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Effect of Losartan Treatment on the Proteinuria in Normotensive Patients Having Proteinuria due to Secondary Amyloidosis

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ABSTRACT

Secondary amyloidosis (AA amyloidosis) is a well known cause of nephrotic syndrome and renal failure. Several studies in patients with nephrotic syndrome have suggested a beneficial effect of angiotensin-converting enzyme inhibitors (ACEI). Angiotensin II (ATII) receptor antagonists effect on the long term is not known. In this study, we intended to study the effect of losartan, as an ATII receptor antagonist, on proteinuria and renal functions in patients with normotensive secondary amyloidosis. In total 44 patients with biopsy proven AA amyloidosis associated with nephrotic proteinuria were included. The first group of patients (n=22) was treated with losartan 50 mg/day. The second group of patients (n=22) did not receive any specific antiproteinuric treatment. Urinary protein loss was effectively lowered by losartan from 4.38±1.0 to 2.8±0.61 g/day ($p<0.0001$), whereas the control group showed a slight fall in proteinuria as 4.21±1.06 to 4.12±1.07 g/day ($p=0.176$). Hypoalbuminemia improved significantly from 2.52±0.69 to 2.78±0.46 g/dl ($p=0.004$), in the losartan group, whereas serum albumin had fallen in the control group from 2.44±0.57 to 2.27±0.41 ($p=0.041$). Serum creatinine increased in the control group from 1.52±0.42 to 2.39±0.51 mg/dl ($p<0.0001$), and in the losartan group from 1.59±0.50 to 1.84±0.6 mg/dl ($p<0.001$), after 24 months of treatment. The ATII receptor blocker losartan is effective in protecting against the progression of nephropathy due to AA amyloidosis. Symptomatic treatment of proteinuria with losartan is therefore to be considered, especially with severe proteinuria even in normotensive patients.

INTRODUCTION

Secondary amyloidosis (AA amyloidosis) is a well known cause of nephrotic syndrome and renal failure. The most common underlying conditions are inflammatory diseases such as familial Mediterranean fever, rheumatoid arthritis, or ankylosing spondylitis, and infections such as tuberculosis, or in association with bronchiectasis. Amyloid of the AA type has a tendency to localize in small vessels and parenchymal organs. Renal disease, often with the nephrotic syndrome and/or renal failure, is the chief manifestation and the major cause of death [4]. Several studies in patients with nephrotic syndrome have suggested a beneficial effect of angiotensin-converting

enzyme inhibitors (ACEI) on the evaluation of renal function accompanied by a clear reduction of proteinuria in most patients [3, 14]. Despite the recognised beneficial effects of ACEI on proteinuria in nephrotic syndrome, ATII receptor antagonists effect on the long term is not known. We designed a study to evaluate the long-term influence of losartan, an ATII receptor antagonist on proteinuria and renal function evaluation in patients with AA amyloidosis associated with nephrotic proteinuria in normotensive patients.

PATIENTS AND METHODS

All patients referred to our nephrology department and diagnosed as having AA amyloidosis during the period 1997–1999 were included in this study. We prospectively studied patients who met the following criteria: persistent nephrotic-range proteinuria (>3.5g/24h), normotension without using any antihypertensive drugs (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg). Patients with diabetes mellitus or systemic disease were excluded. Clinical diagnosis were Familial mediterranean fever (FMF) in twenty nine, bronchiectasia in six patients, tuberculosis in five, rheumatoid arthritis in two, and ankylosing spondylitis in two. The histological diagnosis of AA amyloidosis was made by the demonstration of amyloid deposits by Congo red staining on light microscopy. Potassium permanganate test for bleaching was performed to all amyloid positive materials. Potassium permanganate sensitive samples were evaluated as AA amyloid. Detailed history, physical examination and laboratory tests including white blood cell, erythrocyte sedimentation rate, serum urea nitrogen, creatinine, sodium, potassium, total protein, albumin, daily proteinuria were evaluated every three month. All patients were recommended to limit sodium intake and to eat 0.6–0.8 g protein/per kg/per day.

