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ORIGINAL ARTICLE

Long-term beneficial effects of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy for patients with advanced immunoglobulin A nephropathy and impaired renal function

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Abstract
Background There are few reports analyzing the effects of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) on the long-term renal survival of advanced immunoglobulin A nephropathy (IgAN) patients.
Patients and methods In this retrospective cohort analysis, we divided 66 IgAN patients with an estimated glomerular filtration rate (eGFR) <60 ml/min into three groups: ACEI group ($n = 20$, treated with ACEIs), ARB group ($n = 23$, treated with ARBs), and control group ($n = 23$, treated with antiplatelet agents), and analyzed the clinical and histological background, renal survival rate until the primary endpoint of 50% decrease of eGFR from baseline, and the secondary endpoint of progression to end-stage renal disease, and the risk factors for progression.
Results The clinical and histological background without serum IgA and C3 were not significantly different among the three groups. The renal survival rate until the primary and secondary endpoints was significantly higher in the ACEI and ARB groups than in the control group. The independent risk factors for progression were higher mean blood pressure (hazard ratio [HR] 1.76, $P = 0.04$), higher histological grade (HR 2.54, $P = 0.0184$) at baseline, and without ACEIs or ARBs (HR 7.09, $P = 0.001$), but decreased proteinuria and blood pressure. The risk factors with resistance to ACEIs or ARBs were higher blood pressure and lower eGFR at baseline. There was no difference regarding the survival rate and the risk for progression between ACEI s and ARBs.
Conclusion ACEIs or ARBs were effective for long-term renal survival of advanced IgAN, although proteinuria and blood pressure did not decrease.

Keywords IgA nephropathy · Angiotensin-converting enzyme inhibitors · Angiotensin receptor blockers · Urinary protein excretion

Introduction

More than four decades have passed since immunoglobulin A nephropathy (IgAN) was first reported by Berger and Hinglais [1]. Over these four decades, the beneficial effects of several therapies, such as tonsillectomy and treatment with agents such as corticosteroids, immunosuppressive agents, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), antiplatelet agents, etc., have been attempted [2–4], and these therapies appeared to be effective for improving the prognosis and outcome of IgAN patients [5, 6]. ACEIs and ARBs have been reported to have renoprotective effects by reducing glomerular hyperfiltration and urinary protein excretion [7, 8]. Therefore, these drugs are probably more suitable for patients with advanced IgAN who show marked glomerular hyperfiltration due to a reduction in the number of nephrons by glomerulosclerosis, than for patients with early-stage and active IgAN who show crescent formation. Few studies, however, have investigated the effects of ACEI and/or ARB treatment in patients with advanced IgAN with deteriorating renal function. Furthermore, while a number of reports have shown the short-term beneficial effects of

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ACEIs and ARBs in reducing urinary protein excretion, there are few reports about the long-term beneficial effects of treatment with these drugs, in terms of delay of the progression to end-stage renal disease (ESRD) and prognosis. As almost 13 years have elapsed since the first ARB, losartan potassium, was used for the treatment of hypertension in Japan, it is time to analyze the long-term beneficial effects of ARBs and ACEIs because the main goal of IgAN therapy is to improve long-term prognosis.

In this retrospective cohort study, we analyzed the long-term beneficial effects of ACEI and/or ARB treatment in patients with advanced IgAN with an estimated glomerular filtration rate (eGFR) <60 ml/min, in comparison with disease progression in a control group composed of advanced IgAN patients treated with antiplatelet agents.

