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Therapeutic Effect of Angiotensin Receptor Antagonist on Patients with IgA Nephropathy

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The aim of the present study was to examine the antiproteinuric effects of two angiotensin II receptor blockers (ARB), losartan and candesartan, in patients with IgA nephropathy. Seventeen patients (7 men and 10 women; mean age, 43.2 ± 12.9 years) were enrolled in this study. Fifteen patients was given 12.5～100 mg/day of losartan, and two patients ware given 2～8 mg/day of candesartan. Nine patients responded to the treatment (R group) and 8 patients did not (NR group). The clinical parameters, including the percentage of patients who also received steroid or angiotensin-converting enzyme inhibitor combination therapy, were not significantly different between the groups. The administration of an ARB significantly reduced the proteinuria from a basal value of 1.0 ± 0.4 g/day to 0.4 ± 0.4 g/day ($p<0.05$), with this effect appearing 3.0 ± 2.2 months after the start of treatment. An additional reduction in proteinuria was observed when the ARB dose was increased in the R group, but this effect was not observed in the NR group. Moreover, the ARB treatment significantly reduced the mean arterial pressure (MAP) from a basal value of 98.2 ± 12.8 mmHg to 90.5 ± 13.3 mmHg in the R group ($p<0.05$). However, the MAP remained unchanged throughout the study in the NR group (93.8 ± 16.8 vs. 99.6 ± 10.7 mmHg). After the ARB treatment, a weak but significant correlation was found when the MAPs were compared with the levels of proteinuria ($r = 0.271$, $p = 0.024$). Finally, no significant difference in the pathological factors of the two groups was observed. In conclusion, our study shows that, the addition of an ARB to the conventional therapy for IgA nephropathy has an additive anti-proteinuric effect that is related to a reduction in blood pressure.

Key words: IgA nephropathy, angiotensin receptor antagonist (ARB), proteinuria, hypertension, renal pathology

Introduction

IgA nephropathy is the most common form of idiopathic glomerulopathy in Japan[1] and other countries[2]. The clinical course of this disease is not always benign, and up to 30% of patients may progress to end-stage renal disease within 10 years[3]. Proteinuria, hypertension, and persistent microscopic hematuria have been associated with

a deterioration in renal function in patients with IgA nephropathy[3]. A recent report has suggested that the onset of progressive renal insufficiency is preceded by the development of proteinuria and hypertension[4].

The renal hemodynamic actions of angiotensin II (AII) blockade have been extensively studied in both normal volunteers[5][6] and in non-diabetic patients with moderate renal insufficiency[7]. The action of AII subtype 1 (AT1) receptor antagonism generally seems to be comparable with that of angiotensin-converting enzyme (ACE) inhibition, although some differences have been reported, including the effects of these actions on bradykinin, prostaglandins, and renal sympathetic nerve activity[8].

Several studies have shown that in various kinds of glomerular diseases, AII contributes to the appearance of proteinuria, while ACE inhibitor significantly reduces proteinuria[9][10]. The reduction of proteinuria by ACE inhibition is considered to be mediated by a reduction in intraglomerular pressure that is independent of the reduction in systemic blood pressure and/or the non-hemodynamic intrarenal effects of the ACE inhibitor[11][12]. However, the renoprotective effects of AII receptor blockade (ARB) in IgA nephropathy have not been elucidated.

The aim of the present study was to examine the antiproteinuric effects of losartan and candesartan, two different ARBs, in patients with IgA nephropathy.

Patients and Methods

Seventeen patients with IgA nephropathy (7 men and 10 women; mean age, 43.2 ± 12.9 years) were enrolled in this study. All of them were outpatient. In each patient, the diagnosis of IgA nephropathy was based on renal biopsy findings, including predominant IgA deposition with or without C3 staining in the glomerular mesangial areas. None of the patients had any clinical or laboratory evidence of liver disease, Henoch-Schönlein purpura, or other systemic diseases. The mean duration from the time of onset was 9.6 ± 4.3 years.

