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Clinicopathological Factors that Affect the Therapeutic Benefits of Inhibitors of the Renin Angiotensin System in Patients with IgA Nephropathy

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Recent studies have shown that inhibitors of the renin-angiotensin system (I-RAS) such as angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB) are effective for IgA nephropathy (IgAN). However, the precise mechanism of the effects remains unknown. The present study was conducted to elucidate the pathological factors affecting the therapeutic benefits of I-RAS in IgAN. Twenty-six IgAN patients were studied retrospectively. The patients were divided into two groups according to the grade of reduction of urinary protein excretion: the responder group ($n = 12$) and the non-responder group ($n = 14$). The modality of treatment was determined by the clinical and histological findings of each patient. No significant difference before treatment was observed between the responder and non-responder groups. In the evaluation of the outcome after treatment, the amounts of urinary protein excretion one year after treatment and at the final observation significantly decreased in the responder group but remained unchanged in the non-responder group. However, the levels of serum-creatinine, urinary red blood cell sediment, and mean blood pressure were not significantly different between both groups. Histologically, the rate of glomerular obsolescence, interstitial inflammatory cell infiltration and interstitial fibrosis tended to be higher in the non-responder group than in the responder group, and the rate of crescent formation tended to be higher in the responder group than in the non-responder group, but did not reach statistical significance. The grades of mesangial cell proliferation and mesangial matrix increase were not significantly different between both groups. The grade of arterio- and arteriolo-sclerosis was significantly higher in the non-responder group than in the responder group (0.92 ± 0.52 vs 1.91 ± 1.08, $p = 0.043$, 1.08 ± 0.79 vs 1.78 ± 0.97, $p = 0.033$). These findings suggest that arterio- and arteriolo-sclerosis could be a predictor for the effectiveness of I-RAS in IgAN patients.

Key words: IgA nephropathy, inhibitors of the renin-angiotensin system, urinary protein excretion, arterio- and arteriolo-sclerosis

Introduction

IgA nephropathy (IgAN) was firstly described by Berger and Hinglais in 1968[1]. Although the prognosis of IgAN was previously considered as relatively good, long term observation revealed that 20-40% of IgAN patients could progress to end stage renal disease (ESRD)[2]. To prevent the progression to ESRD, several therapeutic intervensions have been applied to IgAN patients, and inhibitors of the renin angiotensin system (I-RAS) are one of the renoprotective and anti-proteinuric therapies. Several studies on I-RAS such as angiotensin converting enzyme inhibitor (ACE-I)[3)~11)], angiotensin II receptor blocker (ARB)[7)9)12)~14)] and their use in combined therapy[15)~17)] have been performed for IgAN, and considerably clear evidence was seen that they can have an effect on every grade of IgAN.