Patients and methods

Patients

From January 1984 to December 2007, 718 patients were diagnosed as having primary IgAN by renal biopsy at Tokyo Women's Medical University. The diagnosis of IgAN was based on the light microscopic findings of mesangial proliferative changes, immunofluorescence study findings of mesangial IgA and C3 deposition, and electron microscopic findings of electron-dense deposits in the mesangial area. Patients with systemic diseases such as diabetes mellitus, collagen diseases, abnormal hypergammaglobulinemia and chronic liver diseases were excluded from this study. From the remaining patients, we selected all patients who met the following criteria: (1) eGFR <60 ml/min at the time of renal biopsy, (2) urinary protein excretion under the nephrotic range (3.5 g/day) at the time of renal biopsy, (3) treated with ACEIs or ARBs, and/or antiplatelet agents soon after renal biopsy, and (4) not treated with a combination of ACEIs and ARBs, steroids, immunosuppressive agents, or tonsillectomy during the observation period. There were 66 patients who met these criteria, and there was no patient selection bias. The prescription of the drugs was according to the each doctor's own decision. We divided these 66 patients into three groups according to the treatment they had received: ACEI group (treated with ACEIs, $n = 20$), ARB group (treated with ARBs, $n = 23$), and control group (treated with antiplatelet agents, $n = 23$). The clinical data analyzed in each group included sex, age, body mass index (BMI), systolic, diastolic, and mean blood pressure (S-BP, D-BP, and M-BP), interval from the onset to renal biopsy (interval from onset), and laboratory data such as serum total protein (TP), serum albumin (Alb), blood urea nitrogen (BUN), serum creatinine (S-Cre), eGFR, serum uric acid (UA), serum potassium (K), serum total cholesterol (T-Cho), LDL cholesterol (LDL-C), triglyceride (TG), serum IgA, serum C3, urinary protein excretion (U-Prot), urinary red blood cell (U-RBC), urinary beta-2 microglobulin (U-β2MG), urinary *N*-acetylglutamate (NAG), and the clinical grade at the time of renal biopsy as determined according to the clinical grading criteria of the Japanese Society of Nephrology [9] (Grade 1, U-Prot <0.5 g/day; Grade 2, eGFR ≧60 ml/min and U-Prot ≧0.5 g/day; Grade 3, eGFR <60 ml/min and U-Prot ≧0.5 g/day). U-RBC was assessed by semi-quantitative analysis as 0 count of RBC/high power field (HPF), <1 RBC/20 HPF, 1 RBC/10–19 HPF, 1 RBC/5–9 HPF, 1 RBC/1–5 HPF, 1–5 RBCs/HPF, 5–9 RBCs/HPF, 10–19 RBCs/HPF, 20–29 RBCs/HPF, 30–49 RBCs/HPF, 50–99 RBCs/HPF, and >100 RBCs/HPF, and we selected the lowest number of RBCs in each grade as the data of U-RBC. We also performed survival analysis until the primary endpoint as the decrease of the eGFR was >50% of the value at the time of the renal biopsy, and the secondary endpoint as progression to ESRD (requiring dialysis or renal transplantation). We analyzed the risk factors to progress to the primary endpoint and to resist ACEI or ARB treatment.

Histological findings in the 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 thick sections. The sections were stained with H&E, periodic acid−Schiff (PAS), silver methenamine, and Masson trichrome for light microscopic examination.

The histological findings were graded according to the histological grading criteria of the Japanese Society of Nephrology [9] (Grade 1, glomerular lesions under percentage of affected glomeruli <24.9% of the total number of glomeruli; Grade 2, percentage of affected glomeruli between 25% and 49.9% of the total number of glomeruli; Grade 3, percentage of affected glomeruli between 50% and 74.9% of the total number of glomeruli; Grade 4, percentage of affected glomeruli >75% of the total number of glomeruli. Glomerular lesions were classified as global sclerosis, segmental sclerosis, and crescent formation. The grades were appended with 'A' when there were active lesions, e.g., cellular and fibrocellular crescents, and with 'C' when there were chronic lesions, e.g., global sclerosis, segmental sclerosis and fibrous crescents. These histological parameters were compared between the control and ACEI/ARB groups. Also, the combination of clinical and histological grade according to the Japan Society of Nephrology [9] (Table 1) was also evaluated, i.e., Low risk: the cases which have a low risk to progress to the ESRD; Middle risk: the cases which have a middle risk to progress to ESRD; High risk: the cases which have a high

