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Effects of Ramipril and Valsartan on Proteinuria and Renal Function in Patients with Nondiabetic Proteinuria

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A B S T R A C T

The renin-angiotensin system is involved in the progression of chronic renal disease of both diabetic and nondiabetic origin. The angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have been demonstrated to reduce urinary protein excretion and attenuate the development of renal injury. This prospective, randomized, 12-month study assessed the effects of ramipril (N=23) vs. valsartan (N=22) vs. combination of ramipril and valsartan (N=26) on proteinuria, renal function and metabolic profile in 71 patients with nondiabetic proteinuria with normal or slightly impaired renal function. Monotherapy with ramipril or valsartan and combination of these two drugs significantly reduced proteinuria, serum creatinine, cholesterol and triglycerides as well as systolic and diastolic arterial blood pressure. There was no significant difference among three study groups according to reduction of arterial blood pressure, serum cholesterol and triglycerides. At one year, a significant reduction in serum creatinine was recorded in all three study groups, whereas at 3 and 6 months a statistically significant reduction in serum creatinine was only observed in patients on combination therapy. In addition, at 3 months the reduction of proteinuria was significantly greater in patients on combination therapy than in those on either monotherapy. These results indicated the combination therapy with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers to be more efficacious than either monotherapy in reducing proteinuria and serum creatinine level in the first 3 (proteinuria and serum creatinine) or 6 (serum creatinine) months of treatment.

***Key words**: angiotensin-converting enzyme inhibitors, angiotensin II receptors blockers, proteinuria, renoprotection*

Introduction

Many experimental and clinical data have shown that the renin-angiotensin-aldosterone system (RAAS) has an important role in the progression of nondiabetic renal disease[1–5]. Of the various mechanisms that contribute to renal function deterioration, hypertension has an important role[6]. Angiotensin-converting enzyme (ACE) inhibitors are more efficacious than conventional antihypertensive drugs in delaying the progression of nondiabetic renal disease. The renoprotective effects of ACE inhibitors are independent of their systemic antihypertensive action and are related to their antiproteinuric properties[6–11]. Despite administration of the maximal dose of ACE inhibitors, the reduction of proteinuria varies among different individuals, which can lead to different outcomes. Even the patients that initially benefit from the renoprotective properties of ACE inhibitors can deteriorate suddenly after a period of several years with impairment of renal function. These findings suggest that monotherapy with ACE inhibitors is insufficient for complete inhibition of the RAAS, which would prevent or halt the progression of nondiabetic renal disease. It has been shown that long-term therapy with ACE inhibitors does not completely reduce angiotensin II production. Angiotensin II is also synthesized by chymase, a pathway not regulated by ACE inhibitors. Because of the generation of angiotensin II *via* non-ACE pathways, monotherapy with an ACE inhibitor may result in suboptimal blockade of the RAAS, even at maximally effective dose[12,13]. On the

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other hand, blocking the angiotensin II type 1 receptor by angiotensin II receptor blocker (ARB) monotherapy results in a compensatory rise in renin and consequently in angiotensin II, with so far unknown consequences. Combined therapy may decrease angiotensin II production by inhibiting ACE activity and antagonize the effects of chymase-produced angiotensin II by blocking the angiotensin II receptors. Some authors demonstrated the progressive antiproteinuric and renoprotective effects of ACE inhibitor and ARB combination in patients with nondiabetic proteinuric nephropathy[14–18]. We postulated that complete inhibition of the RAAS would be most beneficial in the management of progressive nondiabetic renal disease. This might be achieved by dual blockage with ARB and ACE inhibitors. In this prospective, randomized study we investigated the effect of ACE inhibitor and ARB as monotherapy and combination therapy on proteinuria and renal function in patients with significant nondiabetic proteinuria.