The patients were divided into two groups, losartan group included 22 patients (14 males, 8 females; aged 19–44 years, mean age 34.3±5.9 years), control group included 22 patients (14 males, 8 females; aged 17–41 years, mean age 32.2±4.3 years). The first group of patients were treated with losartan 50 mg/day. The second group of patients did not receive any specific antiproteinuric treatment.

During that period of treatment, other treatments that would change the course of the disease such as diuretics and albumin perfusion, were avoided. No change in the

Table 1. Patient characteristics

Parameter	Pretreatment values		Values after 24 months	
	Control group	Losartan group	Control group	Losartan group
Number	22	22	21	20
Sex (m/f)	14/8	14/8	13/8	13/7
Age	32.2±4.3	34.3±5.9	32.3±4.2	34.1±5.7
MAP (mmHg)	93.9±6.2	93.6±6.4	93.5±5.2	90.1±4.7
Proteinuria (g/day)	4.21±1.06	4.38±1.0	4.1±1.07	2.8±0.61
Serum creatinine (mg/dl)	1.52±0.42	1.59±0.50	2.39±0.51	1.84±0.6
Serum albumin (g/dl)	2.44±0.57	2.52±0.69	2.27±0.41	2.78±0.46

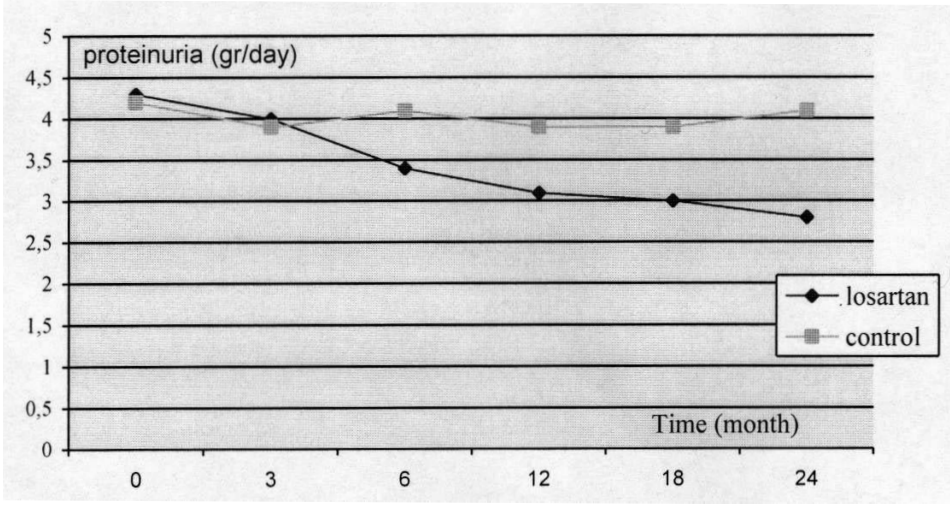

Fig. 1. The effect of losartan treatment on proteinuria over time

diet was then introduced during the study. Blood pressure was measured every three month with a standard mercury sphygmomanometer. Systolic and diastolic blood pressures were measured after 10 minutes of rest in a sitting position; the average of two measurements was recorded. Mean arterial pressure (MAP) was calculated as the diastolic blood pressure plus one third of the pulse pressure. Routine laboratory autoanalyser methods were used for measurements of biochemical parameters. Proteinuria was measured by the sulfosalicylic acid method. Adverse events were recorded at every visits.

To asses the effects of long-term antiproteinuric treatment on proteinuria and renal function all patients who continued treatment for 24 months were used for a prospective study. Of the 22 patients in the control group, one had died due to infection. From the losartan group sufficient data could be obtained from 21 patients of total 22 patients. The losartan had to be withdrawn in one patient because of hypotensive complaint at the end of six months.