risk to progress to ESRD; Very high risk: the cases which have a high risk to progress to ESRD within 5 years.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) for normally distributed data and median ± inter quartile range (IQR) for non-normally distributed data, and analyzed using JMP® 8.0.1 (SAS Institute Inc., NC, USA). Unpaired Student's *t* test for normally distributed data and Mann–Whitney's *U* test for non-normally distributed data were used to compare the clinical findings. The chi-squared test was used to compare the clinical and histological grades and the sex distribution at the time of renal biopsy between the control and ACEI/ARB groups. The cumulative renal survival rate until the primary and secondary endpoints was calculated according to the Kaplan–Meier method and the log-rank test. Multivariate Cox regression analysis was used to evaluate the risk factors to progress to the primary endpoint in three groups, and multivariate-adjusted logistic analysis was used to evaluate the response to ACEI and ARB treatment. Each statistical method was expressed as C: chi-squared test, S: Student's *t* test, and M: Mann–Whitney's *U* test in each table. *P* values of <0.05 were considered to be statistically significant in all the analyses.

Results

Comparison of the clinical findings among the three groups at the time of renal biopsy

Table 2 shows the clinical findings at the time of renal biopsy in the three groups: ACEI, ARB and control. The proportion of female patients tended to be lower, and age tended to be higher in the ARB group, blood pressure was slightly higher in the ACEI group, and the interval from onset to renal biopsy was shorter in the control group, but none of the differences were significant. The S-Cre, but not the eGFR, was slightly lower in the ARB group as compared with the values in the other two groups. The serum C3 significantly higher ($P = 0.044$) in the ARB group than in the control group by the Student's *t* test. The U-Prot and U-β2MG tended to be lower in the ARB group and the U-RBC tended to be lower in the ACEI group, although the differences were not significant.

Comparison of the clinical and histological grades among the three groups according to the classification system proposed by the Japanese Society of Nephrology

In all groups, patients with clinical Grade 3 were seen more frequently and those with clinical Grade 1 were seen less frequently with no significant differences among the three groups. With regard to histological changes, patients with Grades 2 and 3 changes tended to be seen more frequently, as were those with chronic changes, with no significant differences among the three groups by chi-squared test (Table 3). Also, in the combination of clinical and histological grade, the patients of high risk and very high risk grade were seen more frequently, but none of the differences were significant (Table 3).

Comparison of the clinical data at the time of renal biopsy and at 1 year after treatment in each group (Table 4), and the median each data decline among three groups (Table 5)

Table 4 showed the comparison of clinical data at renal biopsy and at 1 year after treatment. M-BP and U-Prot were significantly decreased in the ACEI and ARB group, though the control group was not. U-RBC was significantly decreased in the ARB group and control group, though the ACEI group was not. eGFR was maintained in the ACEI group and the control group, though the ARB group was not. In Table 5, median U-Prot at 1 year after treatment was the lowest in the ARB group among three groups and it was significantly lower than the control group (control; 1.12 g/g Cre, the ACEI group; 0.69 g/g Cre, the ARB group; 0.55 g/g Cre, control vs. the ARB group; $P = 0.0121$), and the median rate of U-Prot decline from baseline in the ARB group was also highest among the three groups and it was significantly lower than the control group (control; 24.7% increase, ACEI group; 38.0% decrease, ARB group; 55.8% decrease, control vs. ARB group: $P = 0.0238$); however, both data were not significantly different from the ACEI-group.

