 1 The changes in proteinuria values of both groups during the study period.

Although an increase was noticed in mean serum creatinine in the losartan group, it did not reach statistically significant level ($P > 0.05$). No significant change was observed between the baseline and 12-month serum creatinine and CrCl values of the groups when intra- and inter-group comparisons were made ($P > 0.05$). Serum cholesterol levels were significantly reduced in the losartan group ($P < 0.01$). The changes in mean serum triglyceride levels of the losartan group, and in serum mean cholesterol and triglyceride levels of the control group were not significant ($P > 0.05$; Table 2).

The changes in MAP values did not reach significant levels ($P > 0.05$) in either of the groups. The changes observed after 12 months in the losartan and the control group were $5.3 \pm 6.0\%$ and $-1.2 \pm 4.8\%$, respectively, $P > 0.05$. In addition, there was no correlation between the percentage changes in MAP and in proteinuria of the losartan group ($r = 0.2251$, $P > 0.05$) after 12 months. The decrease in proteinuria values in the losartan group was negatively correlated with the increment in serum albumin levels ($r = -0.5648$, $P = 0.0443$). No side-effects such as hyperkalaemia, hypotension, cough, or acute renal failure were observed.

Discussion

Proteinuria is an independent risk factor for the progression of renal disease [8]. Control of proteinuria may be essential to prevent complications and morbidity associated with this disease, but whether reduction of proteinuria is the cause of a better prognosis or the result of favourable changes within the glomeruli is not clear. The CSs are the first line of treatment in FSGS patients with nephrotic syndrome. Patients who respond to CSs usually have a satisfactory renal prognosis, even in the long term. Those who suffer from frequent relapses or show steroid dependence may benefit from therapy with cytotoxic drugs or calcineurin inhibitors. Treatment of steroid-resistant patients remains difficult [9].

The ACE inhibitors are widely used for their antiproteinuric and renoprotective effects. Prasher *et al.* assessed the efficacy of enalapril in controlling the proteinuria in steroid-resistant idiopathic nephrotic syndrome and found that enalapril exerted a long-lasting effect [10]. All patients who responded to the treatment continued to have reduced levels of proteinuria during a follow-up of more than 6 months. Oedema disappeared and hypoproteinaemia and hypercholesterolaemia returned to normal in these 12 patients. Other authors have reported a similar effect [11, 12].

Clinical trials have demonstrated that AT1 blockers like ACE inhibitors reduce proteinuria [12–18]. Despite the dissimilar mechanisms of action, and the theory that enhanced bradykinin levels with ACE inhibition would facilitate better reduction of glomerular arteriolar dilatation [13], these two groups of drugs have been shown to similarly control both systemic and glomerular capillary pressure and to improve glomerular permselectivity to proteins, thereby reducing proteinuria. Moreover, they are similarly effective in attenuating both glomerulosclerosis and tubulointerstitial fibrosis [14–18]. However, Crenshaw *et al.* [19] reviewed demographic, biopsy and treatment data in the charts of all patients entering the ESRD programme with a primary diagnosis of FSGS. They found that neither the ACEIs nor the CSs had significant impact on the progression to ESRD. In our study, we included FSGS patients who had no or partial remission with CS or cytotoxic drugs. We observed that 1 year of losartan therapy caused a reduction in proteinuria compared with the control group. Of five patients with nephrotic syndrome one had complete remission, one had partial remission and two had proteinuria below the nephritic range. Of eight patients with nephritic range of proteinuria three had complete

remission and four had partial remission. Amongst 13 patients, the baseline proteinuria levels in those four who achieved complete remission after losartan therapy were 2.2 ± 0.4 g 24 h^{-1} and in the rest, 4.3 ± 0.7 g 24 h^{-1}. However, baseline proteinuria levels did not affect the response to treatment. No significant change was observed in proteinuria levels of two patients (9 and 2.8 g). These results may be affected by the small number of patients. In the control group, 24 h proteinuria levels were not changed significantly after 1 and 6 months compared with the baseline values, but a significant increment was seen after 12 months, especially prominent in three patients. Losartan treatment of these three started at the end of the study.

In a prospective, randomized, double-blinded multicentre trial, the GISEN group has reported that ramipril safely reduced proteinuria, and the rate of glomerular filtration rate (GFR) decline in patients with nondiabetic chronic nephropathies, and proteinuria by 3 g 24 h^{-1} or more [20]. In the follow-up study, the same group has demonstrated that ramipril reversed the tendency of GFR to decline over time [21]. An answer to the question, whether or not antiproteinuric effects of AT1As in the long term provide renal protection, was offered by two newly conducted multicentre studies [22, 23]. These studies demonstrated that AT1As significantly decreased the incidence of twofold elevation of serum creatinine and progression to ESRD in type 2 diabetes mellitus patients with hypertension and nephropathy when compared with placebo and/or amlodipine groups. Significant reduction in proteinuria was evident in both studies. As far as we know, our study is the first one evaluating the effects of losartan given to patients with FSGS during a 12-month period. Admittedly, the follow-up period was shorter than in the above-mentioned studies, but still it is worth noting that during these 12 months, no deterioration of renal functions was observed in patients given losartan. However, even in the control group, no deterioration in renal functions was observed. Therefore, the patients have to be followed up for a longer period to make it possible to verify an effect of losartan on the protection of renal function.

The superiority of renin–angiotensin system (RAS) blockade in providing renoprotection has been attributed to class-specific BP-independent mechanisms. In a recent study, Bidani *et al.* [24] demonstrated that RAS blockade provides renoprotection in the rat remnant kidney model of progressive glomerulosclerosis, primarily through BP-dependent and BP-independent mechanisms. However, we found that the decrease of proteinuria in the losartan group was independent of reduction in BP.

A significant decrease in proteinuria was observed in treated patients and an increase in nontreated ones after 1 year of follow-up. Although our study included a small group, we show that not only did AT1As decrease proteinuria, but they also preserved renal function during a 12-month period. However, our data do not support that AT1As preserve renal function in the long term. Longer follow-up period for this cohort of patients as well as other larger population studies will help clarify the renoprotective effects of AT1As. We still follow up our patients in the study group who are responsive to therapy. But already at this stage we believe that AT1As may be an alternative or adjuvant therapy in FSGS patients with nephritic or nephrotic syndrome who are resistant to immunosuppressive treatment.

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