Patients and Methods

This single-center, prospective, randomized, open-label, parallel group, comparative study evaluating renal effects of therapy with ramipril, valsartan, or a combination of ramipril and valsartan included 75 patients with nondiabetic renal disease and proteinuria ≥0.5 g/day. All patients gave their written informed consent to participate in the study, which was approved by the local Ethics Committee. Between February 2001 and May 2003, consecutive renal patients were screened for inclusion and exclusion criteria. Patients were selected from our renal department. Out of 75 patients screened, four were excluded from the study (two patients continued their dialysis treatment, one patient withdrew from the study on his own decision, and one patient died due to amyloidosis). Inclusion criteria were age 18–60, nondiabetic nephropathy established by patient history, physical examination, urinalysis, serum biochemistry tests and renal biopsy (in most patients), and persistent proteinuria ≥0.5 g/day for a minimum of 3 months after first visit, without evidence of urinary tract infection or heart failure. Patients were examined monthly by nephrologist for the first 6 months, then every 3 months. At each visit, physical examination and laboratory tests including blood cell count, blood chemistry and urinalysis were done according to standard laboratory procedures. The primary endpoint of the study was to assess the glomerular filtration rate (GFR). GFR was determined at baseline, and at 3, 6 and 12 months using the Gault-Cockroft equation. Secondary objectives were to assess long-term effects of therapy with ramipril or valsartan or their combination on the grade of proteinuria, arterial blood pressure, serum creatinine, cholesterol and triglycerides. Exclusion criteria were treatment with nonsteroidal anti-inflammatory drugs, renal failure, acute myocardial infarction or stroke, severe uncontrolled hypertension, chronic pulmonary disease, evidence or suspicion of renovascular disease, obstructive uropathy, diabetes mellitus, cancer, pregnancy, and infectious disease. Before enrollment, the wash-out period was 4 weeks in patients taking ACE inhibitors or ARB and 2 weeks in patients without antihypertensive treatment. Upon initial screening, patients were randomized into three groups: patients initially prescribed 5 mg/day ramipril (group 1); patients initially prescribed 80 mg/day valsartan (group 2); and patients treated with a combination of ramipril and valsartan in equivalent dosage, depending on blood pressure values (group 3). After 4 weeks, the dose of ramipril and valsartan was increased to 10 mg and 180 mg once daily (only a few patients), respectively, if blood pressure exceeded the target systolic blood pressure of <140 mm Hg and diastolic blood pressure of <90 mm Hg. Additional antihypertensive agent other than ACE inhibitors or ARB was urapidil, which was prescribed to achieve the target blood pressure control. None of the patients were on calcium channel blockers, which may affect proteinuria, and all had well-controlled blood pressure during the study period. Patients were also administered lipid-lowering drugs. All patients received advice on low sodium diet. Patients with various glomerular diseases were additionally treated with standard protocols as necessary. Only five patients were receiving diuretics (2 patients on ramipril, 2 patients on valsartan, and 3 patients on combination therapy) to control edema; the dosage was reduced after several months of treatment as the edema decreased. The study was conducted simultaneously in all three groups and patients were evaluated at the beginning of the study and at 3, 6 and 12 months of therapy introduction by medical history, clinical examination, blood pressure, proteinuria in 24-h urine sample, serum creatinine, creatinine clearance, serum cholesterol and triglyceride determination. At the end of baseline and each active treatment phase, sodium excretion was assessed in complete 24h urine collection. All patients were given advice on low salt diet. Randomization codes were kept in a sealed envelope for each study patient and were opened upon completion of the inclusion criteria.

Statistics

Changes in daily urinary protein excretion, blood pressure, serum creatinine, cholesterol and triglycerides were analyzed by repeated-measures ANOVA. Baseline characteristics were compared by Kruskal-Wallis and Mann-Whitney tests, t-test and χ^2-test. Analyses were done with the SPSS for Windows software. Statistical significance was set at $p<0.05$.

