

## Additive Antiproteinuric Effect of Combination Therapy with ACE Inhibitor and Angiotensin II Receptor Antagonist: Differential Short-term Response between IgA Nephropathy and Diabetic Nephropathy

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In previous studies, the synergistic antiproteinuric effect of the combination therapy of ACE inhibitors and angiotensin II receptor antagonists (ATRA) has been inconsistent in relation to underlying renal diseases. The influence from the blood pressure (BP)-reducing effect in some studies might also contribute to this inconclusiveness. To examine the possibility of the benefit being different according to underlying renal diseases, we undertook a crossover therapeutic trial of the combination therapy in two selected homogenous groups of patients with diabetic and non-diabetic renal diseases. The BP-reducing effect was excluded during the study.

Nineteen biopsy-proven IgA nephropathy, as examples of non-diabetic renal diseases, and 24 type 2 diabetic nephropathy patients were selected as the study subjects. The subjects had to meet the follow criteria: a creatinine clearance (Ccr) between 25-90 ml/min/1.73 m<sup>2</sup>, 24-hr urinary protein excretion rate over 1.0 g/day and a BP maintained at less than 130/80 mmHg, with more than six-month therapy of ramipril, ( $5.7 \pm 0.4$  mg/day,  $13 \pm 2$  month). The baseline data between the two groups showed no significant differences. After a 12-week stabilization period (control period), 4 mg, once daily, dose of candesartan (combination period) followed by a placebo (placebo period), or vice versa, were administered in addition to the ramipril, for 12 weeks. The combination, with candesartan, did not change the Ccr, BP, serum and urinary electrolytes or the urea. The 24 hour urinary protein excretion rate was significantly reduced by the combination therapy in the patients with IgA nephropathy ( $3.1 \pm 0.3$  g/day in combination,  $4.2 \pm 0.3$  in control, and  $4.3 \pm 0.2$  in placebo;  $p < 0.05$ ). However, the patients with diabetic

nephropathy showed no reduction in their proteinuria with the combination therapy ( $3.8 \pm 0.2$  g/day in combination,  $3.9 \pm 0.3$  in control, and  $4.1 \pm 0.3$  in placebo;  $p = \text{NS}$ ). The changes in proteinuria showed no relationship with the changes in the BP in IgA nephropathy.

In conclusions, the benefit of combination therapy of its antiproteinuric effect was different between IgA and diabetic nephropathy over the 12-week trial. The difference in the pathophysiological role, and the importance of the renin-angiotensin system, between the two diseases might contribute to the discrepancy in the result. We suggest the discrimination of the underlying renal diseases in the study subjects is an important prerequisite for future studies on this issue.

**Key Words:** ACE inhibitors, angiotensin II receptor blockade, IgA nephropathy, diabetic nephropathy

### INTRODUCTION

Angiotensin II (ATII) plays an important role in the progression of chronic renal diseases. A number of landmark clinical trials have shown that the pharmacological inhibition of the renin-angiotensin system (RAS), with angiotensin converting enzyme (ACE) inhibitors, has renoprotective effects in renal diseases.<sup>1-3</sup> However, ACE inhibitors alone might not inhibit the RAS completely, as the ATII is synthesized through not only ACE, but non-ACE pathways, such as serine protease.<sup>4,7</sup> In some patients with chronic renal disease, proteinuria remains uncontrolled despite the long-term use of ACE inhibitors, which may be due to the lack of a persistent decline in the systemic ATII caused by the ACE inhibitors

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alone.<sup>4</sup>

Angiotensin II receptor antagonists (ATRA) inhibit the RAS at the ATII subtype 1 receptor (AT<sub>1</sub>) level in the kidney.<sup>8</sup> A number of studies have shown that they also have similar hemodynamic, antiproteinuric or antisclerotic effects as ACE inhibitors.<sup>9-12</sup> Theoretically, the effect of the combined use of these drugs on ACE inhibitors can induce a greater blockade of the RAS, since both drugs inhibit the action of ATII at different levels. A bradykinin effect of ACE inhibitors can be advantageous in terms of cardioprotection and blood pressure-lowering effects. Unopposed stimulation of the ATII subtype 2 receptors (AT<sub>2</sub>) of ATRA has recently been known to counterbalance the adverse effects of ATII through AT<sub>1</sub>. These additional benefits will not interfere when both drugs are used concomitantly.

