ADDITIVE EFFECT OF COMBINATION THERAPY OF ANGIOTENSIN–CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKER ON PROTEINURIA IN CHRONIC KIDNEY DISEASE PATIENTS

Li-Chun Chang, Chwei-Shiun Yang

Background: Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were frequently prescribed in the case of chronic kidney disease (CKD) to reduce proteinuria and, if any, to retard the deterioration of renal function. It remains to be determined whether ACEI plus ARB provide more additional effects than either ACEI or ARB monotherapy in Chinese population with CKD.

Methods: We observed the effects of combination therapy of ACEI plus ARB with either ACEI or ARB alone in 19 CKD patients. CKD was defined as serum Cr ≥ 1.5 mg/dl or Upro ≥ 150 mg/day in non-DM group or urine protein > 300 mg/day in DM group. All 19 patients were given one kind of ARB (Irbesartan 150 mg, Telmisartan 40 mg, Valsartan 80 mg, Losartan 50 mg, Cardesartan 8 mg) or ACEI (Ramipril 10 mg, Quinapril 10 mg, Cilazapril 2.5 mg) for at least 3 months and one kind of ACEI or ARB was added for combination therapy. We focused on the effect of combination therapy after first 3 and 6 months. Nineteen CKD patients were divided into two groups, that is, 11 in the diabetes mellitus (DM) group (age: 69.4 ± 10, 46-85) and 8 in the non-DM group (age: 47.8 ± 12, 29-67). Blood pressure, urine protein/urine creatinine (Upro/Ucr) were recorded at each visit.

Results: There were no significant changes in the renal function and electrolytes during this period. As shown in table 1 and figure 2, in the DM group, Upro/Ucr (mg/mg) showed 4.4 ± 2.3, 3.1 ± 2.9 (↓28.85%, p<0.05), and 2.4 ± 2.6 (↓39.89%, p < 0.01) in 0, 3, and 6 months, respectively. In the non-DM group, Upro/Ucr showed 2.6 ± 1.8, 2.0 ± 1.2 (↓22.87%, p < 0.05), and 1.3 ± 0.7 (↓40.46%, p < 0.05) in 0, 3, and 6 months, respectively. Totally, Upro/Ucr showed 3.6 ± 2.3, 2.6 ± 2.6 (↓26.24%, p < 0.05), and 1.9 ± 1.9 (↓30.13%, p < 0.001) in 0, 3, and 6 months, respectively. The lowering of blood pressure was not statistically significant among all patients.

Conclusions: ACEI/ARB combination therapy provides additional beneficial effect on reducing proteinuria beyond controlling the blood pressure and its anti-proteinuric effects were significant in both DM and non-DM CKD patients. (Acta Nephrologica 2009; 23: 84-89)

Key words: Combination therapy, ACEI, ARB, proteinuria, chronic kidney disease, renin-angiotensin-aldosterone system

INTRODUCTION

In chronic proteinuric glomerular disease, glomerular filtration rate (GFR) continues to decline even after removing the initial insult, leading to end-stage renal failure in many patients. Hypertension plays a major role in sustaining renal function deterioration. Limitation of systemic and glomerular hypertension reduces urinary protein excretion and renal function deterioration in both experimental animals and also in humans with insulin-dependent diabetes mellitus. Among the hypertensive medications, angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) are more effective than other conventional drugs with regard to the limitation of the progression of renal disease, even with similar blood pressure control. In diabetic patients, both losartan and enalapril decreased proteinuria significantly without any significant changes in GFR.
The renin-angiotensin system serves as one of the most powerful regulators of arterial pressure and sodium balance. ACEIs block the production of angiotensin II and ARBs block type I receptor of angiotensin II. Although administration of ACEI causes plasma level of angiotensin II to become undetectable, there are evidences that chronic use of ACEI results in partial “angiotensin II escape” because angiotensin II can also be produced by chymase in humans. In contrast, ARBs block angiotensin II type I receptor which has direct vascular effect caused by angiotensin II, such as vasoconstriction, inflammation, vascular remodeling, and thrombosis. Combining both ACEI and ARB may provide a complete blockade of the renin-angiotensin system in the treatment of CKD. Several studies have compared the anti-proteinuric and anti-hypertensive effects of the combination therapy of ACEI plus ARB with those of either drug class alone. Most are parallel-group or cross-over studies, and many are small (< 25 patients) and short term (≤ 12 weeks). However, it remains to be determined whether the combination of ACEI and ARB provides additional effects in reducing proteinuria in Chinese CKD population. Thus, in a retrospective, open-label study, we compared the effects of combination therapy with either ACEI or ARB alone on office pressure and proteinuria.

