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Effect of low-dose valsartan on proteinuria in normotensive immunoglobulin A nephropathy with minimal proteinuria: a randomized trial

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Background/Aims: Immunoglobulin A nephropathy (IgAN) is a generally progressive disease, even in patients with favorable prognostic features. In this study, we aimed to investigate the antiproteinuric effect and tolerability of low-dose valsartan (an angiotensin II receptor blocker) therapy in normotensive IgAN patients with minimal proteinuria of less than 0.5 to 1.0 g/day.

Methods: Normotensive IgAN patients, who had persistent proteinuria with a spot urine protein-to-creatinine ratio of 0.3 to 1.0 mg/mg creatinine, were recruited from five hospitals and randomly assigned to either 40 mg of valsartan as the low-dose group or 80 mg of valsartan as the regular-dose group. Clinical and laboratory data were collected at baseline, and at 4, 8, 12, and 24 weeks after valsartan therapy.

Results: Forty-three patients (low-dose group, n = 23; regular-dose group, n = 20) were enrolled in the study. Proteinuria decreased significantly not only in the regular-dose group but also in the low-dose group. The change in urine protein-to-creatinine ratio at week 24 was –41.3% ± 26.1% ($p < 0.001$) in the regular-dose group and –21.1% ± 45.1% ($p = 0.005$) in the low-dose group. In the low-dose group, blood pressure was constant throughout the study period, and there was no symptomatic hypotension. In the regular-dose group, blood pressure decreased at weeks 8 and 12. No significant change in glomerular filtration rate, serum creatinine level, or serum potassium level was observed during the study period.

Conclusions: Our results suggest that low-dose valsartan can significantly reduce proteinuria without causing any intolerability in normotensive IgAN patients with minimal proteinuria.

Keywords: Angiotensin receptor antagonists; Glomerulonephritis, IGA; Proteinuria; Safety; Treatment outcome

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INTRODUCTION

Immunoglobulin A nephropathy (IgAN), the most prevalent primary glomerular disease worldwide, is an important cause of end-stage renal disease (ESRD) [1]. IgAN causes a progressive decrease in renal function, with a 50% incidence of ESRD over a 20-year period [2]. Clinical parameters that correlate with an increased risk of renal progression include reduced glomerular filtration rate (GFR), hypertension, and proteinuria above 0.5 to 1.0 g/day [3,4]. In particular, persistent proteinuria is the strongest prognostic factor for IgAN, and exhibits a dose-dependent relationship [5,6]. IgAN patients with time-averaged urinary protein excretion of more than 1.0 g/day have a risk of ESRD 46-fold that of patients with values of less than 0.5 g/day. Furthermore, the renal outcome for patients with minimal proteinuria of less than 0.5 g/day is better than that of patients with proteinuria of 0.5 to 1.0 g/day [7]. However, the threshold of proteinuria for the risk of kidney disease progression in adults is uncertain. Although patients with no or minimal proteinuria (defined as less than 0.5 to 1.0 g/day) have a low risk of progression, at least over the short term [3,8], a substantial proportion of these patients may increase the amount of urinary protein excretion and develop renal insufficiency over the long term [3,6,9-11]. Those patients may ultimately progress to ESRD, despite the generally low frequency of progression [4,11]. These findings suggest that the clinical features known to be "favorable" for proteinuria of less than 1.0 g/day with normal renal function and absence of hypertension do not always indicate a favorable or benign course of IgAN. IgAN is a generally progressive disease, even in patients with favorable prognostic features. Therefore, attenuation of persistent proteinuria may be vital in the treatment of IgAN, even if the urinary protein excretion rate is only 0.5 to 1.0 g/day. Based on these findings, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggested that angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) should be used for treatment if urinary protein excretion is 0.5 to 1.0 g/day. An increased dose of ACE-I or ARB to the extent that adverse events are acceptable can be used to achieve urinary protein excretion of less than 1 g/day [12].

High-dose ACE-I or ARB therapy is more efficacious in terms of reducing proteinuria compared with a normal dose of ACE-I or ARB in IgAN patients [13]. However, treatment with a high or even regular dose of ARB in some normotensive IgAN patients may be limited due to patient intolerance, as evidenced by symptoms such as symptomatic hypotension. In addition, although ARB decreases systemic blood press (BP), which does not cause symptomatic hypotension requiring discontinuation of ARB, a systolic BP of less than 110 mmHg may be associated with a higher risk of kidney disease progression in patients with nondiabetic kidney disease [14].