Clinical and laboratory data for the 17 patients were evaluated with regard to sex, age at time of onset, disease duration, and the presence of hypertension (defined as a systolic blood pressure of more than 140 mmHg and/or diastolic pressure of more than 90 mmHg). The following laboratory findings were also evaluated at the time of the renal biopsy and at the time of the final observation: mean arterial pressure (MAP, mmHg), serum creatinine (sCr, mg/dl), creatinine clearance (Ccr, ml/min), urinary protein excretion (U-P, g/day), and the grade of hematuria (U-RBC, RBC/HPF). To measure the U-P, patients collected their urine at home for 24 hours, and measured urine volume. The protein concentration in the part of their urine were examined.

Light microscopy was used to determine the histological grade of the IgA nephropathy, as previously described[13]. The percentage of glomeruli exhibiting glomerular obsolescence, crescent formation, and glomerular tuft adhesion to Bowman's capsule were examined. Interstitial changes were evaluated on the basis of inflammatory cell infiltration and graded into four degrees of severity: grade 0, no abnormality; grade 1, mild; grade 2, moderate; and grade 3, severe. Vascular changes concerning arterio- and arteriolosclerosis were also evaluated using a similar grading scale: grade 0, no abnormality; grade 1, mild; grade 2, moderate; and grade 3, severe.

We administered candesartan (2～8 mg/day) to 2 patients and losartan (12.5～100 mg/day) to 15 patients. The mean observation time was 12.1 ± 5.5 months. Patients in whom the final proteinuria level was less than 30% of the initial proteinuria level were placed in the response (R) group, while the remaining patients were placed in the non-

Table 1 Clinical characteristics of IgAN patients before treatment

Pt. No	Sex	Age	Onset age	Duration of therapy	Complication	MAP (mmHg)	sCr (mg/dl)	Ccr (ml/min)	U-RBC (/HPF)	U-P (g/day)
Responder group (n=9)										
1	m	26	17	9	(−)	95.3	1.15	78.5	0	0.40
2	m	49	38	11	HT	116.2	1.62	74.7	3	1.25
3	m	37	19	18	HT	92.4	0.97	120.0	10	1.12
4	f	65	55	10	HT	100.1	1.24	59.9	0	0.85
5	m	52	40	12	HT, DM, HL	92.7	1.25	86.1	0	0.74
6	f	25	19	6	(−)	72.9	1.00	70.8	15	1.80
7	f	46	39	7	HT	103.3	0.89	82.7	30	0.99
8	f	43	31	12	HT	114.0	1.39	43.0	0	0.41
9	m	51	39	12	HT	96.9	1.24	87.8	6	1.26
mean	m 5	43.8	33.0	10.8		98.2	1.19	78.2	7.1	0.98
s.d.	f 4	12.8	12.7	3.5		12.8	0.23	21.1	10.1	0.44
Non-responder group (n=8)										
10	m	30	23	7	HT	83.3	1.56	65.4	6	1.95
11	m	51	47	4	HT	100.7	1.31	91.0	6	4.10
12	f	47	31	16	HT, HL	100.3	1.44	48.2	15	3.24
13	f	64	54	10	HT	84.3	1.71	43.2	0	1.57
14	f	43	37	6	HT, HL	96.7	0.99	88.6	100	0.99
15	f	57	49	8	HT, DM	126.7	1.06	57.0	0	0.64
16	f	32	18	14	(−)	88.0	1.03	78.0	3	0.93
17	f	25	24	1	(−)	70.0	0.74	93.8	50	0.61
mean	m 2	43.6	35.4	8.3		93.8	1.23	70.7	22.5	1.75
s.d.	f 6	13.8	13.5	5.0		16.8	0.33	20.0	35.4	1.29

HT: hypertension, DM: diabetes mellitus, HL: hyperlipidemia.