### MATERIAL AND METHODS

This was a retrospective, open-label intervention study on the effects of combination therapy of ACEI plus ARB, compared with either ACEI or ARB alone, in nineteen chronic kidney disease (CKD) patients. Between March 2006 and July 2007, nineteen CKD patients (age: 59.2 ± 15 years, mean ± SD; eight men and eleven women) were selected from our renal clinic who met the enrollment criteria. Nineteen CKD patients were divided into two groups shown as figure 1:11 patients in diabetes mellitus group (DM group) and 8 patients in non-diabetes mellitus group (non-DM group). The inclusion criteria for the selection of CKD patients were arbitrarily defined as serum creatinine > 1.5 mg/dl, or daily urine protein > 300 mg in the DM group and daily urine protein > 150 mg in the non-DM groups. In the non-DM group, there are 5 chronic glomerulonephritis (clinically diagnosed, not biopsy-proved), 2 IGA nephropathy and 1 focal segmental glomerular sclerosis (pathology proved). DM nephropathy was diagnosed by the presence of proteinuria more than 300 mg per day in DM patients and none were biopsy-proved. The main exclusion criteria were pregnant or nursing women, patients on immunosuppressive drugs, and patients with refractory edema or rapidly deteriorating renal function after combination therapy.

The study was performed on an ambulatory basis. Before enrollment, all 19 patients have taken one kind of ARB (Irbesartan 150 mg, Telmisartan 40 mg,Valsartan 80 mg, Losartan 50 mg, Candesartan 8 mg) or ACEI (Ramipril 10 mg, Quinapril 10 mg, Cilazapril 2.5 mg), one tablet everyday for at least three months. Other classes of anti-hypertensive drugs such as β-blocker and calcium channel blocker were continued to use without changing the dose throughout the study. Their blood pressure, renal function and serum electrolyte remained stable throughout the study. Then one tablet of ACEI or ARB was added for combination therapy. At each visit, seated systolic and diastolic blood pressure were measured by using a sphygmomanometer, and the Korotkoff sound phase 1 and 5 were used as systolic and diastolic blood pressure, respectively. Ratio of spot urine protein to urine creatinine (Upro/Ucr) was recorded at each visit and was used as an alternative method for daily urine protein. We compared the systolic and diastolic blood pressure, Upro/Ucr at 0, 3, and 6 months after combination therapy. Each patient’s baseline data served as his/her own control.

### Statistical analysis

Results are expressed as means ± s.d. For statistical analysis, student’s t test was used to compare the difference of serum creatinine, potassium and HbA1C. Non-parametric Wilcoxon signed rank test was used to compare the difference in blood pressure and Upro/Ucr. A p value less than 0.05 was considered significant.

### RESULTS

There were no significant changes in the renal function and electrolytes during this period. As shown in figure 2 and table 1, compared with baseline, blood pressure (BP) in the DM group didn’t show any significant reduction after combination therapy for 3 and 6 months except systolic BP after 6-month combination therapy showed significant reduction (138 ± 15 mmHg versus 158 ± 19 mmHg, p < 0.005). In the non-DM group, blood pressure didn’t show any significant reduction after combination therapy for 3 and 6 months.

As for proteinuria, in the DM group, Upro/Ucr showed significant reduction (3.1 ± 2.9 versus 4.4 ± 2.3, 28.85%, p < 0.05) and in 6-month (2.4 ± 2.6 versus 4.4 ± 2.3, 39.89%, p < 0.01) after combination therapy. In the non-DM group, Upro/Ucr also showed significant reduction in 3-month (2.0 ± 1.2 versus 2.6 ± 1.8, 40.46%, p < 0.05) and in 6-month (1.3 ± 0.7 versus 2.6 ± 1.8, 40.46%, p < 0.05) after combination therapy.
Proteinuria of total nineteen patients, as Upro/Ucr, showed significant change in 3-month (2.6 ± 2.6 versus 3.6 ± 2.3, ↓ 26.24%, p < 0.05) and in 6-month (1.9 ± 1.9 versus 3.6 ± 2.3, ↓ 30.13%, p < 0.001) after combination therapy. Anti-proteinuric effect of combination therapy appeared to be beyond the blood pressure control throughout the study period as shown in table 1.