Therefore, it is important to establish a tolerable therapy that can prevent progression of proteinuria in normotensive IgAN patients with minimal proteinuria. Information on the efficacy and safety of ARB in normotensive IgAN patients with minimal proteinuria is scarce. Only a few randomized controlled clinical trials on the effect of ARB in normotensive IgAN patients have been performed [15-18]. Therefore, we designed this study to determine whether low-dose valsartan therapy could reduce proteinuria without causing intolerability in normotensive IgAN patients with minimal proteinuria.

METHODS

This study was conducted as a prospective, randomized, open-label, two-dose comparative multicenter trial. Adult normotensive IgAN patients were recruited from five hospitals between May 2008 and January 2010. The entry criteria were (1) biopsy-proven IgAN, (2) normal BP defined as less than 140/90 mmHg without any antihypertensive medications, (3) persistent proteinuria defined as a spot urine protein-to-creatinine ratio (UPCR) of 0.3 to 1.0 mg/mg creatinine for more than two consecutive months before enrollment, and (4) a GFR of more than 60 mL/min/1.73 m^2, calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation. Patients who had any of the following criteria were excluded from the study: secondary IgAN, pregnant or lactating females, any immunosuppressive medications, known allergy to ARB, a history of diabetes, hepatic disease, infections, malignancies, or renovascular disease, hypotension defined as a systolic BP less than 100 mmHg, and recent treatment (within 4 weeks

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of enrollment) with ACE-I or ARB. The use of steroids, immunosuppressants, nonsteroidal anti-inflammatory drugs (for more than 7 days) and antiplatelet agents was not allowed during the study. Patients were withdrawn from the study if symptomatic hypotension requiring discontinuation of ARB or hypertension needing additional antihypertensive drugs other than valsartan occurred.

The study was approved by the Institutional Review Board of Konkuk University Medical Center (IRB approval number: KUH101027). After informed consent was obtained, eligible patients were randomly assigned to the low-dose group (40 mg of valsartan) or the regular-dose group (80 mg of valsartan). Randomization was performed using a computer-generated list with a 1-to-1 ratio in permuted blocks stratified by the center.

Patients were examined at baseline and then 4, 8, 12, and 24 weeks after valsartan therapy. Clinical and laboratory data, including BP, UPCR, GFR, and blood chemistry, were measured at the time of enrollment and throughout the study period. At each visit, patients were asked about clinical symptoms, including hypotensive symptoms and other possible treatment complications. BP was measured using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes of rest. The average of two measurements was recorded. If the systolic BP decreased below 90 mmHg or hypotensive symptoms occurred, the study medication was stopped.

Histopathological classifications of IgAN were performed using the Oxford classification system based on the presence or absence of mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis [19].

Statistical analysis and outcome measures

Sample size was calculated using the primary end point. Based on previous studies of the antiproteinuric effect of ARBs in IgAN patients [15-17,20], it was expected that UPCR would be reduced by 22% to 45% with 25 standard deviations (SD) from baseline to week 24 after administration of the regular-dose and low-dose of valsartan. To detect the anticipated difference between the two groups with 80% power at a significance level of 0.05, we calculated that at least 22 patients were needed in each group, assuming a dropout rate of 10%.

The primary outcome was the percentage change in UPCR estimated at week 24. The percentage changes in UPCR at week 24 were compared to the corresponding level at baseline. In addition, the percentage changes in UPCR of the low-dose valsartan group were compared to those of the regular-dose group. Secondary outcome measures included changes in UPCR according to the magnitude of baseline UPCR, decrease in BP, increase in serum potassium, and decrease in GFR. For safety analysis, all patients who had taken valsartan at least once were included in the subject population.

Data are expressed as means and SDs. Differences between groups were examined using Student *t* test. Changes in variable parameters, such as UPCR, serum creatinine, GFR, serum potassium, and BP, from the baseline to the follow-up were compared using a paired-sample *t* test. A significant difference was defined as a *p* value of less than 0.05.

RESULTS

Patients' demographics and clinical characteristics

Forty-three normotensive IgAN patients were randomly assigned to either the low-dose group (n = 23; male:female ratio, 7:16) or the regular-dose group (n = 20; male:female ratio, 9:11). Three patients were withdrawn from the study for various reasons. Forty patients completed the 24-week treatment with valsartan (Fig. 1). Baseline demographics, clinical characteristics, and laboratory values were similar in the two groups (Table 1). The histopathologic features of the two groups are summarized in Table 2. Renal biopsy findings using the Oxford classification revealed no difference between the two parallel groups.