Statistical method. Results are expressed as mean±standard error of the mean. Effect of treatment was tested for each parameter using Wilcoxon's test within groups, and Mann-Whitney U test between groups. That whether or not any relationship between the decrease of MAP and the decrease in proteinuria in losartan group was investigated by using Spearman's correletaion test. The level of significance was set at $p<0.05$.

RESULTS

The baseline demographic, clinical, and laboratory characteristics of the two groups were similar. In two groups patients predominance of males was observed, the outcomes for these patients are summarized in table 1.

Urinary protein excretion significantly fell from 4.38±1.0 to 2.8±0.61 g/day

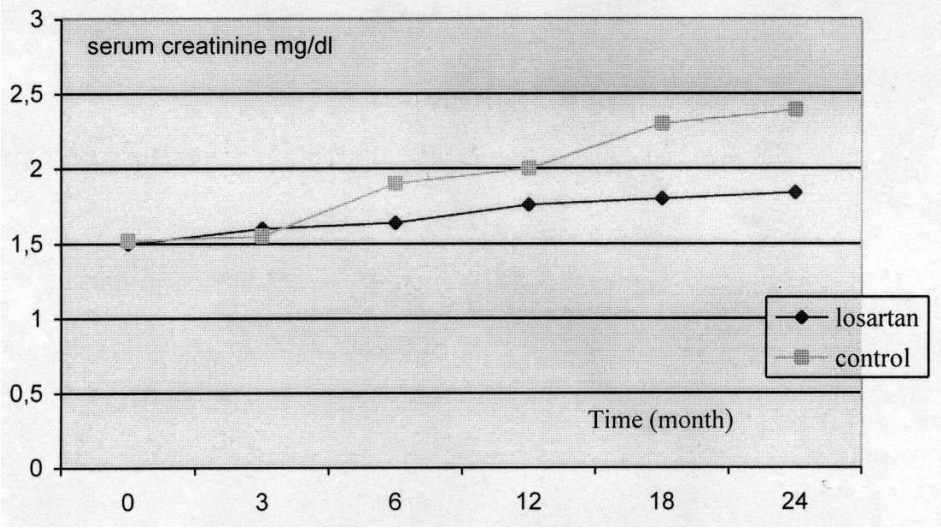

Fig. 2. The effect of losartan treatment on serum creatinine levels over time

($p<0.0001$) after 24 months of treatment of the losartan group (table 1). In the control group, urinary protein excretion also tended to decrease from 4.21±1.06 to 4.12±1.07 g/day ($p=0.176$). The decrease in proteinuria was found 36.1% in losartan group and 2.2% in control group. At the end of the period of treatment urinary protein leakage of losartan using group was significantly lower than control group ($p<0.0001$), (figure 1). On long-term evaluation serum creatinine increased in the losartan group from 1.59±0.50 to 1.84±0.6 mg/dl ($p<0.001$), and in the control group from 1.52±0.42 to 2.39±0.51 mg/dl ($p<0.0001$) after 24 months of treatment (figure 2). There was a statistical difference in serum creatinine levels between the two groups at the end of the treatment ($p<0.001$). There were no differences between pretreatment MAPs ($p=0.724$). However MAP fell in the losartan group from 94.5±6.0 to 89.04±4.3 mmHg ($p=0.004$) and in the control group from 93.9±6.2 to 93.5±5.2 mmHg ($p=0.572$). There was a statistical difference in MAP between the two groups at the end of the treatment ($p=0.005$). The decrease of proteinuria in the losartan group was independent from the decrease of MAP ($p=0.722$), ($r=–0.80$). The symptomatic treatment of proteinuria resulted in a significant rise in serum albumin concentration from 2.52±0.69 to 2.78±0.46 g/dl in the losartan group ($p=0.004$). Serum albumin fell in the control group from 2.44±0.57 to 2.27±0.41 ($p=0.041$).