In spite of these theoretical expectations, in many previous clinical studies the results have been controversial as to the therapeutic effects of the combination therapy.<sup>13-18</sup> Even though many factors, such as drug dosing, blood pressure-reducing effects, baseline blood pressure, renal function and proteinuria, etc, may be involved, the heterogeneity of the subjects in previous studies might be a leading factor contributing to the inconclusiveness.<sup>13-17</sup> Based on our review of literature, the combination therapy seemed to be more effective in non-diabetic glomerulonephritides<sup>13,15,16</sup> compared to diabetic nephropathy.<sup>14,17,18</sup> Under this hypothesis, we undertook a randomized crossover trial in two homogenous groups, one with diabetic nephropathy and the other with IgA nephropathy, representative of non-diabetic nephropathy. Proteinuria was measured, as a surrogate marker, since it is a well-known predictor of the progression of renal diseases. To avoid a blood pressure reducing effect, the combination was performed in the patients maintaining long term optimal blood pressures. Therefore, the main aim of the present study was to examine if the same regimen of combination therapy of an ACE inhibitor and ATRA was equally effective in diabetic and non-diabetic nephropathy, with the same baseline renal function and proteinuria, when the blood pressure-reducing effect was excluded.

## MATERIALS AND METHODS

### Subjects

The present study was undertaken at the Inha University Inha General Hospital, under the approval of the hospital ethics committee. Of the patients followed with biopsy-proven IgA nephropathy and type 2 diabetic nephropathy, we selected the subjects: 1) whose blood pressure had remained below 130/80 mmHg, on receiving more than 5 mg of ramipril, once daily, for at least six months, 2) whose creatinine clearance was between 25 and 90 ml/min/1.73 m<sup>2</sup>, and 3) whose 24-hour urinary protein excretion was more than >1.0 g/d. The IgA nephropathy patients with a previous history of steroid or cytotoxic treatment within the last six months were excluded. Nineteen biopsy-proven IgA nephropathy and 24 diabetic nephropathy patients consented to the study, but two diabetic patients dropped out as a result of the progression of azotemia and hyperkalemia in one, and intractable hypotension in the other, which occurred during the study period. Finally, 41 patients including 19 IgA nephropathy and 22 diabetic nephropathy patients completed the study. The mean age of the subjects was 34 ± 5 years, with a female:male ratio of 22:19 (Table 1). All subjects received a mean daily dose of ramipril of 5.7 ± 0.4 mg (range 5.0 - 7.5), and showed acceptable blood control, with a mean arterial pressure of 92 ± 2 mmHg. The duration of the ramipril administration was 13 ± 2 months (range 6 - 17). Antihypertensive agents, other than ramipril, were administered to 14 patients (34.1%). The mean creatinine clearance and 24-hour urinary protein were 60.1 ± 4.0 ml/min/1.73 m<sup>2</sup> and 3.9 ± 0.3 g/day, respectively.

### Study design

The present study was conducted as a double blinded randomized crossover trial. All subjects underwent a 12-week observational period, with no changes in their medications (control period), which was to evaluate whether a further increase of ramipril would be required, and to obtain the baseline data for the ramipril single therapy. After the control period, the subjects randomly

**Table 1.** Characteristics of Total Subjects at Baseline

	Total (n=41)
Age (years)	34 ± 5 (24-53)
Female: male	22:19
Duration of ramipril treatment (months)	13 ± 2 (8-23)
Ramipril dose (mg/day)	5.7 ± 0.4 (5.0-7.5)
Antihypertensives other than ramipril	14
+ Diuretic	10
+ Diuretic + Ca <sup>2+</sup> blocker	2
+ Diuretic + Ca <sup>2+</sup> blocker + Vasodilator	2
Mean arterial pressure (mmHg)	92 ± 2
Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	60.1 ± 4.0
24-hour urinary protein (g/day)	3.9 ± 0.3

Mean ± SEM (range).