Results

Patient characteristics at therapy introduction are shown in Table 1. There was no significant difference among the three therapeutic groups according to age, systolic and diastolic blood pressure, level of proteinuria, serum creatinine, creatinine clearance, serum triglycerides and cholesterol. Renal biopsy was performed in 49 patients. Membranous nephropathy was present in 18, focal segmental glomerulosclerosis in 12, IgA nephropa-

TABLE 1
BASELINE CHARACTERISTICS AND LABORATORY FINDINGS ($\overline{X}$±SD) OF 71 PATIENTS WITH NONDIABETIC PROTEINURIA

	ACEI	ARB	ACE + ARB
Number of patients	23	22	26
Age (years)	46.3±16.4	47.4±16.9	46.1±18.3
Systolic blood pressure (mmHg)	138.7±19.8	145.7±26.8	148.5±19.4
Diastolic blood pressure (mmHg)	87.4±10.1	88.2±10.4	91.0±10.1
Proteinuria (g/day)	4.9±6.5	3.7±3.9	5.5±6.1
Creatinine (μmol/L)	109.6±97.6	104.5±45.8	111.7±79.8
Creatinine clearance (mL/min)	73.8±36.8	78.2±33.6	74.3±34.2
Triglycerides (mmol/L)	2.7±1.5	2.6±1.3	3.0±1.2
Cholesterol (mmol/L)	7.4±2.6	6.7±2.4	7.9±2.7

$\overline{X}$ – mean, SD – standard deviation, ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker

TABLE 2
RENAL BIOPSY HISTOPATHOLOGY (NUMBER OF PATIENTS)

	ACEI	ARB	ACEI + ARB
Membranous glomerulonephritis	6	5	7
Focal segmental glomerulosclerosis	5	3	4
Membranoproliferative glomerulonephritis	2	1	1
Mesangioproliferative glomerulonephritis	2	3	1
Post streptococcal glomerulonephritis	0	0	1
IgA nephropathy	2	2	1
Minimal change disease	0	1	1
Nephronophthisis	1	0	0
Total	18	15	16

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker

thy in five, mesangioproliferative glomerulonephritis in six, membranoproliferative glomerulonephritis in four, minimal change disease in two patients, and post-streptococcal glomerulonephritis and chronic glomerulonephritis in one patient each (Table 2). Twenty three patients were treated with ramipril, 22 with valsartan, and 26 with ramipril + valsartan. There was a statistically significant correlation between follow-up periods (points of measurement) and level of proteinuria in all three groups. Proteinuria decreased with the length of treatment ($p<0.001$ at 3 months; $p<0.01$ between 3 and 6 months; and $p<0.001$ between 6 and 12 months) (Figure 1). There was a statistically significant effect of treatment on the level of proteinuria. At 3 months, patients on combination therapy had a significantly greater decrease in proteinuria than patients on monotherapy ($F_{(2,60)}=3,565$; $p<0.05$). There was no statistically significant difference in the mean sodium excretion among the three patient groups. The mean serum creatinine decreased with time in all three groups ($F_{(1.7,66)}=8,125$; $p<0.001$) (Figure 2). There was no statistically significant effect of the type of therapy on serum creatinine at one year ($F_{(2,66)}=0,429$; $p>0.05$), but a statistically significant correlation between the type of therapy and point of measurement was recorded at 3 and 6 months ($F_{(3.5,66)}=2,203$; $p<0.05$). In the group on combination therapy, a significant decrease in serum creatinine was recorded between successive points of measurement to up to 6 months (between therapy introduction and 3 months;

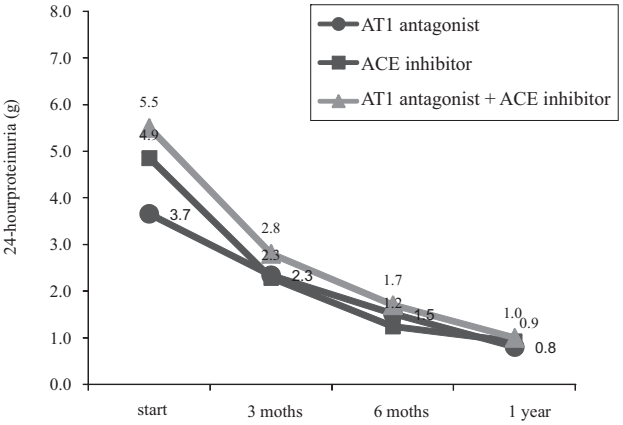

Fig. 1. Mean 24-hour protein excretion at four points of measurement in three patient groups. AT1 antagonist – angiotensin II receptor blocker, ACE – angiotensin converting enzyme.