Table 2 Comparison of clinical parameters in responder (R) group and non-responder (NR) group

	R group (n=9)	NR group (n=8)	p-value
Age (years)	43.8±12.8	43.6±13.8	n.s.
Sex (male/female)	5/4	2/6	n.s.
Onset age (years)	33.0±12.7	35.4±13.5	n.s.
Duration of therapy (months)	10.8±3.5	8.3±5.0	n.s.
Proteinuria (g/day)	0.98±0.44	1.75±1.29	n.s. (0.11)
U-RBC (/HPF)	7.1±10.1	22.5±35.4	n.s. (0.23)
sCr (mg/day)	1.19±0.23	1.23±0.33	n.s.
Ccr (ml/min)	78.2±21.1	70.7±20.0	n.s.
MAP (mmHg)	98.2±12.8	93.8±16.8	n.s.
Complication of HT	7/9	6/8	n.s.
Combination of PSL	5/9	4/8	n.s.
Combination of ACE-I	5/9	2/8	n.s.
Combination of Ca antagonist	3/9	3/8	n.s.
Combination of β blocker	1/9	0/8	n.s.
Serum aldosterone (pg/ml)	13.2±8.9	11.9±4.2	n.s.

response (NR) group. The clinical courses and renal pathologies were then compared between these two groups. Statistical analysis between two groups was performed by the Student unpaired *t* test. Correlation efficient was determined by regression analysis. Significance was