Ig A, immunoglobulin A.

underwent a sequence of either, a combination of candesartan (combination period) or a placebo, (placebo period) or vice versa, for 12 weeks. During the combination period, candesartan was administered at a dose of 4 mg, once daily, to all the subjects. Although moderate salt restriction (7 g/day) has been a policy of our center for patients with hypertensive chronic renal diseases, the intensity of the education, before, and after the study period remained unchanged.

The blood pressure, serum creatinine and potassium, urinary protein, sodium, potassium and urea were measured at the end of the three periods. The 24-hour blood pressures were measured using an oscillometric blood pressure monitor (90207, SpaceLabs Inc, Redmond, WA, USA). The mean 24-hour systolic and diastolic pressures were used to calculate the mean arterial pressures, defined as the sum of one third of the systolic, and two third of the diastolic, pressures. The mean of two arterial pressures, measured at the 11<sup>th</sup> and 12<sup>th</sup> weeks of each period, were used for the analysis. The serum and urinary parameters were also measured twice in the same week from serum and 24-hour urine sample collections. The creatinine clearance was calculated based on the urine volume and creatinine measurements in the serum and 24-hour urine

samples.

## Statistics

The data are presented as the mean ± SEM. Repeated measures ANOVA tests, with multiple comparisons and a chi-squared test, were used to compare the parameters between each period. A t-test was used to compare the parameters between the IgA nephropathy and diabetic nephropathy. The changes in the parameters of each disease group were analyzed by repeated measures ANOVA test, with multiple comparisons or a chi-square test. A Pearson correlation analysis was used to analyze the relationship between the changes in the blood pressures and proteinuria after the combination. A *p* value of less than 0.05 was considered significant.

## RESULTS

### Characteristics and effects of combination therapy in total subjects

Of the nineteen IgA nephropathy patients, the WHO classifications, at the time of biopsy, were II in 1, III in 10 and IV in 8. Five of the diabetic

nephropathy patients received subcutaneous insulin, 14 oral hypoglycemic agents and 3 received both. Twelve of the patients with IgA nephropathy and 18 with diabetic nephropathy had been on 5 mg/day, and others on 7.5 mg/day, of ramipril. No patient required further elevation of their ramipril dose during the control period. The mean arterial pressure, creatinine clearance and 24-hr protein excretion rate remained unchanged, at the baseline levels after the control period (Table 1 and 2) (all  $P=NS$ ).

In all the subjects, the combination of candesartan did not change the mean arterial pressure, serum potassium and creatinine, or the urinary electrolytes and urea excretions (all  $P=NS$ ) (Table 2). Only the 24-hour urinary protein excretion rate was significantly decreased, to  $3.5 \pm 0.2$  g/day, compared to  $4.0 \pm 0.2$  and  $4.1 \pm 0.3$  g/day for the control and placebo periods, respectively ( $p < 0.05$ ).

#### Comparisons between IgA nephropathy and diabetic nephropathy

A subgroup analysis between the IgA nephropathy and diabetic nephropathy was undertaken. All the baseline characteristics, with the exception of the age, showed no statistical differences between the two groups (Table 3; all  $p < 0.05$ ). The mean age of the patients with diabetic nephropathy was higher than that of the IgA nephropathy patients ( $43 \pm 4$  versus  $30 \pm 1$  years;  $p <$

$0.05$ ), reflecting the age distribution of each disease. The mean arterial blood pressure, creatinine clearance and 24-hour urinary protein excretion, at the baseline, showed no differences between the two groups (all  $p=NS$ ), and the control period did not significantly change these parameters (all  $p=NS$ ) (Table 3 and 4).

The combination with candesartan tended to decrease the mean arterial pressure slightly more in diabetic nephropathy, but no statistical significance was found (Table 4). The serum potassium and creatinine clearance were not affected by either the candesartan or the placebo in the two groups (all  $p=NS$ ). A change in 24-hour urinary protein excretion was only found with IgA nephropathy, which decreased significantly during the combination period ( $3.1 \pm 0.3$  g/day versus  $4.2 \pm 0.3$  in control and  $4.3 \pm 0.2$  in placebo;  $p < 0.05$ ) (Fig. 1A). This effect was independent of the blood pressure-lowering effect, as the blood pressure was not significantly changed, and the change in the 24-hour protein excretion rate did not correlate with the mean arterial pressure during the period of the combination therapy (Fig. not shown;  $r=0.172$ ,  $p=NS$ ). On the other hand, the diabetic nephropathy group showed no change in 24-hour urinary protein excretion during the combination period ( $3.8 \pm 0.2$  g/day versus  $3.9 \pm 0.3$  in control and  $4.1 \pm 0.3$  in placebo;  $p=NS$ ) (Fig. 1B). There was also no significant difference in the blood pressure.