Survival analysis until doubling of S-Cre and ESRD

Figures 1 and 2 show the survival analysis until the primary endpoint as 50% decrease of eGFR from baseline (Fig. 1) and the secondary endpoint as the development of

Table 1 Combined clinical and histological grade according to the criteria of Japanese society of nephrology

Clinical Grade	Histological Grade 1	Histological Grade 2	Histological Grade 3 and 4
Clinical Grade 1	Low risk	Middle risk	High risk
Clinical Grade 2	Middle risk	Middle risk	High risk
Clinical Grade 3	High risk	High risk	Very high risk

Table 2 Clinical findings in the three groups at the time of renal biopsy

	Control	ACEI group	ARB group	*P* value	
Sex (male/female)	10/13	10/10	6/17	NS	C
Age (years)	39.8 ± 9.9	39.7 ± 9.5	46.4 ± 12.3	NS	K
BMI	22.4 ± 2.4	21.6 ± 2.5	23.0 ± 3.9	NS	K
S-BP (mmHg)	130.7 ± 20.0	134.7 ± 13.1	130.5 ± 16.2	NS	K
D-BP (mmHg)	76.4 ± 15.2	84.4 ± 11.6	79.6 ± 11.3	NS	K
Interval from onset (years)	8.0 (1.5–10.5)	9.0 (3.0–15.0)	10.0 (5.0–12.0)	NS	K
TP (g/dl)	6.8 ± 0.7	6.8 ± 0.6	6.7 ± 0.6	NS	K
Alb (g/dl)	3.8 ± 0.5	3.9 ± 0.4	3.9 ± 0.4	NS	K
BUN (mg/dl)	19.6 ± 3.9	19.5 ± 5.4	18.5 ± 5.2	NS	K
S-Cre (mg/dl)	1.11 ± 0.22	1.14 ± 0.25	1.04 ± 0.29	NS	K
eGFR (ml/min)	48.2 ± 8.2	47.7 ± 8.4	48.8 ± 10.2	NS	K
UA (mg/dl)	6.5 ± 1.6	6.7 ± 1.7	6.5 ± 1.2	NS	K
K (mEq/l)	4.2 ± 0.4	4.3 ± 0.3	4.3 ± 0.4	NS	K
T-Cho (mg/dl)	205.4 ± 31.8	191.8 ± 31.2	207.8 ± 27.9	NS	K
LDL-C (mg/dl)	121.6 ± 35.7	114.7 ± 22.3	123.2 ± 24.0	NS	K
TG (mg/dl)	153.6 ± 86.2	104.6 ± 41.6	124.9 ± 50.9	NS	K
IgA (mg/dl)	383.9 ± 163.8	343.7 ± 112.5	287.9 ± 81.5	NS	K
C3 (mg/dl)	77.9 ± 22.1	76.3 ± 22.5	93.4 ± 18.4*	0.0048	K
U-Prot (g/g Cre)	1.21 ± 0.74	1.26 ± 0.75	0.87 ± 0.66	NS	K
U-RBC (counts/HF)	30.0 (8.0–70.0)	7.0 (2.75–50.0)	10.0 (5.0–30.0)	NS	K
U-β2MG (μg/l)	139.5 (16.6–277.8)	86.4 (68.5–154.4)	60.5 (39.5–92.8)	NS	K
NAG (U/l)	5.1 (3.9–6.3)	5.5 (4.4–6.7)	5.1 (3.1–8.2)	NS	K
CKD stage (stage 3/4/5)	23/0/0	20/0/0	20/3/0	NS	C