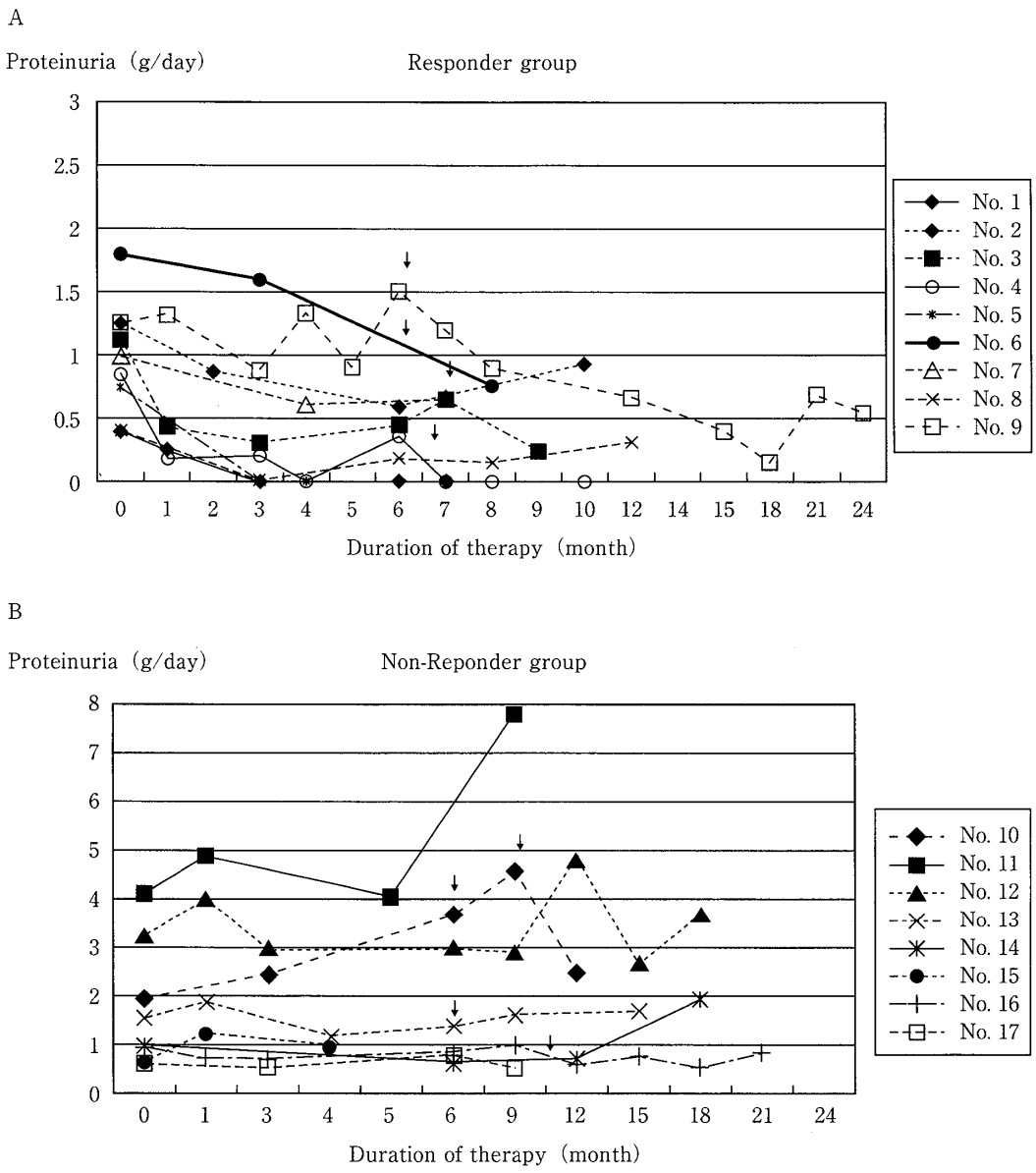

Fig. 1 Changes in proteinuria after treatment with ARB
A: Responder group, B: Non-responder group.
"↓" shows the point that dose of ARB increased. Patients in whom the final proteinuria level was less than 30% of the initial proteinuria level were placed in the response (R) group, while the remaining patients were placed in the non-response (NR) group.

assumed at $p<0.05$.

Results

Of the 17 patients with IgA nephropathy, 9 patients were placed in the R group and 8 patients were placed in the NR group. The clinical characteristics of the IgA nephropathy patients before ARB treatment are summarized in Table 1.

Table 2 compared the clinical parameters in the R and NR groups. No significant difference in clinical parameters, such as the onset age, sex, duration of disease, U-P, U-RBC, sCr, Ccr, MAP and serum aldosterone level was observed between the two groups. Furthermore, the percentage of patients who received combination therapy with steroid or ACE inhibitor also did not differ significantly between the two groups.

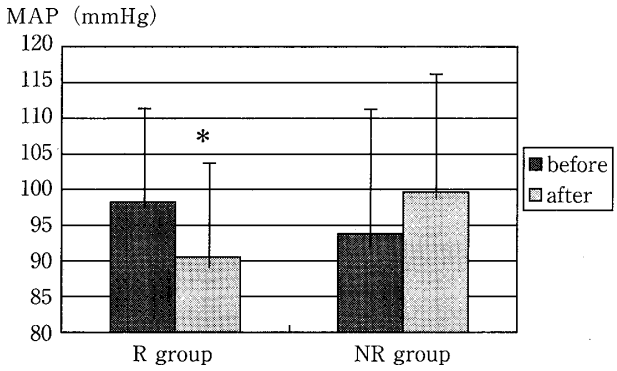

Fig. 2 Effect of ARB on MAP reduction
In responder (R) group, ARB reduced MAP from the basal value of 98.2 ± 12.8 mmHg to 90.5 ± 13.3 mmHg. *$p<0.05$.

The changes in urinary protein excretion in both the R and NR groups are shown in Fig. 1. ARB therapy significantly reduced the level of proteinuria from its basal value of 1.0 ± 0.4 g/day to 0.4 ± 0.4 g/day ($p<0.05$), in the R group; this effect appeared 3.0 ± 2.2 months after the start of treatment. An additional reduction in proteinuria was observed when ARB dose was increased in the R group, but this effect did not appear in the NR group (data not shown).