**DISCUSSION**

The present findings indicate that the combination of ACEI and ARB in Taiwanese CKD patients with proteinuric nephropathy produces a more profound decrease in proteinuria than either drug alone, no matter what kind of ACEI or ARB was used. The magnitude of the additive antiproteinuric effect is more remarkable than the effect on systemic blood pressure, and is not dependent on changes in creatinine clearance. Although the DM group was older and has heavier proteinuria than the non-DM group, the extent of reducing proteinuria was similar between the two groups (Table 1 and Fig. 2). Several studies\(^{17-25}\) have compared the effects of combination therapy with monotherapy and most reported that the antiproteinuric effect of dual-class therapy was superior to that of monotherapy in diabetic nephropathy or other proteinuric renal disease. However, different methods were adopted. For example, some compared dual therapy with ACEI only but not with ARB therapy; patients were first stabilized on an ACEI treatment and then randomly assigned to additional treatment with an ARB or placebo.\(^{19,20}\) One study found that a dual-class regimen resulted in a greater antiproteinuric benefit compared with ARB therapy but not with ACEI treatment.\(^{17}\) As for blood pressure, some reported a significant benefit for combination therapy,\(^{17,23}\) but the results of other studies were equivocal.\(^{18-22}\) A meta-analysis by Doulton et al.\(^{23}\) reported that combination therapy resulted in a statistically significant BP-lowering effect, but again, the authors suggest that the observed difference may stem from the different design of studies included in the analysis.

In this study, office seated blood pressure values were slightly lower with the combination therapy than with ACEI or ARB alone, when compared with baseline

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**Table 1.** Sex, age, blood pressure and Upro/Ucr in 0,3,6 months after combination therapy

<table>
<thead>
<tr>
<th></th>
<th>DM (male/female)</th>
<th>s/p 3 mo</th>
<th>s/p 6 mos</th>
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<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>158 ± 19</td>
<td>145 ± 18</td>
<td>138 ± 15</td>
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<td><strong>Diastolic BP (mmHg)</strong></td>
<td>79 ± 10</td>
<td>77 ± 5</td>
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<tr>
<td><strong>Upro/Ucr (mg/mg)</strong></td>
<td>4.4 ± 2.3</td>
<td>3.1 ± 2.9</td>
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<td><strong>Creatinine (mg/dl)</strong></td>
<td>2.8 ± 1.8</td>
<td>3.1 ± 2.4</td>
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<td><strong>Potassium (mEq/L)</strong></td>
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<tr>
<td><strong>HbA1C</strong></td>
<td>7.3 ± 1.0</td>
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<td><strong>Systolic BP (mmHg)</strong></td>
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<td>131 ± 20</td>
<td>128 ± 12</td>
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<td><strong>Upro/Ucr (mg/mg)</strong></td>
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<td>1.3 ± 0.7</td>
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<td><strong>Creatinine (mg/dl)</strong></td>
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<tr>
<td><strong>Potassium (mEq/L)</strong></td>
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<th>s/p 6 mos</th>
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<td>146 ± 20</td>
<td>139 ± 20</td>
<td>133 ± 14</td>
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<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>79 ± 9</td>
<td>76 ± 7</td>
<td>77 ± 5</td>
</tr>
<tr>
<td><strong>Upro/Ucr (mg/mg)</strong></td>
<td>3.6 ± 2.3</td>
<td>2.6 ± 2.6</td>
<td>1.9 ± 1.9</td>
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ACTA NEPHROLOGICA

ACEI AND ARB IN CKD

Total enrolled, n = 19

DM group, n = 11

ARB 1 tablet for at least 3 months, n = 10

Combination therapy for 6 months, n = 10

ACEI 1 tablet for at least 3 months, n = 1

Combination therapy for 6 months, n = 1

Non-DM group, n = 8

ARB 1 tablet for at least 3 months, n = 8

Combination therapy for 6 months, n = 8

Fig. 1. Enrollment, allocation, and follow-up of patients in the study

Fig. 2. Mean (± SD) systolic/diastolic blood pressure at baseline, 3 and 6 months after combination therapy in (a) diabetic group (DM group) and (b) non-diabetic group (non-DM group); Mean (± SD) spot urine protein / urine creatinine (Up/Ucr) at baseline, 3 and 6 months after combination therapy in (c) DM group and (d) non-DM group.
value (Table 1 and Fig. 2), although no significant differences were observed with the exception of systolic BP in the 6-month combination therapy (158 ± 19 versus 138 ±15 mmHg, p < 0.005). In a previous study on patients with IgA nephropathy, the effect of blood pressure reduction on the antiproteinuric effect of combination therapy was not completely excluded, since only office sitting blood pressure was recorded in the morning, after drug intake. We only recorded seated blood pressure at each office visit and office time may be in the morning, evening or the night. In addition, white-coat hypertension should be considered. Thus, the observed differences in the antiproteinuric effect of ACEI, ARB or combination therapy can only be explained in part by reducing the blood pressure.