But the underlying mechanism by which I-RAS

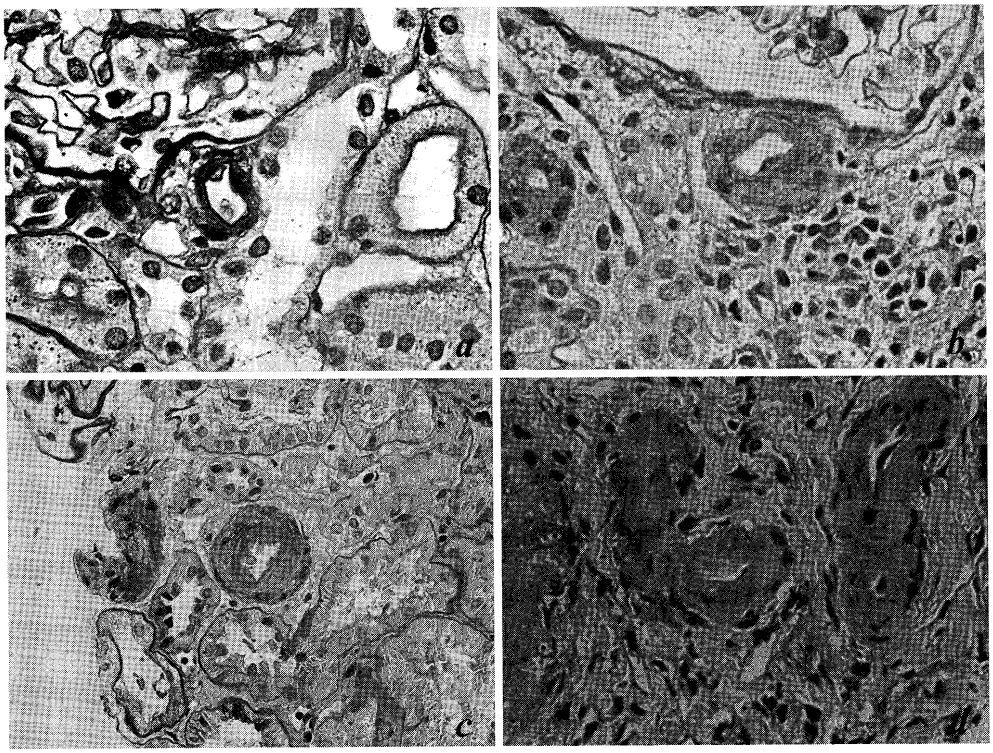

Fig. 1

Qualitative analyses of the arteriolo-sclerosis as a marker of vascular changes are shown in Figs. a-d, which are evaluated using a following grading scale, a: grade 0, no abnormality; b : grade 1, mild; c : grade 2, moderate; and d: grade 3, severe.

exerts its anti-proteinuric and renoprotective effect is unclear. The efficacy of I-RAS was based on the hypothesis that reducing proteinuria by itself induced the histological and functional damage in glomerular epithelial and mesangial cells, tubular cells, and interstitium, and arteriolar vasodilatation of the glomeruli, thereby decreasing the intraglomerular hypertension causing the proteinuria[3)4)12)13)], reducing the size of large unselective pores in the glomerular basement membrane[3)5)6)14)], reducing urinary podocytes[7)], decreasing transforming growth factor-β (TGF-β) production[8)], and blocking a nitric oxide (NO)[9)].

No study has, however, described the correlation between the benefits of I-RAS and the pathological findings. Such a correlation might become an indication of I-RAS therapy for not only IgAN but also other glomerulonephritis. Thus we studied the correlation between the benefits of I-RAS and the pathological findings.

Patients and Methods

Patients

From February 1993 to July 2000, 327 patients were diagnosed as having primary IgA nephropathy by renal biopsy at the Department of Medicine, Kidney Center, Tokyo Women's Medical University. The diagnosis of IgAN was based on light microscopic findings showing mesangioproliferative changes, mesangial IgA and C3 deposition in an immunofluorescence study and the presence of electron-dense deposits in the mesangial area in electron microscopy. Patients with systemic diseases such as diabetes mellitus, collagen disease, abnormal hyper-gamma globulinemia and chronic liver disease were excluded from this study. Among these patients, we selected 26 patients who were started to treat with I-RAS soon after the renal biopsy, not treated with corticosteroids or any other immunosuppressive agents throughout the term of observation, whose urinary protein excretion was over 0.5 g/day and within 3.5 g/day at the time of renal biopsy, and whose clinical course was

followed for at least 2.5 years after the renal biopsy.

We divided the 26 patients into two groups according to the degree of reduction of urinary protein excretion: (1) the responder group in which urinary protein excretion at final observation had reduced by over 50% compared with the time of renal biopsy, and (2) the non-responder group in which urinary protein excretion at final observation had reduced by 50% or under compared with the time of renal biopsy. The responder group consisted of 12 patients (5 men and 7 women) and the non-responder group of 14 patients (6 men and 8 women).

The clinical data of both groups were evaluated with the age at the time of renal biopsy, follow-up period, and the mean arterial pressure (MAP), and laboratory data were also evaluated with serum creatinine (S-Cr), plasma aldosterone level, urinary protein excretion (U-Prot), urinary red blood cell sediment (U-RBC), and creatinine clearance (Ccr) at the time of renal biopsy. The following laboratory findings were also evaluated before treatment, at one year after treatment and at the final observation: S-Cr, U-Prot, U-RBC, MAP.

Histological examination of renal biopsy specimens

All specimens were obtained by the percutaneous needle biopsy method. The specimens were fixed with 10% phosphate-buffered formalin (pH 7.2), embedded in paraffin, and cut into 4 μm sections. Hematoxylin and eosin, periodic acid Schiff (PAS), silver methenamine, and Masson trichrome stainings were performed for light microscopy. Each specimen was evaluated for the glomerular, interstitial, and vascular changes. The changes were scored semiquantitatively by two independent observers without any knowledge of the clinical data. The percentages of glomeruli exhibiting glomerular obsolescence, crescent formation, and glomerular tuft adhesion to Bowman's capsule were estimated.