Remissions, defined as a gradual fall in urinary protein excretion to less than 150 mg/day, occurred in one of the 22 patients in the losartan group. Preterminal renal failure, defined as a serum creatinine of more than 6 mg/dl, occurred in one of the 22 patients in the control group.

DISCUSSION

Nephrotic syndrome is the most common finding in secondary amyloidosis [4]. Curative treatment of these underlying diseases is not often possible. Symptomatic

treatment of the nephrotic syndrome has been achieved successfully with ACEI in several studies [3, 9, 12, 14].

Despite the recognized beneficial effects of ACEI and ATII receptor antagonists on proteinuria, their mechanism of action has not been elucidated yet. In patients with diabetic nephropathy, the control of blood pressure with ACEI and ATII receptor blockers helps to preserve the residual renal function by decreasing protein excretion [5, 8]. In our study, comprising the use of the ATII receptor blocker losartan, the proteinuria decreased significantly upon treatment with losartan compared to pre-treatment values. It has been showm that besides ACEI use in patients with nephrotic syndrome, a restricted protein intake decreases the progression of renal failure [7, 10]. Recently symptomatic treatment of the nephrotic syndrome was successfully completed with ATII receptor antagonists. Gansevoort et al [2], in a study of patients with proteinuria in nephrotic range , treated them with 50 mg per day as a single dose and made a follow-up after 4 months. At the end of 4 months of treatment, urinary protein excretion significantly decreased by 29%. Generally, in previous studies with ACEI and ATII receptor blocking agents, the patients had either resistant glomerulonephritis or diabetic nephropathy [13, 15]. In both situations, patients had hypertension as well. On the other hand, the cases of nephrotic syndrome due to amyloidosis are either normotensive or hypotensive [4]. All of our patients were normotensive and losartan treatment did not cause symptomatic hypotension except for one of our patients. In our study, a statistically significant difference was found in MAP between the initial value and that after 24 months of treatment in the losartan group. MAP had fallen from 93.6±6.4 mmHg to 90.1±4.7 mmHg after 24 months. Gansevoort et al. [2], as they gave losartan to patients, found that MAP decreased significantly and also, by increasing losartan dosage to 100 mg, the decrease in blood pressure did not continue. Furthermore, we found that the decrease in MAP was independent of the decrease in proteinuria during the treatment. This suggests that the decrease in proteinuria was not influenced by hemodynamic changes.

The interaction between the antiproteinuric and hemodynamic effects of ACEI is temporary [10]. The decrease in blood pressure is reaching maximum level in hours while it takes over 28 days for the antiproteinuric effect to reach its maximum. This shows that other mechanisms than pure hemodynamics are involved. Even though no change occurs in systemic blood pressure, a decrease is observed in proteinuria with the usage of these agents [1, 11]. It is a matter of debate whether ACEI as well as ATII antagonists have a negative influence on kidney functions by decreasing GFR while diminishing proteinuria.

Praga et al. [12], in a study with captopril at the end of their follow-up period of 24 months, divided their group into two subgroups one being treatment-responsive and the other treatment-resistant regarding the mean decrease in their proteinuria. The decrease in endogenous creatinine clearance was significant in the group that was treatment-responsive. In the study of Gansevoort et al [2]. with 50 and 100 mg/day of losartan , glomerular filtration rate was stable during the study. It is not known whether or not AT II antagonists that do not cause a decrease of GFR in the short term, will have advantages over ACEI when protecting kidney functions [6, 11, 16].

In our study, comprising 24 months albumin levels of our patients showed an increase compared to pre-treatment values. Only 8 patients had hypoalbuminemia at the beginning of the study, still 3 of them improved while another patient developed hypoalbuminemia. De Zeeuw et al. [1], in a study of 11 patients of non diabetic glomerulopathy using 50–100 mg of losartan, did not observe any change in serum albumin and total protein levels despite the significant decrease in proteinuria. We observed in the present study that losartan, an ATII antagonist, is effective and safe in preventing proteinuria in patients with nephrotic syndrome caused by amyloidosis.