Effect on proteinuria

Proteinuria decreased significantly not only in the regular-dose group but also in the low-dose group (Fig. 2). In the regular-dose group, UPCR decreased significantly from 0.68 ± 0.24 mg/mg creatinine at baseline to 0.38 ± 0.19 mg/mg creatinine at week 24 ($p < 0.001$) (Table 3). In the low-dose group, UPCR also decreased significantly from 0.57 ± 0.18 mg/mg creatinine at baseline to 0.42 ± 0.28 mg/mg creatinine at week 24 ($p = 0.015$). After 24 weeks, the regular-dose group exhibited a 41.3% average

reduction in UPCR ($p < 0.001$). The low-dose group also showed a significant change in UPCR at week 24 (–21.1% ± 45.1%, $p = 0.005$) (Fig. 2). There was no significant difference in the week-24 UPCR value between the two groups (low-dose group vs. regular-dose group, 0.42 ± 0.28 mg/mg creatinine vs. 0.38 ± 0.19 mg/mg creatinine, $p = 0.600$) and the percentage changes in UPCR from baseline to week 24 (–21.1% ± 45.1% vs. –41.3% ± 26.1%, $p = 0.358$). In the regular-dose group, the percentage changes in UPCR also decreased significantly at weeks 4 and 12 (–13.6% ± 24.6% at week 4, $p = 0.014$; –27.0% ± 39.9% at week 12, $p = 0.004$). In contrast to the regular-dose group, the low-dose group did not show significant decreases in UPCR at weeks 4, 8, and 12 (–10.8% ± 71.3% at week 4, $p = 0.238$; –11.4% ± 47.5% at week 8, $p = 0.149$; –16.5% ± 51.3% at week 12, $p = 0.069$).

Table 1. Demographic and baseline characteristics

Characteristic	Low-dose group (valsartan 40 mg)	Regular-dose group (valsartan 80 mg)	*p* value
Number	23	20	-
Sex, male:female	7:16	9:11	1.000
Age, yr	37.9 ± 10.8	39.9 ± 13.8	0.609
Body weight, kg	59.2 ± 9.3	61.5 ± 9.8	0.442
Height, cm	162.9 ± 7.4	164.1 ± 9.2	0.629
Systolic blood pressure, mmHg	121.4 ± 13.0	125.8 ± 9.9	0.229
Diastolic blood pressure, mmHg	74.8 ± 10.1	77.6 ± 9.6	0.365
UPCR, mg/mg creatinine	0.57 ± 0.18	0.68 ± 0.24	0.103
Serum creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.1	0.893
eGFR, mL/min/1.73 m^2	107.6 ± 26.6	96.6 ± 19.7	0.144
Serum potassium, mEq/L	4.1 ± 0.3	4.0 ± 0.4	0.509

Values are presented as mean ± SD.
UPCR, urinary protein-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

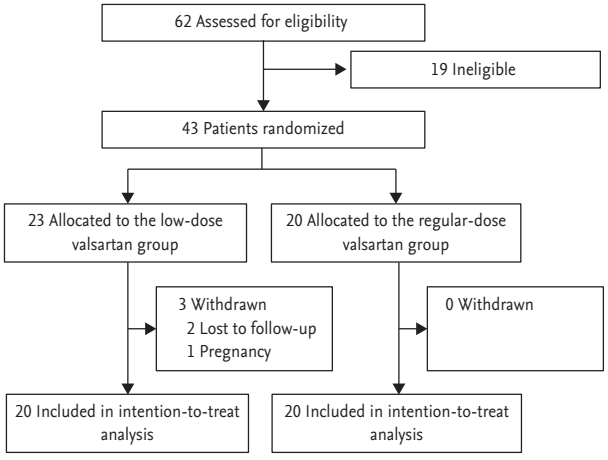

Figure 1. Flow diagram of low-dose and regular-dose valsartan treatment in normotensive immunoglobulin A nephropathy patients presenting with minimal proteinuria. The diagram shows a multicenter trial with a randomized allocation.