Mesangial cell proliferation and mesangial matrix increases were each semi-quantitatively graded into four degrees of severity: grade 0, no abnormality; grade 1, mild; grade 2, moderate; and grade 3, severe. Interstitial changes were evaluated on the basis of inflammatory cell infiltration and interstitial fibrosis. The inflammatory cell infiltration was graded into four degrees of severity: grade 0, no abnormality; grade 1, mild; grade 2, moderate; and grade 3, severe. The extent of interstitial fibrosis was semi-quantitatively graded into four categories according to the proportion of fibrotic lesion to total cortical area: grade 0, less than 5% of the total cortical area; grade 1, 5-20%; grade 2, 21-40%; and grade 3, more than 40%. The arterio- and arteriolosclerosis as a marker of vascular changes were also evaluated using a similar grading scale: grade 0, no abnormality; grade 1, mild; grade 2, moderate; and grade 3, severe (Fig. 1 a-d).

For a quantitative evaluation of vascular changes, we attempted color extraction of arterio- and arteriolo-sclerotic area treated with periodic acid Schiff and Masson-trichrome stain using an image analyzer (Olympus DP70, Olympus, Tokyo, Japan). The wall-to-lumen area ratio of interlobular arteries, wall-to-lumen area ratio of capillaries and area ratio of hyalinosis of capillaries were assessed as the ratio of pathological lesions to whole arterial or capillary walls in all specimens (Fig. 2 a, b).

Protocol of the treatment

The twenty-six cases in this study were selected according to the following criteria: (1) proteinuria: >0.5 g/day and <3.5 g/day, (2) follow up period: >2.5 years, (3) no severe inflammatory activities that were the result of steroid therapy, such as a high degree in the presence of cellular and/or fibrocellular crescents, mesangial interposition with mononuclear cell infiltration, and severe interstitial inflammatory cell infiltration, (4) doubling of serum creatinine was the endpoint of this study. The selection of patients for ACE-I or ARB treatment and dose was randomized, and cases to be treated with the combined therapy of these two medicines were excluded from this study.

In the responder group the following I-RASs were used for treatment; lisinopril 2.5, 10 and 20 mg, enalapril maleate 2.5 mg, trandlapril 0.5 and 2 mg, perindpril erbumine 4 mg, benazepril hydrochloride 5 mg, losartan potassium 12.5, 25 and 100 mg, and

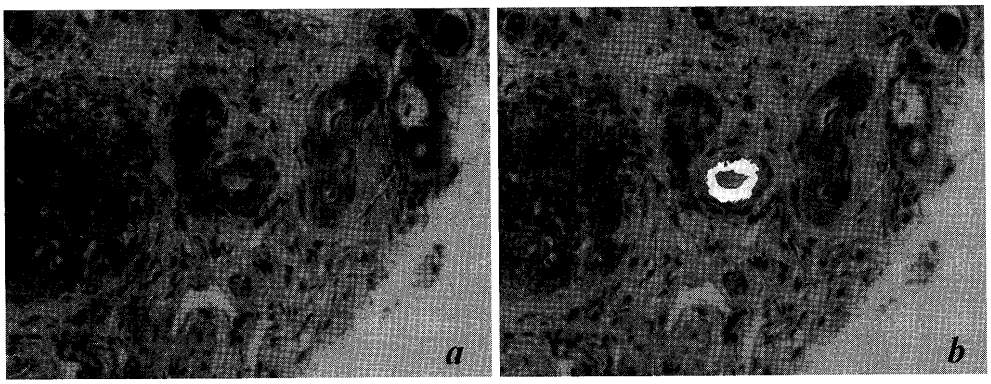

Fig. 2

a : Arteriolo-sclerotic area which is showed as hyalinosis of capillaries.
b : White area in capillary lumen shows hyalinosis of capillaries which is extracted as same color area in Fig. 2-a by image analyzer.