C chi-squared test, *K* Kruskal–Wallis

* $P = 0.04$ versus ACEI by Tukey–Kramer's HSD test

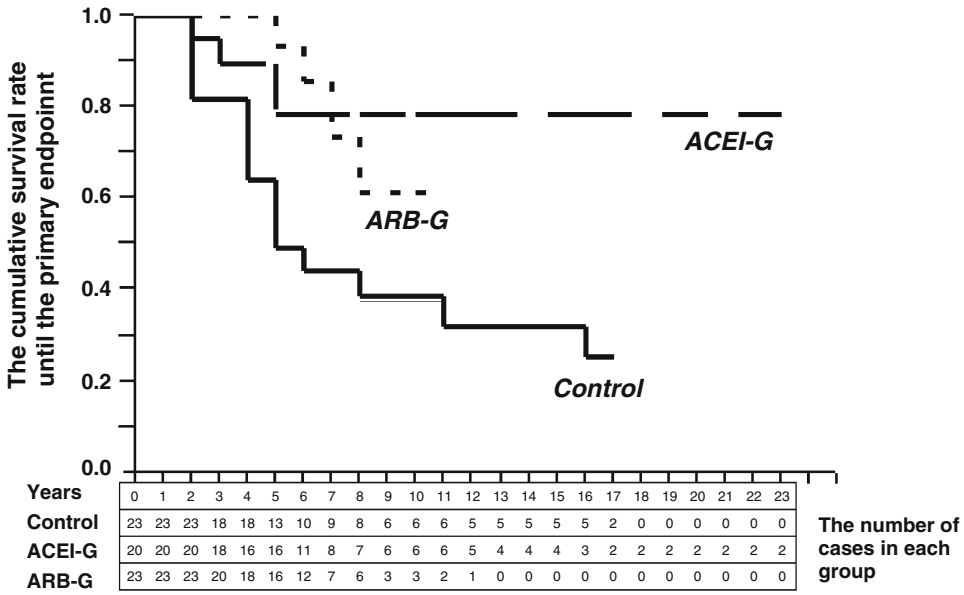

Fig. 1 The cumulative survival rate of each group at the primary endpoints, defined as the 50% decrease of eGFR. The survival rate of the ACEI group (ACEI-G) and the ARB group (ARB-G) was significantly higher than the control group (log-rank test: ACEI-G vs. control, $P = 0.006$; ARB-G vs. control, $P = 0.01$; ACEI-G vs. ARB, not significant)

ESRD (Fig. 2). The median observation period was 5 years (range 2−17 years) in the control group, 6 years (range 2−23 years) in the ACEI group, and 6 years (range 2−12 years) in the ARB group. The cumulative survival rate until the primary and secondary endpoint was significantly higher in the ARB and ACEI groups than that in the control group at both endpoints (log-rank test: primary endpoint: control vs. ARB group, $P = 0.01$; control vs. ACEI group, $P = 0.006$; ARB group vs. ACEI group, not significant; secondary endpoint: control vs. ARB group, $P = 0.04$; control vs. ACEI group, $P = 0.02$; ARB group vs. ACEI group, not significant).