**Table 2.** Effects of Combination Therapy in Total Subjects

	Control	Combination	Placebo
Mean arterial pressure (mmHg)	$93 \pm 1.0$	$91 \pm 1.7$	$92 \pm 1.3$
Serum potassium (mEq/L)	$4.0 \pm 0.1$	$4.0 \pm 0.1$	$3.9 \pm 0.1$
Serum creatinine (mg/dL)	$1.4 \pm 0.1$	$1.5 \pm 0.1$	$1.5 \pm 0.1$
Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	$61.2 \pm 3.7$	$59.3 \pm 4.6$	$60.3 \pm 4.1$
Urinary sodium excretion (mEq/day)	$7.7 \pm 1.1$	$7.4 \pm 0.8$	$7.8 \pm 0.9$
Urinary potassium excretion (mEq/day)	$111.5 \pm 9.0$	$101.4 \pm 10.4$	$111.5 \pm 8.7$
Urinary urea excretion (g/day)	$63.0 \pm 3.0$	$64.1 \pm 2.8$	$63.0 \pm 3.1$
Urinary protein excretion (g/day)	$4.0 \pm 0.2$	$3.5 \pm 0.2^*$	$4.1 \pm 0.3$

Mean  $\pm$  SEM.

\* $p < 0.05$  compared to control and placebo period by repeated measures ANOVA test with multiple comparison.

**Table 3.** Comparisons of Baseline Characteristics between IgA Nephropathy and Diabetic Nephropathy

	IgA nephropathy	Diabetic nephropathy
Patients no.	19	22
Age (years)	30 ± 1 (24-38)	43 ± 4 (36-53)*
Female: male	9:10	13:09
Duration of ramipril treatment (months)	11 ± 2 (8-19)	14 ± 3 (5-23)
Ramipril dose† (mg/day)	5.9 ± 0.4 (5.0-7.5)	5.4 ± 0.3 (5.0-7.5)
Antihypertensives other than ramipril	5	9
+ Diuretic	5	5
+ Diuretic + Ca <sup>2+</sup> blocker	-	2
+ Diuretic + Ca <sup>2+</sup> blocker + Vasodilator	-	2
Mean arterial pressure (mmHg)	92 ± 1.9	93 ± 1.6
Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	65.3 ± 5.9	57.2 ± 3.4
24-hour urinary protein (g/day)	4.0 ± 0.4	4.0 ± 0.3

Mean ± SEM (range).

\**p* < 0.05 compared to IgA nephropathy by t-test.

†Ramipril dose was not changed throughout the study periods in each individual.

Ig A, immunoglobulin A.

**Table 4.** Effects of Combination Therapy According to IgA Nephropathy and Diabetic Nephropathy

		Control	Combination	Placebo
Mean arterial pressure (mmHg)	IgA nephropathy	93 ± 1.8	92 ± 1.8	94 ± 1.9
	Diabetic nephropathy	93 ± 1.5	91 ± 1.0	93 ± 1.3
Serum potassium (mEq/L)	IgA nephropathy	4.0 ± 0.1	4.0 ± 0.1	3.9 ± 0.1
	Diabetic nephropathy	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.1
Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	IgA nephropathy	66.4 ± 6.0	64.7 ± 6.0	65.4 ± 5.9
	Diabetic nephropathy	56.2 ± 4.3	54.4 ± 4.1	59.2 ± 4.3
Urinary protein excretion (g/day)	IgA nephropathy	4.2 ± 0.3	3.1 ± 0.3*†	4.3 ± 0.2
	Diabetic nephropathy	3.9 ± 0.3	3.8 ± 0.2	4.1 ± 0.3

Mean ± SEM.