As shown in Fig. 2, the ARB treatment also significantly reduced the MAP from its basal value of 98.2 ± 12.8 mmHg to 90.5 ± 13.3 mmHg in R group ($p<0.05$). However, the MAP remained unchanged throughout the study in the NR group (93.8 ± 16.8 vs. 99.6 ± 10.7 mmHg). Fig. 3-A and -B show the correlation between MAP and proteinuria. There was no correlation between MAP and proteinuria before treatment with ARB. However, after the treatment with ARB, a weak but significant correlation was observed when the MAPs were compared with the levels of proteinuria ($r = 0.271$, $p = 0.024$). Before the treatment, patients were treated with ACE inhibitor (7 patients), Ca antagonist (6 patients) and β blocker (1 patient).

Finally, we examined the pathological factors that may have played a role in the anti-

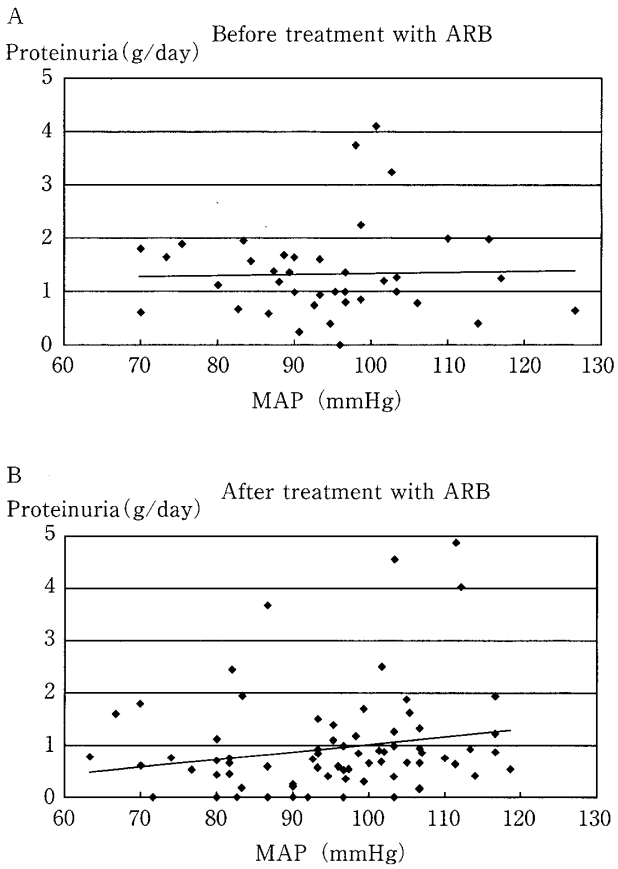

Fig. 3 Relationship between proteinuria and MAP in patients with IgAN after treatment with ARB
A: Before treatment with ARB ($n = 40$ points, $r = 0.027$, n.s.), B: After treatment with ARB ($n = 69$ points, $r = 0.271$, $p = 0.024$).
There was no correlation between MAP and proteinuria before treatment with ARB. However, the correlation between MAP and proteinuria was observed after treatment with ARB.

proteinuric effect of ARB. Table 3 shows a comparison of these pathological factors in the R and NR groups. No significant differences were found for any of the pathological factors.

Discussion

Antihypertensive therapy has been reported to delay the progression of chronic kidney disease in patients with either proteinuric or non-proteinuric nephropathies. Previous studies have shown that the pharmacological blockade of ACE by ACE inhibitors reduces urinary protein excretion and slows the decline in renal function[9)10)].

Table 3 Comparison of pathological factors in responder (R) group and non-responder (NR) group

	R group (n=9)	NR group (n=8)	p-value
gl. obsolescence (%)	17.3±12.9	28.0±21.2	n.s. (0.25)
gl. crescent (%)			
total crescent	14.9±18.5	10.6±12.7	n.s.
cellular & fibrocellular	7.6±9.4	3.8±3.8	n.s. (0.33)
gl. tuft adhesion (%)	22.6±16.5	20.6±12.2	n.s.
mes. cell proliferation	1.50±0.54	1.14±0.38	n.s. (0.16)
mes. matrix increase	1.75±0.46	1.57±0.79	n.s.
interstitial. cell infilt.	0.75±0.46	1.29±0.76	n.s. (0.12)
interstitial. fibrosis (grade: 0 ~ 3)	1.63±0.52	1.71±0.95	n.s.
Arteriosclerosis	0.83±0.75	0.33±0.52	n.s. (0.21)
Arteriolosclerosis (grade: 0 ~ 3)	1.00±0.93	0.71±0.76	n.s.