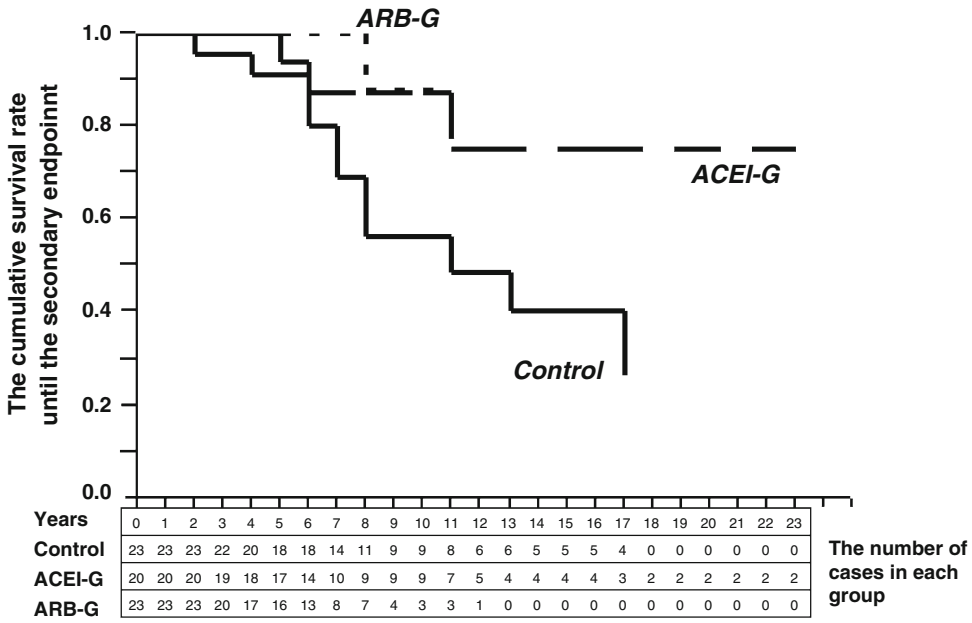

Fig. 2 The cumulative survival rate of each group until the second endpoint, defined as ESRD. The survival rate of the ACEI group (ACEI-G) and the ARB group (ARB-G) was significantly higher than the control group (log-rank test: ACEI-G vs. control, $P = 0.04$; ARB-G vs. control, $P = 0.02$; ACEI-G vs. ARB-G, not significant)

Table 3 Clinical and histological grades in the three groups

	Control	ACEI group	ARB group	*P* value
Clinical grade				NS
Grade 1	4	3	7	
Grade 2	0	0	0	
Grade 3	19	17	16	
Histological grade				
Grade 1 (total/A/AC/C)	4/1/2/1	3/1/0/2	2/0/0/2	NS
Grade 2 (total/A/AC/C)	6/0/2/4	5/0/0/5	7/0/3/4	NS
Grade 3 (total/A/AC/C)	8/0/4/4	4/0/1/3	9/0/2/7	NS
Grade 4 (total/A/AC/C)	4/0/2/2	4/0/2/2	4/0/2/2	NS
Out of evaluation	1	4	1	
Clinical and histological grade				
Low/middle/high/very high	3/1/6/12	1/1/8/6	1/3/5/14	NS

Risk factors to progress to primary endpoint in all groups

The HR of possible risk factors of 50% decrease of eGFR in all group are listed in Table 6. Higher M-BP and higher histological grade were independent risk factors for progression (M-BP: HR 1.76/10 mmHg, $P = 0.0449$; histological grade: 2.54/1 grade, $P = 0.0184$). Without ARB or ACEI treatment was also an independent risk factor (HR 7.09, $P = 0.0014$). However, the decrease in M-BP, U-Prot, and U-RBCs at 1 year after treatment was not effective for the progression of renal disease.

Factors which affect response to ACEI or ARB treatment

We also performed multivariate-adjusted logistic analysis to evaluate the factors which affect the response to ACEI or ARB treatment at the time of biopsy. Lower M-BP and higher eGFR at the time of renal biopsy were associated with a good response to ACEIs or ARBs (lower M-BP: HR 0.23/10 mmHg, $P = 0.013$; higher eGFR: HR 0.19/10 ml/min, $P = 0.0299$). There was no difference regarding prognosis between ACEIs and ARBs.

Discussion

Previous prospective and randomized trials have indicated that ACEIs [10–12] and ARBs [12–16] exert beneficial effects in IgAN patients by reducing urinary protein excretion and improving renal survival rate. Furthermore, trials have shown that a combination therapy with an ACEI plus an ARB may be superior to monotherapy with an ACEI or ARB for reducing urinary protein excretion, lowering blood pressure, and slowing the progression of renal dysfunction [17–20]. All of these trials were short-term studies to evaluate the effects of the drugs in decreasing urinary protein excretion; they did not evaluate the long-term outcome which is most important for the treatment of IgAN. Moreover, these studies involved cases with almost normal renal function. The effect of ACEIs and ARBs should be evaluated in cases with advanced IgAN with deteriorating renal function; treatment for

Table 4 Comparison of clinical parameters in the three groups at renal biopsy and at 1 year after treatment