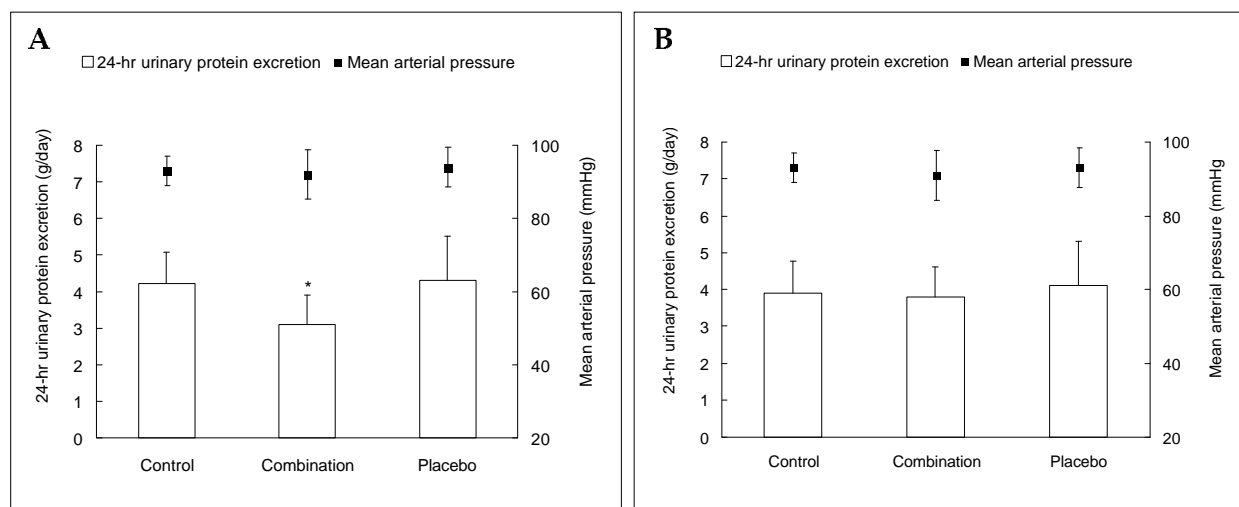
\**p* < 0.05 compared to control and placebo period by repeated measures ANOVA test with multiple comparison.†*p* < 0.05 compared to diabetic nephropathy by t-test.

Ig A=immunoglobulin A.

### Side effects

Two of the diabetic nephropathy patients were intolerable to the combination therapy, as described in the Method. One showed the progres-

sion of azotemia and hyperkalemia, and dropped out in the second study week. The other showed dizziness and hypotension on the addition of the candesartan, and refused to continue with the study in the third week of the combination period.



**Fig. 1.** The changes in the mean arterial pressure and 24-hour urinary protein excretion rate in the patients with IgA nephropathy (A) and diabetic nephropathy (B). In IgA nephropathy patients, urinary protein excretion decreases significantly during the combination period (candesartan 4 mg/day and ramipril) compared to the control and placebo periods (both ramipril alone). The change in proteinuria is not shown in diabetic nephropathy. The mean arterial blood pressure shows no significant change on the addition of candesartan at a dose of 4 mg/day. Ramipril doses were the same in all three periods ( $5.7 \pm 0.4$  mg/day). \* $p < 0.05$  versus control and placebo periods.

All the others tolerated the addition of a 4 mg, once daily, dose of candesartan well, so continued the candesartan, with no renal impairment or hyperkalemia.

## DISCUSSION

The present study showed that the synergistic antiproteinuric effects of the combination therapy of ACE inhibitor and ATRA were different between IgA nephropathy and diabetic nephropathy. A further reduction in the proteinuria was found in the IgA nephropathy patients only. The same regimen induced no reduction in the diabetic nephropathy patients, with similar renal dysfunctions and proteinuria, over the study period. The blood pressure-reducing effect could be excluded from the present result as it remained unchanged during the combination period, and the change in the proteinuria of the IgA nephropathy patients was not related to the change in the blood pressure.