Several studies evaluated the effect of dosage on the antiproteinuric effect of RAS blockade. One of these, a randomized, crossover study that examined normotensive and proteinuric (1 to 3 g/d) patients with IgA nephropathy (n = 10) for four 1-wk-long treatment periods, reported that antiproteinuric effects were dosage-dependent only with combination therapy. Doubling the dosage of enalapril and losartan during the single-agent phase of the study (from 10 to 20 mg/d for enalapril and from 50 to 100 mg/d for losartan) did not further reduce proteinuria. However, combination therapy with each agent at the lower dosages produced significantly greater antiproteinuric effects than did monotherapy. Laverman et al, investigated the optimal antiproteinuric dosage of lisinopril and losartan in patients with non-diabetic, proteinuric (mean 4.5 g/d) renal disease (n = 9), then used those dosages in a combination regimen for 6 weeks. The most effective antiproteinuric dosage varied with the individual. In addition, Anderson et al, compared the long-term effects (12 months) of the combination of candesartan (16 mg/d) and lisinopril (20 mg/d) (n = 38) with high-dose lisinopril (40 mg/d) (n = 37) in type 1 and type 2 diabetic patients. There was no statistically significant difference in the reduction of blood pressure and urinary albumin excretion. Taken together, there is still controversy in the antiproteinuric and anti-hypertensive effects in the combination therapy of ACEI and ARB. Individual differences, probably due to ineffectual drug dosage, severity of hypertension or increased sodium intake should also be taken into account for the negative findings.

Two small crossover studies compared full-dosage ACEI and ARB monotherapy with half-dosage combination RAS blockade in hypertensive CKD patients, and different results were obtained. Patients in the study showing no antiproteinuric benefit with combination therapy had more severe hypertension (mean systolic BP > 149 mmHg, and a mean of 2.6 antihypertensive agents) than the other study. In addition, higher sodium intake can blunt the antiproteinuric effect of ACEI, patients in the negative study excreted less sodium than those in the positive study (mean sodium excretion 129 to 168 versus 192 to 204 mEq/d). In our study, although severity of hypertension and the extent of proteinuria tends to be worse in the DM group than in the non-DM group, antiproteinuric effect with combination therapy seems to be equivalent in both DM and non-DM groups. We presumed that sodium balance is stable because it is difficult to collect 24-hour urine to monitor daily sodium excretion. However, fewer sodium intake due to diet control in older diabetic patients may offset the effects of hypertension and proteinuria.

Considerations of patient safety with dual RAS blockade include reduced renal function and hyperkalemia. No obvious change of serum creatinine and potassium were observed during out study. A meta-analysis of 21 randomized, controlled trials examined the safety of combination therapy. Combination therapy resulted in a small but significant increase in serum potassium level (weighted mean difference 0.11 mEq/L) and a non-significant decrease in GFR (weighted mean difference 1.4 ml/min). The authors concluded that the available data demonstrated the safety of combination therapy in the short term. The COOPERATE trial in Japan showed that combination therapy (trandolapril 3 mg daily and losartan 100 mg daily) was safe. None of the 263 randomized non-diabetic patients was withdrawn due to severe adverse events. The authors attributed these finding to gradual increase in drug dosage. Thus, adverse events such as hyperkalemia and reduced renal function should be checked regularly, but it cannot prevent us from using combination therapy.

This study has several limitations. Firstly, this is a small study which enrolled small number of patients (n = 19) and the observation period was done for only 6 months. A low statistical power with possible type II errors would occur due to a small number of patients. Since patients were enrolled from a single clinic, and not all patients who met the inclusion criteria were enrolled in this study, the selection bias and heterogeneity of study group may interfere the accuracy of this report. Furthermore, there were no control groups to compare. Secondly, thinking of the different individual responses to RAS blockade, the fixed dose of RAS blockade we use may not provide the maximal anti-proteinuric effect and blood pressure reduction. Thirdly, in this study we could not clarify the different antiproteinuric effects of different combination therapy.

In conclusion, this study indicated that in Taiwanese CKD patients, the combination of ACEI and ARB has a stronger additive antiproteinuric effect than the observed...
magnitude of decrease in blood pressure. Dual blockade of renin-angiotensin system seems to enhance the anti-proteinuric effect of single-agent ACEI or ARB therapy. The ultimate goal of reducing proteinuria by combination therapy is to preserve renal function. More long-term, prospective, parallel group and prospective studies are needed to address this issue.

REFERENCE