	At biopsy	1 year after treatment	*P* value	
Control				
M-BP (mmHg)	94.5 ± 15.9	92.3 ± 8.8	0.9415	P
eGFR (ml/min)	48.2 ± 8.2	45.3 ± 11.7	0.1883	P
U-Prot (g/g Cre)	1.21 ± 0.74	1.12 (0.37–2.89)	0.3979	W
U-RBC (counts/HF)	30.0 (8.0–70.0)	5.0 (0.5–25)	0.0101	W
ACEI group				
M-BP (mmHg)	101.2 ± 10.6	95.0 ± 10.4	0.0069	P
eGFR (ml/min)	47.7 ± 8.4	47.7 ± 8.4	0.5749	P
U-Prot (g/g Cre)	1.26 ± 0.75	0.69 (0.51–1.08)	0.0121	W
U-RBC (counts/HF)	7.0 (2.75–50.0)	6.0 (0.625–10)	0.0658	W
ARB group				
M-BP (mmHg)	97.0 ± 10.9	88.2 ± 11.0	0.0107	P
eGFR (ml/min)	48.8 ± 10.2	43.3 ± 11.9	<0.0001	P
U-Prot (g/g Cre)	0.87 ± 0.66	0.55 (0.0–0.72)	0.0466	W
U-RBC (counts/HF)	10.0 (5.0–30.0)	7.5 (1.0–20.0)	0.0080	W

P paired *t* test, *W* Wilcoxon signed rank test

Table 5 Comparison of the clinical parameters among the three groups at 1 year after treatment and median rate of each data decline

	Control	ACEI group	ARB group	*P* value
Data at 1 year after treatment				
M-BP (mmHg)	92.3 ± 8.8	95.0 ± 10.4	88.2 ± 11.0	NS
eGFR (ml/min)	45.3 ± 11.7	47.7 ± 8.4	43.3 ± 11.9	NS
U-Prot (g/g Cre)	1.12 (0.37–2.89)	0.69 (0.51–1.08)	0.55 (0.0–0.72)*	0.0029
U-RBC (counts/HF)	5.0 (0.5–25)	6.0 (0.625–10)	7.5 (1.0–20)	NS
The median rate of each data decline				
S-BP (%)	0 (−12.3 to 12.8)	6.72 (−0.9 to 13.4)	9.3 (0.98–18.3)	NS
eGFR (%)	6.85 (−9.8 to 25.6)	1.33 (−11.1 to 9.8)	12.86 (4.3–19.6)	0.0409
U-Prot (%)	−24.7 (−115.8 to 60.7)	37.9 (−3.73 to 50)	55.8 (−26.4 to 100)**	0.0407
U-RBC (%)	75 (12.5–96.9)	12.5 (−82.5 to 18.75)	75 (0–90)	NS

The median rate of each data decline = (data at renal biopsy − data at 1 year after treatment)/data at renal biopsy × 100

* $P = 0.0121$ versus control by Tukey–Kramer HSD test

** $P = 0.0238$ versus control by Tukey–Kramer HSD test

patients with early-stage IgAN with a low histological grade, low S-Cre and shorter interval between onset and the start of treatment, has almost been established in Japan by combined tonsillectomy plus steroid pulse therapy [21–24]. These results regarding the antiproteinuric effect of ACEIs and ARBs allowed us to hypothesize that ACEIs and ARBs may have long-term beneficial effects in patients with advanced IgAN with impaired renal function, especially via the effect of reducing urinary protein excretion and lowering blood pressure, which are risk factors for progression of renal dysfunction. We selected advanced IgAN patients with an eGFR <60 ml/min at the time of renal biopsy. The clinical and histological grades as defined by the Japanese Society of Nephrology tended to be higher and histological examination showed that about 50% of all glomeruli showed chronic changes, such as global and segmental sclerosis, and fibrous crescents. The maximum follow-up duration was 23 years for the ACEI group, 17 years for the control group, and 12 years for the ARB group. Our results showed good prognosis in the ACEI and ARB groups in comparison to the control group by the Kaplan–Meier method and the log-rank test (Figs. 1, 2). Cattran et al. [25] reported that ACEI therapy produced a greater decrease of U-Prot and prevented deterioration of renal function in comparison to other hypertensive agents in patients with severe IgAN with an average S-Cre value of 1.7 mg/dl and average Ccr of 59 ml/min, even though the observation period was only 2 years. Asaba et al. [6]