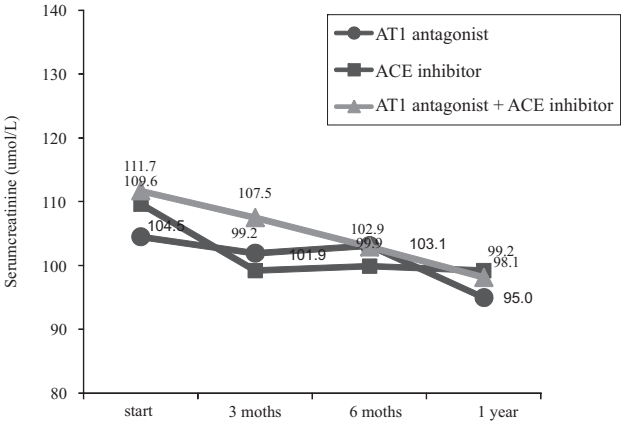

Fig. 2. Mean serum creatinine values at four points of measurement in three patient groups. AT1 antagonist – angiotensin II receptor blocker, ACE – angiotensin converting enzyme.

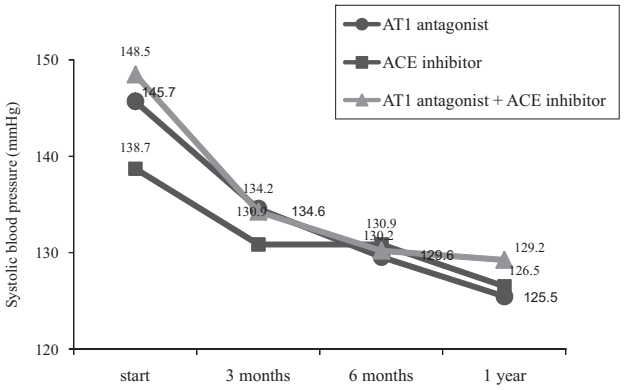

Fig. 4. Mean systolic blood pressure at four points of measurement in three patient groups. AT1 antagonist – angiotensin II receptor blocker, ACE – angiotensin converting enzyme.

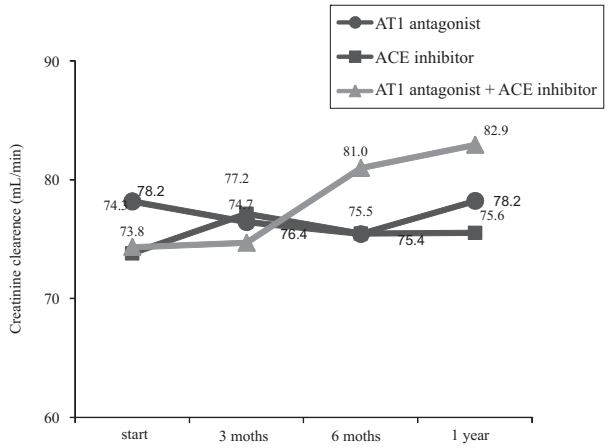

Fig. 3. Mean creatinine clearance values at four points of measurement in three patient groups. AT1 antagonist – angiotensin II receptor blocker, ACE – angiotensin converting enzyme.

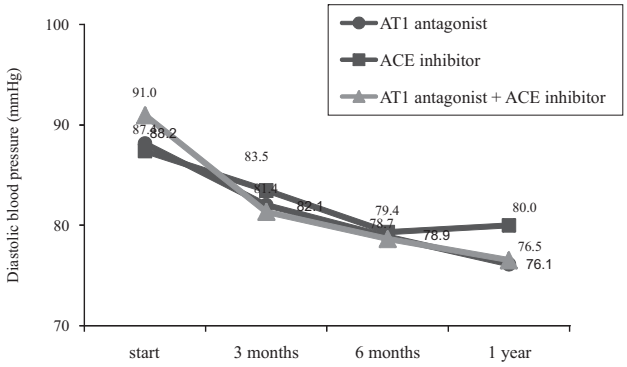

Fig. 5. Mean diastolic blood pressure at four points of measurement in three patient groups. AT1 antagonist – angiotensin II receptor blocker, ACE – angiotensin converting enzyme.