Table 1 Regimens of ACE-I/ARB treatment of both groups

	Responder (n=12)		Non-responder (n=14)	
	mg	cases	mg	cases
Perindpril erbumine	4	1	4	2
Enalapril maleate	2.5	1	2.5	1
Trandlapril	0.5	1	0.5	1
	2	1		
Lisinopril	2.5	1	5	2
	10	1	10	1
	20	1		
Imidapril hydrochloride			5	2
Cilazapril			0.25	2
			0.5	1
Benazepril hydrochloride	5	1		
Candesartan cilexetil	1	1	1	1
Losartan potassium	12.5	1	25	1
	25	1		
	100	1		

candesartan cilexetil 1 mg. In the non-responder group, on the other hand, the following I-RASs were used for treatment; lisinopril 5 (2 cases) and 10 mg, enalapril maleate 2.5 mg, trandlapril 0.5 mg, perindpril erbumine 4 mg (2 cases), imidapril hydrochloride 5 mg (2 cases), cilazapril 0.25 mg (2 cases) and 0.5mg, losartan potassium 25 mg and candesartan cilexetil 1 mg (Table 1).

An anti-platelet drug (aspirin, dipyridamole and dilazep dihydrochloride) was administrated in combination with the I-RAS in 12 cases in the responder group and in 12 cases in the non-responder group (100.0 vs 87.5%, not significantly different). Hypertension was treated with an ACE-I or ARB and other anti-hypertensive drugs. A calcium receptor antagonist and/or alpha blocker was administrated to 3 cases in the responder group and 3 cases in the non-responder group (25.0 vs 21.4%, not significantly different), but no combined therapy of ACE-I and ARB was performed.

Statistical analysis

Data was expressed as mean ± standard deviation (SD), and were compared by the unpaired t-test between the responder and the non-responder group. Significance was accepted as $p < 0.05$ in all analyses.

Results

The comparison of the clinical findings of the patients in each group at the time of renal biopsy is summarized in Table 2. The follow-up period (61.1 ±

Table 2 Clinical characteristics of patients with IgA nephropathy

	Responder	Non-responder	p-value
Case (n)	12	14	
Sex (males/females)	5/7	6/8	NS
Age (years)	42.8 ± 12.6	40.4 ± 11.3	NS
Study period (months)	61.1 ± 28.6	65.6 ± 24.0	NS
S-Cr (mg/dl)	1.35 ± 0.33	1.25 ± 0.23	NS
Ccr (ml/min)	67.5 ± 17.1	70.6 ± 20.5	NS
U-Prot (g/day)	1.41 ± 0.76	1.50 ± 0.90	NS
U-RBC (/HPF)	35.7 ± 58.4	39.6 ± 53.6	NS
PAC (pg/ml)	21.1 ± 17.9	15.9 ± 10.8	NS
MAP (mmHg)	100.1 ± 10.5	97.3 ± 8.73	NS
Hypertension {%(+/−)}	33.3 (4/8)	35.7 (5/9)	NS
ACE-I/ARB {%(ACE-I/ARB)}	66.8 (8/4)	85.7 (12/2)	NS
Anti-hypertensive {%(+/−)}	25.0 (3/9)	21.4 (3/11)	NS
Anti-platelet drug {%(+/−)}	100.0 (12/0)	85.7 (12/2)	NS

S-Cr: serum creatinine, Ccr: creatinine clearance, U-Prot: 24 hr urinary protein excretion rate, U-RBC: red blood cell counts in urine under light microscopy, PAC: plasma aldosterone concentration, MAP: mean arterial pressure, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker.

Table 3 Changes in clinical parameters at the time of renal biopsy and after treatment

	Biopsy	1 year	Final	
Responder (n=12)				
S-Cr (mg/dl)	1.35 ± 0.33	1.35 ± 0.43	1.51 ± 0.51	
U-Prot (g/day)	1.41 ± 0.76	0.81 ± 0.63*	0.41 ± 0.41**	┐
U-RBC (/HPF)	35.70 ± 58.40	9.63 ± 11.10	5.84 ± 6.94	│
MAP (mmHg)	100.10 ± 10.50	95.10 ± 7.05	92.80 ± 9.19	│ ***
Non-responder (n=14)				
S-Cr (mg/dl)	1.25 ± 0.23	1.27 ± 0.30	1.64 ± 0.68	│
U-Prot (g/day)	1.50 ± 0.90	1.32 ± 1.29	1.53 ± 1.28	┘
U-RBC (/HPF)	39.60 ± 53.70	7.71 ± 6.69	11.40 ± 13.80	
MAP (mmHg)	97.30 ± 8.70	92.50 ± 8.87	91.60 ± 9.67	