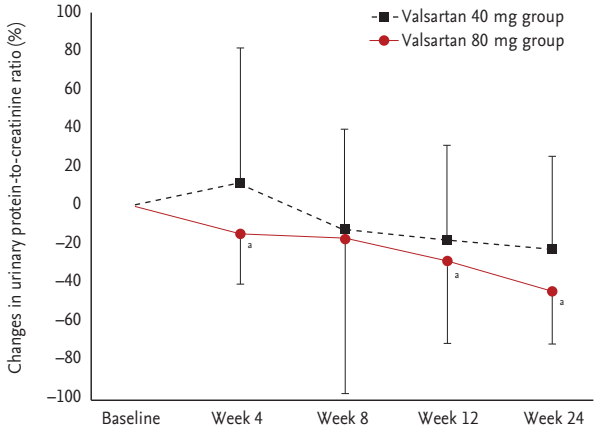

Figure 2. Changes in urinary protein-to-creatinine ratio over time following administration of valsartan in normotensive immunoglobulin A nephropathy patients presenting with minimal proteinuria. [a]$p < 0.05$ vs. baseline.

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Table 2. Histopathologic findings of immunoglobulin A nephropathy based on the Oxford classification

Histopathologic finding	Low-dose group (valsartan 40 mg)	Regular-dose group (valsartan 80 mg)	*p* value
Mesangial hypercellularity, Mo:M1	66.6:33.4	64.7:35.3	NS
Segmental glomerulosclerosis, So:S1	53.3:46.7	35.2:64.7	NS
Endocapillary hypercellularity, Eo:E1	3.3:96.7	5.8:94.2	NS
Tubular atrophy/interstitial fibrosis, To:T1:T2	78.3:21.7:0.0	67.7:23.5:8.8	NS

Values are presented as percentage.
NS, not significant.

Table 3. Effects of valsartan on urinary protein-to-creatinine ratio (mg/mg creatinine) over time in normotensive immunoglobulin A nephropathy patients presenting with minimal proteinuria

Week	Low-dose group (valsartan 40 mg)		Regular-dose group (valsartan 80 mg)			
	Mean ± SD	*p* value[a]	Mean ± SD	*p* value[a]	*p* value[b]	*p* value[c]
0	0.57 ± 0.18	-	0.68 ± 0.24	-	0.103	-
4	0.61 ± 0.40	0.649	0.57 ± 0.24	0.021	0.672	0.164
8	0.50 ± 0.29	0.308	0.54 ± 0.56	0.371	0.737	0.815
12	0.47 ± 0.30	0.130	0.47 ± 0.27	0.008	0.954	0.468
24	0.42 ± 0.28	0.015	0.38 ± 0.19	< 0.001	0.599	0.228

Values are presented as mean ± SD.
[a]*p* value vs. baseline of each treatment group.
[b]*p* value for testing the differences in urinary protein-to-creatinine ratio (UPCR) between the low-dose group (40 mg of valsartan) and the regular-dose group (80 mg of valsartan).
[c]*p* value for the differences in percentage change in UPCR from baseline between the low-dose and regular-dose groups.

Effects on blood pressure and other parameters

BP in the low-dose group did not change significantly in the 24-week period, with the exception of week 8 (systolic BP/diastolic BP, 121.8 ± 12.7 mmHg/74.9 ± 10.1 mmHg at baseline; 115.6 ± 11.1 mmHg/68.9 ± 10.4 mmHg at week 8, $p < 0.05$) (Fig. 3). In the regular-dose group, systolic BP decreased significantly at weeks 8 and 12 during the study period (systolic BP/diastolic BP, 125.1 ± 10.3 mmHg/77.3 ± 9.6 mmHg at baseline; 123.5 ± 10.7 mmHg/73.3 ± 12.9 mmHg at week 8, $p < 0.001$; 118.6 ± 10.9 mmHg/74.1 ± 12.1 mmHg at week 12, $p = 0.002$). Despite a transient decrease in systolic BP, there were no symptomatic hypotensive episodes that required discontinuation of study medication in either group throughout the 24-week period. In the regular-dose group, BP was restored to the baseline level at week 24 (121.9 ± 15.3 mmHg/73.9 ± 12.0 mmHg, *p* value vs. baseline > 0.05).

Serum creatinine, GFR, and serum potassium levels remained constant during the 6-month period in both the low-dose and regular-dose groups (Table 4). There were no serious adverse events that caused withdrawal of treatment during the study period.

DISCUSSION

In this study, we found that low-dose valsartan therapy could reduce proteinuria without causing any intolerability in normotensive IgAN patients with minimal proteinuria presenting as a UPCR of 0.3 to 1.0 mg/mg creatinine.