It has been debated whether the renoprotective effect of the combination therapy of ACE inhibitors and ATRAs is synergistic. Even though early experimental data have suggested they are,<sup>8</sup> the

results in human renal diseases have been controversial. Clinical data on the combination therapy was first reported by Zocali, et al.,<sup>13</sup> with subjects consisting mostly of chronic glomerulonephritis; the effects of the addition of losartan, on a various kind of ACE inhibitors, induced a further reduction in the proteinuria. Russo et al also reported favorable results in IgA nephropathy subjects with moderately impaired<sup>15</sup> and normal renal functions,<sup>16</sup> however, other studies have failed to demonstrate such benefits. Interestingly, a common finding of these studies was that the subjects mostly consisted of diabetic nephropathy (Table 5).<sup>14,17</sup>

Based on these findings, we presumed the therapeutic effects of the combination therapy might be different in relation to the underlying causes of the renal disease. The focus of the present study was on the direct comparison between diabetic and non-diabetic renal diseases. IgA nephropathy was chosen as a representative of non-diabetic glomerulonephritis, as a homogenous control to diabetic nephropathy was required, and because practically, it is a common form of chronic glomerulonephritis. The subjects with IgA nephropathy consisted of those with similar of blood pressures, renal functions and

**Table 5.** Literatures on Combination Therapy of ACE Inhibitors and ATII Receptor Antagonists

	Subject	Characteristics	Protocol	Results of the combination
Zoccali, et al, 1997 <sup>13</sup>	11 8CGN, 2 DM, 1CPN	Proteinuria $4.7 \pm 2.1$ g/day Ccr $62 \pm 6$ ml/min	ACE inhibitors + Losartan 50 mg	Significant reduction in proteinuria No changes in Ccr and BP
Herbert, et al, 1999 <sup>14</sup>	7 IDDM	Proteinuria 0.2-17.6 g/day Serum cr 1.1-3.0 mg/dL	ACE inhibitors + Losartan 50-100 mg	No changes in proteinuria, serum cr, and BP
Russo, et al, 1999 <sup>15</sup>	8 IgA nephropathy	Normotensive Proteinuria 1-3 g/day Ccr 69-119 ml/min	ACE inhibitors + Losartan 50 mg	Significant reduction of proteinuria No changes in Ccr and BP
Russo, et al, 2001 <sup>16</sup>	10 IgA nephropathy	Normotensive Proteinuria 1-3g/day Normal renal function	Enalapril 10-20 mg/d + Losartan 50-100 mg	Significant reduction of proteinuria No change in BP
Agarwal, et al, 2001 <sup>17</sup>	16 12 DM, 4 CGN	Proteinuria >1g/day Ccr >30 ml/min	Lisinopril 40 mg/d + Losartan 50 mg/d	No changes in proteinuria and BP 14% increase of GFR
Present study	41 19 IgA nephropathy 21 NIDDM nephropathy	Proteinuria >1 g/day Ccr 25-90 ml/min	Ramipril 5-7.5 mg/d + candesartan 4 mg/d	Significant reduction of proteinuria-only in IgA nephropathy No changes in Ccr and BP

ACE, angiotensin converting enzyme; ATRA, angiotensin II receptor antagonist; Ccr, creatinine clearance; BP, blood pressure; CGN, chronic glomerulonephritis; DM, diabetes mellitus; CPN, chronic pyelonephritis; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; IgA, immunoglobulin A; GFR, glomerular filtration rate.

proteinuria to the diabetic patients.

False favorable results can be caused when ATRAs, in addition to suboptimal doses of ACE inhibitors, are administered to patients, or if the blood pressure was inadequately controlled. To avoid this occurring, we selected the subjects from those maintaining a blood pressure of less than 130/80 mmHg with a maximal dose of ramipril over a six month period. Adequate blood pressure control and ramipril doses were confirmed during a 12-week of control period. The benefits of the combination therapy have occasionally been reported in association with a concomitant reduction in the systemic blood pressure.<sup>18,19</sup> In these cases, the reduction of proteinuria could result from the blood pressure-reducing effect alone. However, this confusion

could be excluded in the present study.