between 3 and 6 months; and between 6 and 12 months, $p<0.05$ all). In patients on monotherapy, only the difference in serum creatinine measured at therapy introduction and at one year was statistically significant ($p<0.01$), whereas the difference in serum creatinine between therapy introduction and 3 months, and between 3 and 6 months did not reach statistical significance ($p>0.05$). At follow-up measurements, the mean creatinine clearance increased from the baseline value, but the difference was not statistically significant (main effect of repeat measures $F_{(3,66)}=1,33$; $p>0.05$; main effect of therapy ($F_{(2,68)}=444.87$; $p>0.05$) (Figure 3). There was no significant difference among study groups according to baseline systolic blood pressure. Systolic blood pressure decreased significantly with the time of measurement ($F_{(1.8,68)}=29.425$; $p<0.001$) (Figure 4). Systolic blood pressure decreased continuously with time in all three groups, except for the period between 3 and 6 months ($p<0.001$ between therapy introduction and 3 months; $p>0.05$ between 3 and 6 months; and $p<0.05$ between 6 and 12 months). The type of therapy had no statistically significant effect on the systolic blood pressure decrease ($F_{(2,68)}=0.623$; $p>0.05$). There was no significant difference among study groups according to baseline diastolic blood pressure. Diastolic blood pressure decreased significantly with the time of measurement in all three patient groups ($F_{(2.3,68)}=37.831$; $p<0.001$) (Figure 5). Therapeutic effect appeared to have reached maximum at 6 months in all three groups ($p<0.001$ between therapy introduction and 3 months; $p<0.05$ between 3 and 6 months; and $p>0.05$ between 6 and 12 months), with no statistically significant difference among the groups ($F_{(2,68)}=0.282$; $p>0.05$). Thus, both systolic and diastolic blood pressure significantly decreased with time in all 3 groups. In all three groups, the peak therapeutic effect on diastolic blood pressure was achieved at 6 months and on systolic blood pressure at one year (Figures 4 and 5). A statistically significant decrease was recorded in total serum cholesterol ($F_{(1.9,68)}=43.956$; $p< 0.001$) and triglycerides ($F_{(2.5,68)}=30.399$; $p<0.001$) over four points of measurement, however, without statistically significant differences among the three therapeutic groups. Two patients treated with ramipril had dry irritating cough lasting for up to 3 months of therapy introduction, then it resolved spontaneously. No side effects were observed in the other

two patient groups. The more so, neither did plasma potassium level change as a result of treatment throughout the study (data not shown).