It has been recommended that angiotensin inhibition should be prescribed in IgAN patients with proteinuria above 1.0 g/day [12,20-22], because ACE-I and ARB could decrease proteinuria and slow renal deterioration in IgAN patients. IgAN patients showed a favorable out-

come when time-averaged urinary protein excretion was reduced to less than 1.0 g/day. However, whether or not the long-term outcome differs in IgAN patients with a proteinuria of 0.5 to 1.0 g/day, compared with those with less than 0.5 g/day, remains uncertain [23]. Recently, several studies have shown that a considerable portion of normotensive IgAN patients with proteinuria of less than 0.5 to 1.0 g/day experience slow disease progression [6,9-11,24]. Furthermore, the renal outcome is reported to be better with a time-averaged proteinuria value of less than 0.5 g/day compared to 0.5 to 1.0 g/day [7]. Partial remission of proteinuria is also associated with a better renal outcome in IgAN patients [9,25]. Therefore, the KDIGO guidelines suggest ACE-I or ARB treatment in patients with proteinuria of 0.5 to 1.0 g/day. In addition, it is recommended that the dose of ACE-I or ARB should be increased to the extent that adverse events are acceptable to achieve urinary protein excretion of less than 1 g/day [12].

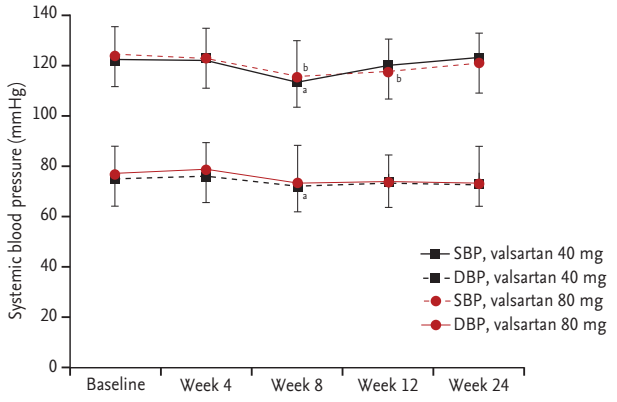

Figure 3. Effects on systemic blood pressure following administration of valsartan 40 or 80 mg in normotensive immunoglobulin A nephropathy patients presenting with minimal proteinuria. SBP, systolic blood pressure; DBP, diastolic blood pressure. [a]$p < 0.05$ vs. baseline SBP/DBP on the low-dose group (valsartan 40 mg). [b]$p < 0.05$ vs. baseline SBP of the regular-dose group (valsartan 80 mg).

However, whether or not ARB reduces proteinuria without causing intolerability, such as symptomatic hypotension, in normotensive IgAN patients with minimal proteinuria is questionable. A recent study reported that losartan at 12.5 mg/day can reduce proteinuria in normotensive IgAN patients with mild-to-moderate proteinuria; however, BP decreased after low-dose losartan therapy [15]. When the initial dose of olmesartan (5 mg) was increased stepwise to 10, 20, and 40 mg after confirming tolerability at weeks 4, 8, and 12, an antiproteinuric effect of olmesartan was observed in normotensive IgAN patients with a UPCR of 0.5 to 3.0 mg/mg creatinine [16]. However, 56% of patients did not complete the course of olmesartan due to its intolerability.

Similarly, some normotensive IgAN patients may have experienced a decrease in systemic BP after ARB therapy. Although it is not common, they may be unable to tolerate even moderate doses of ARB. In addition, a meta-analysis by the ACE Inhibition in Progression Renal Disease (AIPRD) Study Group found an association between a systolic BP of less than 110 mmHg and higher

Table 4. Changes in laboratory parameters following administration of valsartan in normotensive immunoglobulin A nephropathy patients presenting with minimal proteinuria: the effects of dose and time

Parameter	Valsartan treatment, mg	Baseline	Week 4	Week 8	Week 12	Week 24
Serum creatinine, mg/dL	40	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	0.9 ± 0.2	0.8 ± 0.3
	80	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	0.8 ± 0.2
	p value	0.893	0.776	0.872	0.943	0.801
eGFR, mL/min/1.73 m^2	40	107.7 ± 26.7	110.5 ± 31.8	102.8 ± 25.4	106.7 ± 27.5	100.1 ± 38.0
	80	96.7 ± 19.8	97.4 ± 19.5	93.6 ± 20.2	95.2 ± 22.4	99.2 ± 32.5
	p value	1.440	0.134	0.256	0.177	0.946
Serum potassium, mEq/L	40	4.1 ± 0.3	4.1 ± 0.2	4.1 ± 0.3	4.1 ± 0.3	4.2 ± 0.3
	80	4.1 ± 0.4	4.0 ± 0.2	4.1 ± 0.3	4.3 ± 0.5	4.2 ± 0.3
	p value	0.509	0.264	0.592	0.138	0.934

Values are presented as mean ± SD. *p* value vs. baseline of each treatment group.
eGFR, estimated glomerular filtration rate.