Moreover, the Ramipiril Efficacy in Nephropathy (REIN) study recently reported that nondiabetics with a proteinuria levels of less than 3 g/day, who were treated with ramipril exhibited a significantly slower decline in their glomerular filtration rates (GFRs) than patients who received the conventional therapy, with no significant difference in blood pressure observed between groups[14].

In patients with IgA nephropathy, antihypertensive therapy with ACE inhibitors has also been shown to be associated with a slower decline in renal function than that of therapy with beta-blockers[15]. A more pronounced anti-proteinuric effect was obtained when ACE inhibitors and ARB were co-administered in normotensive patients with IgA nephropathy[16]. However, only a few studies have evaluated the long-term effects of ARB on proteinuria and renal function in patients with IgA nephropathy[17][18].

The aim of this observational study was to assess whether ARB provides an anti-proteinuric effect when administered to patients with IgA nephropathy and normal or slightly impaired renal function. The present study shows that ARB can exhibit an anti-proteinuric effect in patients with IgA nephropathy. Furthermore, the anti-proteinuric effect of ARB appeares to be associated with a decline in MAP.

The underlying mechanism by which ARB exerts its anti-proteinuric effect is unclear. One explanation is that ARB more completely prevents the changes in renal hemodynamics caused by the portion of AII that is produced through a non-ACE-dependent pathway. This explanation is based on the hypothesis that the positive action of ARB on the glomeruli is not influenced by the incomplete inhibition of the renin-angiotensin system, as is suspected to occur with ACE inhibitors, or by the portion of AII that is produced by chymase in situ. However, whether the reduction in proteinuria is caused by the effects of ARB on systemic hypertension or the inhibition of the effects of AII on renal hemodynamics remains unclear[19].

Roccatello et al[20] examined the effects of renin-angiotensin system blockade on nitric oxide (NO) in patients with IgA nephropathy. The authors showed that the blood levels of NO increased when the renin-angiotensin system was blocked, using enalapril or losartan in these patients. This increase in no way contribute to changes that effect the renal plasma flow in patients with IgA

nephropathy. Woo et al[21] recently showed that ACE inhibitor and/or ARB may modify the distribution of pore sizes in glomeruli by reducing the radius of large, unselective pores; this action would cause the shunt pathway to become less pronounced, resulting in less leakage of protein into the urine. The precise mechanism of ARB's anti-proteinuric effect in patients with IgA nephropathy requires further examination.

Conclusion

In conclusion, our study shows that the addition of ARB to the conventional therapy for IgA nephropathy may have an additive anti-proteinuric effect that is thought to be related a reduction in blood pressure.