Biopsy: data at the time of renal biopsy, 1 year: 1 year after I-RAS treatment, Final: data at the time of final observation. S-Cr: serum creatinine, U-Prot: 24 hr urinary protein excretion, U-RBC: red blood cell counts in urine under light microscopy (×400), MAP: mean arterial pressure.
*$p < 0.05$, **$p < 0.01$ vs at the time of renal biopsy, *** $p < 0.01$ between both groups.

28.6 vs 65.6 ± 24.0 months), age at biopsy (42.8 ± 12.6 vs 40.4 ± 11.3 years), S-Cr (1.35 ± 0.33 vs 1.25 ± 0.23 mg/dl), Ccr (67.5 ± 17.1 vs 70.6 ± 20.5 ml/min), U-Prot (1.41 ± 0.76 vs 1.50 ± 0.90 g/day), U-RBC (35.7 ± 58.4 vs 39.6 ± 53.6 counts/HPF), PAC (21.1 ± 17.9 vs 15.9 ± 10.8 pg/ml), MAP (100.1 ± 10.5 vs 97.3 ± 8.73 mmHg) were not different between both groups. No significant difference was seen between the groups in the number of hypertensive patients (hypertension was defined as systolic blood pressure: >140 mmHg and/or diastolic pressure: >90 mmHg), the ratio of ACE-I and ARB, the number of patients who were being treated with anti-hypertensive drugs without ACE-I and ARB, and the number of patients who were being treated with anti-platelet drugs.

Table 3 and Fig. 3 show the outcome of the treatment in both groups. The amount of U-Prot decreased significantly in the responder groups (before treatment: 1.41 ± 0.76 g/day, at one-year after

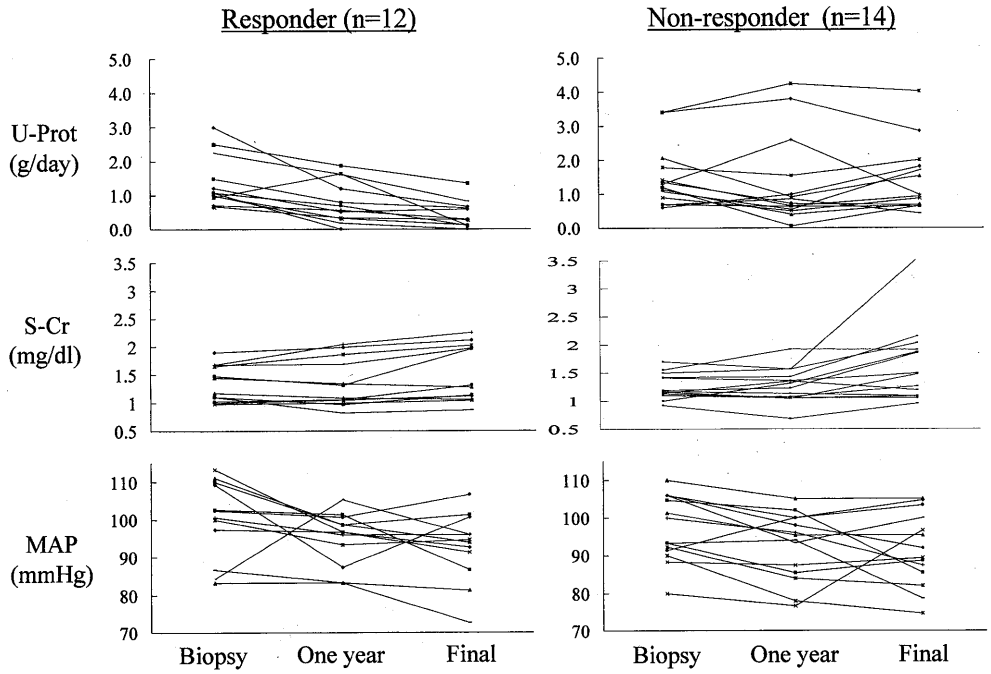

Fig. 3 The outcome of each cases in the responder group and the non-responder group