ACE inhibitors and ATRAs exert their renoprotective benefits through non-hemodynamic anti-inflammatory mechanisms. Their combined use will allow further attenuation of the inflammatory injury through a more complete inhibition of the action of ATII at both the synthesis and receptor binding levels. Additionally, the combination will provide two further anti-inflammatory effects, specific to each drug. ACE inhibitors have additional renoprotective effects by increasing systemic bradykinin. This so-called kinin-mediated renoprotection is exerted through their antiproteinuric, antifibrotic and anti-inflammatory actions.<sup>8</sup> ATRAs are selective blockers of AT1 receptors, and some authors have suggested the renoprotective effects by ATRAs can be po-

tentiated by the unopposed stimulation of AT2 receptors, which are known to counterbalance the adverse effects of ATII, through AT1 receptors.<sup>20-24</sup> Both kinin-mediated renoprotection and the unopposed stimulation of AT2 receptors can be reserved when ACE inhibitors and ATRAs are used in combination. Recent evidence suggests that the combination therapy induces a reduction in urinary TGF- $\beta$ , an inflammatory marker of chronic renal diseases, which supports the anti-inflammatory benefits of the combination therapy.<sup>25</sup>

To explain the differences in the antiproteinuric benefit of the combination therapy between diabetic nephropathy and IgA nephropathy is not easy. However, our findings indicate that the role, and importance, of RAS-mediated inflammatory mechanisms are different between the two diseases. The pathophysiological processes are more complex in diabetic nephropathy, especially when it progresses to an advanced stage.<sup>8</sup> Many other factors, including high glucose per se, glycation end-products and oxidative stress, etc, trigger the inflammatory response through a pathway other than via RAS. The renin-angiotensin-aldosterone states are variable, not only at each stage, but also for between individuals. An atherosclerotic vascular condition is commonly associated with affecting the glomerular hemodynamics. A number of medications that can aggravate renal dysfunction are commonly required for non-renal comorbid conditions. Therefore, the inhibitory effect of RAS can be somewhat obscure. Meanwhile, the pathophysiological mechanism in IgA nephropathy is simpler than that of diabetic nephropathy, in that it inherently originates from an immune-related inflammation, and co-morbid conditions, other than renal diseases, are rare, with infrequent administration of other medications for co-morbidity. The role of RAS would be more critical, and its inhibition benefits in IgA nephropathy clearer, as in our and previous reports.<sup>13-17</sup> Studies evaluating this presumption on a molecular-basis will be required in the future.

The lack of benefit to the renal function in the present study might be due to the short study period, even though it was no shorter than previous studies.<sup>13-17</sup> However, we think the

additive antiproteinuric effects will be related to the favorable effect on renal disease progression in the future, as proteinuria by itself has been known as an important surrogate marker of the progression of renal disease. To conclude, whether the combination therapy is actually beneficial in reversing the progression of renal diseases, further long-term studies are required. Even though the study period can be insufficient for the diabetic nephropathy patients to manifest the antiproteinuric response, this possibility seems to be rare from our additional observations. In 12 diabetic patients who persisted with the combination therapy for at least two additional months, no late response was found.

The present study was different from previous studies in that the blood pressure-reducing effect was excluded, and the beneficial effects were observed and compared in two homogenous groups of patients, with either diabetic or non-diabetic renal diseases. The benefit of the combination therapy has still to be reported in diabetic patients, with studies where the blood pressure effect is strictly excluded. The results of the CALM study<sup>18</sup> and Jacobsen, et al.<sup>19</sup> were associated with the reduction of blood pressure. Methodologically, the present study was very similar to that of Argarwal, et al.<sup>17</sup> The main limitation of their study was that the etiologies of the subjects were heterogeneous. Based on our results, their inconclusive results seem to have arisen from the heterogeneity of the study population. The result for the IgA nephropathy patients in this study was similar to that for the IgA nephropathy patients in the study by Russo, et al's.<sup>15,16</sup> However, the number of subjects in are study was double, and they were in a more advanced stage of renal disease. Above all, our study provides more information on the comparisons of the same regimen for diabetic nephropathy at similar stages.

In conclusion, we found the benefits of the combination therapy of ACE inhibitors and ATRA, in relation to their antiproteinuric effects were different between IgA and diabetic nephropathy. The addition of candesartan to the ramipril maximal dose exerted a synergistic antiproteinuric effect in the patients with moderately advanced IgA nephropathy. This benefit was not



found in the type 2 diabetic nephropathy patients, at a similar stage of renal disease, after a 12 week administration of the same regimen. The difference in the pathophysiological role and importance of the renin-angiotensin system between the two diseases might contribute to the discrepancies in the results. We suggest that the discrimination of underlying renal diseases in the study subjects is an important prerequisite for future studies on this issue.

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