References

1) **Koyama A, Igarashi M, Kobayashi M et al**: Natural history and risk factors for immunoglobulin A nephropathy. Am J Kidney Dis **29**: 526–532, 1997
2) **Rychlik I, Andrassy K, Waldherr R et al**: Clinical features and natural history of IgA nephropathy. Ann Med Interne **150**: 117–126, 1999
3) **D' Amico G:** Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. Am J Kidney Dis **36**: 227–237, 2000
4) **Szeto C, Lai FM, To K et al**: The natural history of immunoglobulin A nephropathy among patients with hematuria and minimal proteinuria. Am J Med **110**: 434–437, 2001
5) **Vos PF, Boer P, Koomans HA**: Effects of enalapril on renal sodium handling in healthy subjects on low, intermediate, and high sodium intake. J Cardiovasc Pharmacol **22**: 27–32, 1993
6) **Burnier M, Rutschmann B, Nussberger J et al**: Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. Hypertension **22**: 339–347, 1993
7) **Gansevoort RT, de Zeeuw D, de Jong PE**: Is the antiproteinuric effect of ACE inhibition mediated by interference with the renin-angiotensin system? Kidney Int **45**: 861–867, 1994
8) **Braam B, Koomans HA**: Renal responses to antagonism of the renin-angiotensin system. Curr Opin Nephrol Hypertens **5**: 89–96, 1996
9) **Cattran DC, Greenmood C, Ritchie S**: Long-term benefits of angiotensin-converting enzyme inhibitor therapy in patients with severe immunoglobulin A nephropathy. A comparison to patients receiving treatment with other anti-hypertensive agents and to patients receiving no therapy. Am J Kidney Dis **23**: 247–254, 1994
10) **Maschio G, Alberti D, Janin G et al**: Effect of the angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med **334**: 939–945, 1996
11) **Gansevoort RT, de Zeeuw D, de Jong PE**: Dissociation between the course of the hemodynamic and antiproteinuric effects of angiotensin converting enzyme inhibition. Kidney Int **44**: 579–584, 1993
12) **Hemmelder MH, de Zeeuw D, de Jong PE**: Antiproteinuric efficacy of verapamil in comparison to trandolapril in non-diabetic renal disease. Nephrol Dial Transplant **14**: 98–104, 1999
13) **Taneda S, Honda K, Nitta K et al**: Clinicopathological study of IgA nephropathy in adults: The influence of onset age on clinical and renal histological findings and on the effect of steroid therapy. Clin Exp Nephrol **3**: 96–103, 1999
14) **The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nephrologia)**: Randomized placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet **349**: 1857–1863, 1997
15) **Rekola S, Bergstrand A, Bucht H**: Deterioration rate in hypertensive IgA nephropathy: Comparison of a converting enzyme inhibitor and beta-blocking agents. Nephron **59**: 57–60, 1991
16) **Russo D, Pisani A, Balletta MM et al**: Additive anti-proteinuric effect of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. Am J Kidney Dis **33**: 851–856, 1999
17) **Gansevoort RT, de Zeeuw D**: The antihypertensive and renal effects of angiotensin II receptor antagonist: Remaining questions. Curr Opin Nephrol Hypertens **9**: 57–61, 2000
18) **Burnier M, Brunner RH**: Angiotensin II receptor antagonists. Lancet **355**: 637–645, 2000
19) **Urata H, Bohem KD, Philip A et al**: Cellular localization and regional distribution of an angiotensin II-forming chymase in the heart. J Clin Invest **91**: 1269–1281, 1993
20) **Roccatello D, Mengozzi G, Gigliola G et al**: Effects of angiotensin II blockade on nitric oxide blood levels in IgA nephropathy. Nephrol Dial Transplant **15**: 988–993, 2000
21) **Woo KT, Lau YK, Wong KS et al**: ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis. Kidney Int **58**: 2485–2491, 2000

IgA 腎症患者に対するアンジオテンシン受容体拮抗薬の治療効果

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IgA 腎症患者に対するアンジオテンシン受容体拮抗薬（ARB）の蛋白尿減少効果を，男性 7 例，女性 10 例の計 17 症例で検討した．このうち，15 例は losartan で，2 例は candesartan で加療した．加療後，30% 以上の蛋白尿減少を認めた群を responder（R）群，それ以外を non-responder（NR）群としたところ，R 群は 9 例，NR 群は 8 例であった．両群間にステロイドや ACE 阻害薬の併用など，臨床上の有意差は認めなかった．また，病理組織学的にも両群間に有意差を認めなかった．一方，R 群では ARB の治療前後において，平均血圧（MAP）を有意に低下させたが，NR 群では降圧効果を認めなかった．また，ARB による降圧効果と蛋白尿減少効果は相関することも明らかになった．以上より，ARB は IgA 腎症患者に対し，血圧に依存して蛋白尿を減少させると考えられる．