Table 4 Comparison of renal pathological findings in two groups of IgA nephropathy

	Responder (n=12)	Non-responder (n=14)	p-value
Obsorescence (%)	30.1 ± 20.6	41.0 ± 20.3	NS
Crescent formation (%)	13.3 ± 14.2	5.93 ± 10.4	NS
cellular, fibrocellular (%)	10.2 ± 15.0	4.06 ± 10.20	NS
fibrous (%)	3.06 ± 5.85	0.64 ± 1.57	NS
Adhesion (%)	20.6 ± 19.5	15.6 ± 22.8	NS
Mesangial proliferation (grade)	1.13 ± 0.31	1.11 ± 0.63	NS
Mesangial matrix (grade)	1.42 ± 0.79	1.50 ± 0.48	NS
Interstitial cell infiltration (grade)	1.17 ± 0.94	1.64 ± 0.84	NS
Interstitial fibrosis (grade)	1.50 ± 1.00	2.21 ± 0.80	NS
Grade (active lesion) (score)	2.92 ± 1.56	3.27 ± 1.00	NS
Stage (chronic lesion) (score)	3.92 ± 1.98	4.91 ± 0.94	NS
Arterio-sclerosis (grade)	0.92 ± 0.52	1.91 ± 1.08	0.043
Arteriolo-sclerosis (grade)	1.08 ± 0.79	1.78 ± 0.97	0.033

Mesangial and vascular lesions: grade 0-3 (0: no, 1: mild, 2: moderate, 3: severe),
Interstitial lesions: grade 0-3 (0: < 5%, 1: 6-20%, 2: 21-40%, 3: 41< %),
Grading and staging method described by Shigematsu.

treatment: 0.81 ± 0.63 g/day, p = 0.046, at the final observation: 0.41 ± 0.41 g/day, p = 0.00057). In contrast, in the non-responder group, the amount of U-Prot did not change all through the follow up period (before treatment: 1.50 ± 0.90 g/day, at one-year after treatment: 1.32 ± 1.29 g/day, at the final observation: 1.53 ± 1.28 g/day). Furthermore the amount of U-Prot at the final observation was significantly lower in the responder group than in the non-responder group (0.41 ± 0.41 g/day vs 1.53 ± 1.28 g/day, p = 0.008). On the other hand, no significant differences were observed in the S-Cr levels, U-RBC, MAP between before treatment, at one year after treatment and at the final observation in and between both groups.

Table 4 shows the comparison of the histological findings between the two groups. Glomerular obsolescence (30.1 ± 20.6 vs 41.0 ± 20.3%) tended to be higher in the non-responder group, and crescent formation (13.3 ± 14.2 vs 5.93 ± 10.4%) and adhesion

Table 5 Comparison of vascular lesions in two groups of IgA nephropathy

	Responder (n=12)	Non-responder (n=14)	p-value
Wall-to-lumen area ratio of interlobular arteries	24.20 ± 7.51	19.50 ± 9.04	NS
Wall-to-lumen area ratio of capillaries	17.80 ± 8.45	13.60 ± 6.73	0.02
Area ratio of hyalinosis of capillaries	7.17 ± 9.99	21.00 ± 17.50	0.01

to Bowman's capsule (20.6 ± 19.5 vs 15.6 ± 22.8%) tended to be higher in the responder group, but were not significantly different. The mesangial hypercellularity scores (1.13 ± 0.31 vs 1.11 ± 0.63) and mesangial matrix increase (1.42 ± 0.79 vs 1.50 ± 0.48) were not significantly different between both groups. Grading and staging of glomerulus[18] that suggested active and chronic lesion were not significantly different (2.92 ± 1.56 vs 3.27 ± 1.00, 3.92 ± 1.98 vs 4.91 ± 0.94). The grade of interstitial inflammatory cell infiltration (1.17 ± 0.94 vs 1.64 ± 0.84) and interstitial fibrosis (1.50 ± 1.00 vs 2.21 ± 0.80) tended to be higher in the non-responder group than in the responder group, but not significantly different. However, the grade of arterio- and arteriolosclerosis was significantly higher in the non-responder group than in the responder group (0.92 ± 0.52 vs 1.91 ± 1.08, $p = 0.043$, 1.08 ± 0.79 vs 1.78 ± 0.97, $p = 0.033$). A quantitative analysis revealed that the wall-to-lumen area ratio of capillaries in the responder group (17.8 ± 8.45) was significantly higher than those (13.6 ± 6.73) in the non-responder group ($p = 0.02$), whereas the area ratio of hyalinosis of capillaries in the responder group (7.17 ± 9.99) was significantly lower than those (21.0 ± 17.5) in the non-responder group ($p = 0.01$) (Table 5).