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risk of progression of kidney disease during antihypertensive therapy with or without ACE-I in patients with nondiabetic kidney disease [14]. This finding suggests that avoiding a decrease in BP to less than 110 mmHg after ACE-I or ARB therapy is preferable, whether or not hypotension causes symptoms requiring discontinuation of antihypertensive medication.

In these respects, our study provided meaningful evidence for the antiproteinuric effect and tolerability of low-dose valsartan therapy in normotensive IgAN patients presenting with minimal proteinuria. Our finding that low-dose ARB therapy reduced proteinuria significantly without causing intolerability in IgAN patients with favorable clinical features is consistent with a recent small prospective controlled trial using a low dose of losartan. Similar to our results, losartan (12.5 mg/day) reduced proteinuria in 18 normotensive IgAN patients with proteinuria of more than 0.4 g/day (mean, 0.81 ± 0.51 g/day) and BP remained constant over the 12-month period [17].

Interestingly, in contrast to normotensive IgAN patients with minimal proteinuria, normotensive patients with type 1 diabetes and normoalbuminuria may have different responses to treatment with ARB. Mauer et al. [26] reported that the albumin excretion rate is higher in a losartan (100 mg daily) group than in a placebo group in normotensive patients with type 1 diabetes and normoalbuminuria. However, their unexpected and unexplained finding of an increase in the incidence of microalbuminuria in the losartan group has not been confirmed by other randomized controlled trials. For example, the Diabetic Retinopathy Candesartan Trials did not find a higher incidence of microalbuminuria in normotensive diabetic patients with normoalbuminuria receiving candesartan compared to those receiving placebo [27]. Similarly, our study also did not show a paradoxical increase in proteinuria after valsartan therapy in normotensive IgAN patients with minimal proteinuria.

Our study had several shortcomings. First, we could not determine whether the antiproteinuric effect of valsartan induced a favorable renal outcome in normotensive IgAN patients with minimal proteinuria, because the follow-up period was relatively short. The effects of treatment with low-dose valsartan on long-term renal prognosis remain to be elucidated. Second, our study was not designed to assess the role of renal biopsy findings in reducing proteinuria; therefore, we did not analyze the correlation between biopsy grade and the change in proteinuria. Third, a significant antiproteinuric effect of low-dose valsartan therapy was observed after 24 weeks of treatment in this study; however, compared with the regular-dose group, the BP of the low-dose group did not change significantly during the study period. This finding may be important in the sense that low-dose valsartan therapy could reduce proteinuria without causing hypotension, considering the report of the AIPRD study group that a systolic BP of less than 110 mmHg may be associated with a higher risk of progression of kidney disease in patients with nondiabetic kidney disease [14]. Fourth, this study included relatively few subjects. Finally, the possibility of spontaneous regression of proteinuria could not be completely ruled out in our non-placebo-controlled study, because urinary protein excretion may have decreased spontaneously in IgAN patients [28,29]. Based on the finding that a favorable feature does not always indicate a favorable disease course, we were concerned that the placebo treatment might raise ethical issues even in subjects with minimal proteinuria. Therefore, we adopted a randomized two-armed parallel-group comparative design to overcome this limitation. The possibility that spontaneous regression of proteinuria might distort the results of this study could be eliminated by comparing two groups (the low-dose and regular-dose groups) after equal randomization. However, a randomized placebo-controlled trial is required to exclude completely the possibility that the protein-lowering effect is caused by spontaneous regression of proteinuria instead of ARB therapy.

In conclusion, our study demonstrated that low-dose valsartan therapy could reduce proteinuria significantly in normotensive IgAN patients with minimal proteinuria and normal renal function. The antiproteinuric effect of low-dose valsartan was achieved without causing any intolerability. Further randomized controlled trials are necessary to clarify whether low-dose valsartan has not only a protein-lowering effect but also a long-term renoprotective action in normotensive IgAN patients with minimal proteinuria.

KEY MESSAGE

1. Low-dose valsartan therapy reduced proteinuria significantly without causing any intolerability in normotensive immunoglobulin A nephropathy (IgAN) patients with minimal proteinuria and normal renal function.
2. To achieve an antiproteinuric effect, low-dose valsartan should be used for > 24 weeks in normotensive IgAN patients with minimal proteinuria.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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