In conclusion, proteinuria due to amyloidosis can be effectively lowered by losartan. Losartan treatment had a significant effect on renal function preservation. Symptomatic treatment of proteinuria with losartan is therefore to be considered, especially with severe proteinuria even normotensive patients.

REFERENCES

De, Zeeuw, D. D., Gansevoort, R. T., Dullaart, P. F. & De, Jong, P. E. Angiotensin II antagonism improves the lipoprotein profile in patients with nephrotic syndrome. Journal of Hypertension suppl 13:53–58, 1995.

Gansevoort, R. T., de, Zeeuw, D., Shahinfar, S., Redfield, A. & de, Jong, P. E.: Effects of the angiotensin II antagonist losartan in hypertensive patients with renal disease. J Hypertens Suppl 12:37–42, 1994.

Gansevoort, R. T., Heeg, J. E., Vriesendorp, R., de, Zeeuw, D. & de, Jong, P. E.: Antiproteinuric drugs in patients with idiopathic membranous glomerulopathy. Nephrol Dial Transplant Suppl 1:91–96, 1992.

Gertz, M. A. & Kyle, R. A.: Secondary systemic amyloidosis: response and survival in 64 patients. Medicine 70:246–256, 1991.

Hebert, L. A., Falkenhain, M. E., Nahman, N. S., Cosio, F. G. & O'Dorisio, T. M.: Combination ACE inhibitor and angiotensin II receptor antagonist therapy in diabetic nephropathy. Am J Nephrol 19:1–6, 1999.

Ichikawa, I.: Will angiotensin II receptor antagonist be renoprotective in humans? Kidney Int 50:684–692, 1996.

Kaysen, G. A., Gambertoglio, J., Jiminez, I., Jones, H. & Hutchinson, F. N.: Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int 29:572–577, 1986.

Lewis, E. J., Hunsicker, L. G., Bain, R. P. & Rahde, R. D.: The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. N Engl J Med 329:1456–1462, 1993.

Lewis, E. J., Hunsicker, L. G., Clarke, W. R., Berl, T., Pohl, M. A., Lewis, J. B., Ritz, E., Atkins., R. C., Rohde, R. & Raz, I.: Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851–860, 2001.

Orth, S. R. & Ritz, E.: The Nephrotic Syndrome. N Eng J Med 338:1202–1211, 1998.

Peters, H., Border, W. A. & Noble, N. A.: Angiotensin II blockade and low-protein diet produce additive therapeutic effects in experimental glomerulonephritis. Kidney Int 57:1493–1501, 2000.

Praga, M., Hernández, E., Montoyo, C., Andrés, A., Ruilope, L. M. & Rodicio, J. L.: Long-term beneficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria. Am J Kidney Dis 20:240–248, 1992.

Russo, D., Pisani, A., Balletta, M. M., De, Nicola, L., Savino, F. A., Andreucci, M. & Minutolo, R.: Additive antiproteinuric effect of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. Am J Kidney Dis 33:851–856, 1999.

Thomas, D.M., Hillis, A.N., Coles, G.A., Davies, M. & Williams, J.D.: Enalapril can treat the proteinuria of membranous glomerulonephritis without detriment to systemic or renal hemodynamics. Am J Kidney Dis 18:38–43, 1991.

Weidmann, P., Boehlen, L. M. & Courten, M.: Effects of different antihypertensive drugs on human diabetic proteinuria. Nephrol Dial Transplant 8:582–584, 1993.

Zoccali, C., Valvo, E., Russo, D., Panichi, V. & Zuccala, A.: Antiproteinuric effect of Losartan in patients with chronic renal diseases. Nephrol Dial Transplant 12:234–235, 1997.

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