Discussion

Proteinuria is a significant independent determinant of the progression of chronic kidney disease. There is a strong association between the level of proteinuria and renal function decline[6,9,19]. A large number of experimental studies have provided compelling evidence that proteins filtered by diseased glomeruli induce harmful effects on glomerular and tubulointerstitial structures. An increased renal synthesis of angiotensin II has been demonstrated in proteinuric renal diseases. The increased synthesis of angiotensin II plays a central role in activating the transcription factor NF-κβ and increasing the expression of several cytokines, cell adhesion molecules and growth factors. One of them is the transforming growth factor-β (TGF-β)[20]. TGF-β has a central role in renal scarring, stimulating the synthesis of matrix proteins and increased production of protease inhibitors[21–24]. Angiotensin II blockade by ACE inhibitors or ARB results in a decrease in TGF-β expression and matrix accumulation[25,26]. Any therapeutic intervention to reduce the level of proteinuria should have an important beneficial effect on the progression of proteinuric nephropathies. In order to test whether the antiproteinuric effect of a combination of ACE inhibitors and ARB is superior to ACE inhibitors or ARB alone in patients with nondiabetic proteinuric nephropathy, we compared the effects of three different drug regimens, i.e. the ARB valsartan combined with ACE inhibitor ramipril *versus* ramipril or valsartan alone. The combination of ACE inhibitor and ARB proved significantly better than either individual drug in reducing proteinuria. This result is in agreement with the last large meta-analysis study[27]. At 6-month follow-up, the group on combination therapy showed a significant decrease in serum creatinine as compared to patients on monotherapy. In the group of patients on combination therapy, creatinine clearance showed continuous but statistically non-significant increase from the start to the end of the study, probably due to small sample size. In each treatment group, there were some patients on immunosuppressive drugs (12 patients on ACE inhibitors, 11 patients on ARB, and 12 patients on ACE + ARB), and we suppose that the improvements in proteinuria and glomerular filtration were attributable to immunosuppression. The COOPERATE trial, powered for renal outcome as a primary endpoint, reports that the combination group had slower rates of decline in renal function than patients on individual therapy; unfortunately, the results are widely viewed as being unreliable[28,29] and additional, properly conducted prospective trials are needed to answer the question of the efficacy of combination therapy on the chronic kidney damage progression. Most recently, the results of the ONTARGET trial, which compared ACE inhibitor ramipril and ARB (telmisartan) in high-risk patients, showed that the incidence of primary renal outcome (a composite of dialysis, doubling of serum creatinine and death) was comparable between two drugs, and also the combination of both drugs at maximally tolerated dose achieved no further benefits on renal function and was associated with more adverse effects than monotherapy[30]. However, this study is not entirely comparable to our study, because the minority of patients in ONTARGET study had proteinuria (17.1% at baseline), and also patients with diabetes and possible diabetic kidney disease were included. Some studies, in agreement with our study showed the beneficial effects of combination therapy with both ACE inhibitors and ARB, in reducing overt proteinuria more effectively than single-agent therapy in patients with nondiabetic nephropathy[14–17], which could be associated with retarding of renal disease progression. However, it is recommended that patients receiving dual therapy, if clinically justified should be monitored closely for potential adverse effects[31,32].

Conclusion

Study results indicated that treatment with a combination of ACE inhibitor and AT1 receptor blocker may be better in patients suffering from nondiabetic renal disease with significant proteinuria than treatment with either drug alone. This method of treatment does not only provide good blood pressure control, but also appears to slow the progression of renal failure and to decrease proteinuria.

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UČINCI RAMIPRILA I VALSARTANA NA PROTEINURIJU I BUBREŽNU FUNKCIJU U BOLESNIKA S NEDIJABETIČKOM PROTEINURIJOM

S A Ž E T A K

Reninsko-angiotenzinski sustav uključen je u progresiju i dijabetičke i nedijabetičke kronične bubrežne bolesti. Pokazalo se da inhibitori angiotenzin-konvertirajućeg enzima i blokatori receptora angiotenzina II smanjuju proteinuriju i usporavaju razvoj bubrežnog oštećenja. U ovom prospektivnom, randomiziranom, 12-mjesečnom istraživanju uspoređivani su učinci ramiprila (N=23 bolesnika), valsartana (N=22) i kombinacije ramiprila i valsartana (N=26) na proteinuriju, bubrežnu funkciju i metabolički profil u 71 bolesnika s nedijabetičkom proteinurijom s normalnom ili blago oštećenom bubrežnom funkcijom. Monoterapija ramiprilom i valsartanom i kombinacija ova dva lijeka značajno su smanjili proteinuriju, serumski kreatinin, kolesterol i trigliceride kao i sistolički i dijastolički krvni tlak. Nije bilo statistički značajne razlike između 3 skupine u smanjenju krvnog tlaka, serumskog kolesterola i triglicerida. Nakon 12 mjeseci, značajno smanjenje serumskog kreatinina zabilježeno je u sve tri skupine bolesnika, dok je nakon 3 i 6 mjeseci statistički značajno smanjenje serumskog kreatinina opaženo samo u skupini bolesnika na kombinacijskoj terapiji. Osim toga, nakon 3 mjeseca smanjenje proteinurije bilo je statistički značajno veće u skupini na kombinacijskoj terapiji, nego u skupinama bolesnika s monoterapijom ramiprilom i valsartanom. Ovi rezultati pokazuju da je kombinacijska terapija inhibitorom angiotenzin-konvertirajućeg enzima i blokatora receptora angiotenzina II učinkovitija od monoterapije u smanjenju proteinurije i serumskog kreatinina nakon 3 mjeseca i smanjenju serumskog kreatinina nakon 6 mjeseci liječenja.