Discussion

Many studies have reported on the benefits of I-RAS for IgAN, and many hypotheses have been advanced in those reports. In fact, for diabetic nephropathy, ACE-I and ARB became the first selected therapy instead of calcium cannel blockers in the guideline of the American Diabetes Association[19], because of their anti-proteinuric and renoprotective effect. The effectiveness of ACE-I and ARB for non-diabetic glomerulonephritis in any grade of renal impairment was furthermore clearly shown.

The most important hypothesis was that the anti-protenuric effect of I-RAS for IgAN was thought to be related a reduction in blood pressure[3)4)12)13)]. I-RAS caused not only reduction of systemic blood pressure but also lowered intraglomerular hypertension by arteriolar vasodilatation of the glomeruli.

Coppo et al[3], Cattran et al[5], Remuzzi et al[6] and Woo et al[14] reported that the effectiveness of I-RAS was due to improvement in glomerular permselectivity and angiotensin II hyperreactivity. Nakamura et al[7] reported the effectiveness of I-RAS depended on improvement of epithelial cell injury and renal hemodynamics, and the same effect could be seen for both ACE-I and ARB. Nakamura et al[8] also reported that I-RAS prevented disease progression by reducing the mRNA levels of TGF-β, collagen type I and III, one of the extracellular matrix components. Nakao et al[15], Panos et al[16] and Russo et al[17] reported on combination therapy with ARB and ACE-I. They reported the benefit of combined therapy depended on improvement of tissue active angiotensin II and the benefit with the combination therapy was more effective than with ACE-I or ARB alone.

Even though many hypotheses have been reported, the mechanism underlying the anti-proteinuric and renoprotective effects of ACE-I and ARB still remains unclear. Furthermore, no reports have appeared on any pathological factor that might affect the benefits of I-RAS and this aspect still remains obscure. Our study attempted to elucidate this factor especially for IgAN that is the most common glomerulopathy in Japan. The special feature of our study was that all cases were treated with ACE-I or ARB soon after biopsy and did not use any corticosteroids or immunosuppressive agents, which allowed us to assess the pathological factors that affected the benefits of ACE-I and ARB.

Our study suggests that arterio- and arteriolosclerosis are the one of the risk factors that had a bad influence on the benefit of I-RAS. The anti-proteinuric effect was different between the responder group and the non-responder group, whereas the anti-hypertensive effect was equal between both groups. This result means that the anti-proteinuric effect of I-RAS does not depend on the reduction of blood pressure alone. Recent studies reported that tissue ACE activity, angiotensin II hyperreactivity, macrophages, and AT 1 receptors were significantly higher in atherosclerotic lesions than in normal vessels[20)21)]. We advance the hypothesis that these factors weaken the effect of therapeutic effect of I-RAS. Nakao et al[15)] reported that ACE-I and ARB combined therapy had little effect in cases of nephrosclerosis. This result supports our hypothesis.

However, there are some problems in our study. Our study did not use the same drugs and used several types and doses of ACE-I and ARB, because our study was a retrospective one. ACE-I and ARB have a different blockade effect on RAS. ACE-I blocks conversion from angiotensin I to angiotensin II and stimulates proinflammatory peptides including substance P and bradykinin-prostaglandin, whereas ARB blocks the angiotensin type 1 receptor including the kimase pathway that can not be blocked by an ACE-I, and stimulates the angiotensin type 2 receptor. These differences in the underlying mechanism may be the reason behind the different effectiveness between ACE-I and ARB.

On the other hand, Nakamura et al[7)8)], Nakao et al[15)], and Russo et al[17)] did not make any difference between ACE-I and ARB, and did not clarify the differences in therapeutic effect of ACE-I and ARB. Furthermore, the ratio of ACE-I vs ARB in both groups in the present study was not significantly different (66.8 vs 85.7%). In addition, the differences in the therapeutic effect based on the type and dose of ACE-I, such as lisinopril, enelapril maleate and trandrapril, and ARB, such as losartan potassium and candesartan cilexetilor, have not yet been clarified. These results led us to the opinion that using several types and doses of ACE-I and ARB had little effect on this study, although the details of the underlying mechanisms were certainly different.