Table 6 Hazard ratio of possible 50% decrease of eGFR in multivariate Cox regression

	HR	95% CI	*P* value
Age (per 1 year)	0.94	0.86–1.01	0.1038
Male (vs. female)	3.00	0.80–12.7	0.1038
M-BP (per 10 mmHg)	1.76	1.01–3.17	0.0449
eGFR (per 10 ml/min)	0.45	0.19–1.01	0.0537
U-Prot (per 0.5 g/g Cre)	0.96	0.60–1.49	0.8582
U-RBC (per 25 counts/HF)	1.09	0.72–1.60	0.6547
Histological grade (per 1 grade)	2.54	1.17–5.96	0.0184
Control group (vs. ACEIs or ARBs)	7.09	2.08–28.6	0.0014
Change of MBP (decrease vs. increase)	2.57	0.66–11.1	0.1719
Change of U-Prot (decrease vs. increase)	1.11	0.43–2.89	0.2998
Change of U-RBC (decrease vs. increase)	3.75	0.50–11.4	0.1703

Table 7 Multivariate-adjusted logistic analysis of response to ACEI/ARB therapy

	HR	95% CI	*P* value
Age (per 1 year)	0.96	0.82–1.08	0.5051
Male (vs. female)	3.37	0.01–3.14	0.3269
M-BP (per 10 mmHg)	4.25	1.30–31.4	0.0130
eGFR (per 10 ml/min)	0.19	0.02–0.86	0.0299
U-Prot (per 0.5 g/g Cre)	1.36	0.27–1.73	0.4859
U-RBC (per 25 counts/HF)	1.08	0.25–3.18	0.9016
Histological grade (per 1 grade)	1.22	0.25–6.10	0.7941
ARB treatment (vs. ACEIs)	1.70	0.04–6.90	0.6678

reported that ACEI and ARB therapy prevented progression of renal dysfunction over a long-term observation period (average 9.4 ± 1.2 years, maximum 22 years), although the renal function in their patients was almost normal (average S-Cre, 0.94 ± 0.05 mg/dl). Woo et al. [26] reported that ARB therapy could reduce U-Prot and prevent deterioration of renal function in advanced IgAN patients with an average S-Cre of 1.4 mg/dl for more than 10 years, and that this class of drugs was more effective than ACEIs. These reports lend support to our observation of the long-term beneficial effects of ACEIs and ARBs in patients with severe IgAN. We showed that antiplatelet agent alone caused an approximate seven times higher risk for progression of renal disease in comparison to ACEI or ARB treatment (Table 6). Moreover, our result showed that a decrease of blood pressure and urinary protein excretion were not related to a good prognosis. These results indicate that ACEI or ARB treatment has the pleiotropic effect to improve renal prognosis beyond lowering urinary protein excretion and blood pressure. This renoprotective effect of ACEIs and ARBs might be related with the reduction of glomerular hyperfiltration. We also showed that lower blood pressure and higher eGFR at the time of renal biopsy were associated with a good response to ACEI and ARB treatment. These results show that ACEIs or ARBs are necessary for the treatment of advanced IgAN with impaired renal function, even though they cannot decrease blood pressure and urinary protein excretion, and earlier treatment should be introduced for advanced IgAN, even though renal function has already deteriorated (Table 7).

There was, however, a limitation to our study. The study design is a retrospective observational study, not a prospective randomized one. To provide strong evidence and to evaluate our results without bias, a randomized controlled trial is required.

In conclusion, our study showed that treatment with ACEIs and ARBs is simple and safe and can delay progression of renal function impairment to ESRD in patients with severe IgAN with eGFR values <60 ml/min. The most important fact is to introduce ACEI or ARB treatment earlier and continue the treatment even though the renal function has already deteriorated and a decrease in blood pressure and urinary protein excretion cannot be obtained.

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