Second, our study used semi-quantitative and qualitative analyses and did not use a quantitative analysis for grading the pathological factors from renal biopsies, such as mesangial proliferate change, interstitial fibrosis, interstitial inflammatory cell infiltration, except arterio- and arteriolo-sclerosis. The semi-quantitative and qualitative analyses of our pathological observers still demonstrated the significant correlation with the quantitative analysis in our previous study [22)].

Third, escape phenomenon concerning the non-responder group in this study was undeniable. We did not inspect the serum aldosterone level throughout this study, but the blood pressure decreased all through this study through the actions of the ACE-I and ARB. That explained why we thought the possibility of its existence was negative. And even if the escape phenomenon were positive, it might be proof that the cases having arterio- and arteriolo-sclerosis tended to cause the escape phenomenon.

Our study is the first report describing the pathological factor that affects the benefits of ACE-I and ARB. Considering these problems, our study includes an important factor that affects the prognosis of IgAN, because our results allowed us to estimate the therapeutic effect of I-RAS before starting medication for IgAN. In conclusion, our study has reported arterio- and arteriolo-sclerosis as a major clinicopathological factor that affects the benefits of I-RAS in patients with IgAN in whom tend to have little anti-proteinuric and renoprotective effect.

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IgA腎症に対するアンギオテンシン系抑制薬の効果に影響を及ぼす組織学的因子の検討

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近年，高血圧を伴う慢性腎炎において，アンギオテンシン変換酵素阻害薬（ACE-I）およびアンギオテンシン受容体拮抗薬（ARB）は，抗蛋白尿効果と腎保護作用を有すると考えられるようになってきた．本研究の目的は，IgA腎症に対するACE-IとARBの効果に影響する組織学的因子を検討することである．対象は，1993年1月から2000年5月まで当科でIgA腎症と診断された327例のうち，生検直後より2.5年以上にわたってACE-IもしくはARB投与した26症例である．経過中にステロイド加療を受けていない症例を選別した．腎生検時と比較して尿蛋白の減少が50%以上の群を反応群（n＝12），50%未満の群を非反応群（n＝14）に分けて検討した．平均観察期間は61.1±28.6 vs 65.6±24.0ヵ月，生検時の臨床所見では年齢は42.8±12.6 vs 40.4±11.3歳，男女比5：7 vs 6：8，血清クレアチニン値（S-Cr）は1.35±0.33 vs 1.25±0.23 mg/dl，24hrクレアチニンクリアランス（Ccr）は67.5±17.1 vs 70.6±20.5 ml/min，尿中赤血球数は35.7±58.4 vs 39.6±53.6/HPFと両群間に有意差はなかった．両群間で生検時の尿蛋白量に有意差は認められなかったが，1.41±0.76→0.41±0.41（p＝0.0006）vs 1.50±0.90→1.53±1.28（NS）g/dayと反応群では有意に蛋白尿が減少した．最終観察時では，S-Crは1.51±0.51 vs 1.64±0.68 mg/dlと有意差は認めず，血圧は両群とも低下傾向を示したが有意ではなかった．病理所見では，糸球体硬化率，半月体形成率，癒着糸球体率，メサンギウムの増殖性変化，間質炎症細胞浸潤，間質線維化において有意差は認められなかった．しかし，「grade 0：なし，grade 1：軽度，grade 2：中等度，grade 3：高度」とgradingした動脈硬化の評価では，細動脈（0.92±0.52 vs 1.91±1.08，p＝0.043）および小葉間動脈硬化（1.08±0.79 vs 1.78±0.97，p＝0.033）は反応群において有意に軽い傾向を示し，細動脈の硝子様硬化部の面積率は有意に非反応群で高く（7.17±9.99 vs 21.0±17.5，p＝0.01），内腔の面積率は有意に反応群で高かった（17.8±8.45 vs 13.6±6.73，p＝0.02）．これらの結果から，腎生検所見で動脈硬化が軽度なIgA腎症の症例に対して，ACE-IあるいはARBの抗蛋白尿効果がより期待できると考えられた．