Article

Disease Progression, Response to ACEI/ATRA Therapy and Influence of ACE Gene in IgA Nephritis

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Various studies have shown that angiotensin-converting enzyme (ACE) gene insertion/deletion (ID) polymorphism may play a role in the progression to end stage renal failure (ESRF) in patients with IgA nephritis (IgAN). In this randomized controlled trial, patients were followed up for 5 years to determine their long-term renal outcome to ACEI/ATRA therapy and to ascertain if their ACE gene profile could play a role in determining their response to therapy. Seventy-five patients with IgAN were enlisted. Thirty-seven were on ACEI/ATRA therapy for 62 ± 5 months and thirty-eight were untreated and served as controls. All patients had their ACE gene ID polymorphism genotyped. Compared to controls, treated patients had lower serum creatinine ($p < 0.001$), lower proteinuria ($p < 0.002$) and fewer numbers progressing to ESRF ($p < 0.002$). Among patients with genotype II, there were less ESRF in the treatment group when compared to the untreated control group ($p < 0.02$). The advantage of therapy was not seen in patients with ID or DD genotypes. ACEI/ATRA therapy was found to be effective in retarding disease progression in IgAN with years to ESRF significantly extended in patients at all levels of renal function, including patients whose outcome were ESRF. Genotyping showed better response to therapy only for those with genotype II. The common mechanism is probably through lower levels of ACE, glomerular pressure and proteinuria resulting in reduced renal damage and retardation of progression to ESRF. *Cellular & Molecular Immunology*. 2007; 4(3):227-232.

Key Words: ACE gene ID polymorphism, ACEI/ATRA therapy, end-stage renal failure

Introduction

Disease progression in IgA Nephritis (IgAN) depends on clinical and prognostic indices like renal impairment at presentation, degree of proteinuria, degree of glomerulosclerosis and presence of crescents on renal biopsy among other factors (1, 2). However with the advent of ACEI and ATRA therapy it has been shown that the course of renal impairment can be prolonged and in some individuals with mild renal impairment, this can even be reversed (3). In a previous study (4), we reported that patients who had decreased proteinuria also had improvement in renal function. Three out of the 8 patients who had renal impairment prior to angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ATRA) therapy regained normal renal function after therapy with ACEI/ATRA, while the remaining 5 had improvement of renal impairment. However, there were 2 patients who had no decrease in proteinuria and still experienced reversal of their mild renal impairment (the level of proteinuria remained the same after therapy with ACEI/ATRA). Various studies have shown that genomics like ACE gene ID polymorphism may play a role in the development and progression to end stage renal failure (ESRF) in some patients with particular genotypes in IgAN (5, 6).

It has been postulated that individual response to ACEI therapy varies depending on ACE gene polymorphism as those with the D-allele of the ACE gene polymorphism respond better to the antiproteinuria effect of ACEI therapy (6, 7). In this study, 37 patients with IgAN in the treatment group on ACEI/ATRA therapy were compared with other 38 patients with IgAN who were untreated (control group). The 2 cohort of patients were followed up for 5 years to determine their long-term renal outcome (normal renal function, renal impairment, ESRF) in response to therapy. All 75 IgAN patients also had their ACE gene ID polymorphism genotyped to ascertain if their genetic profile could play a

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role in determining their response to therapy.

Materials and Methods

Patients
Seventy-five patients with biopsy proven primary IgAN entered a 5 years control trial, with 37 in the treatment group and 38 in the non-treatment (control) group during the period from October 1999 to December 2000. Their ACE gene ID genotypes were studied in order to compare the effect of ID polymorphism on the response to ACEI/ATRA therapy. Other entry criteria included proteinuria of 1 gram or more and or renal impairment defined as serum creatinine > 1.6 mg/dl. There were no significant differences in the various parameters between the treatment and control group on entry into the trial. In the control group, hypertension was treated with atenolol, propranolol, hydrallazine or methyldopa. All patients were given advice on a low salt diet. The patients in the treatment group were treated with ACEI/ATRA therapy or both and were reviewed at three monthly intervals. Patients were initially prescribed 5 mg Enalapril (ACEI) or 50 mg Losartan (ATRA) which was increased to 10 mg or 100 mg respectively if proteinuria had not decreased to less than 1 gm/day.

Routine tests
Serum creatinine and urinary protein were done on each visit. For this study, each patient was sampled for 2 ml EDTA-blood for DNA extraction and ACE gene ID genotyping. All patients gave their informed consent to participate in the study after the nature of the study was explained to them. The study was approved by the local institution review board and by the hospital ethics committee (No. 58/2003).

Determination of ACE insertion/deletion genotypes
DNA was extracted from 0.2 ml EDTA-blood using the QIAamp DNA Blood Extraction Kit (QIAGEN, Germany). Genotyping was done as the method of Vleming et al. (7). The 50 μl of reaction mixture consisted of 50 ng DNA, 1× PCR buffer (Fermentas), primers concentration 0.4 μM (forward 5'-CTG GAG ACC ACT CCC ATC CTT TCT-3'; reverse 5'-GAT GTG GCC ATC ACA TTC GTC AGA T-3'), 0.2 mM dNTPs and 1 unit Taq polymerase (Fermentas). Amplification was carried out in an automated thermocycler (GeneAmp 9700, USA) for 35 cycles (94°C, 30 s; 60°C, 45 s and 72°C, 60 s). Products were separated in 2% agarose gel and visualised by ethidium bromide staining. Amplification of the I allele produced one band at 490 base pair (bp) for homozygote II. Amplification of the D allele produced one band at 190 bp for homozygote DD. Both bands at 490 bp and 190 bp were produced by heterozygote. Mistyping ACE heterozygotes as DD homozygotes had been reported. Therefore all DD cases were subject to confirmation with a second PCR, performed using the insert specific forward primer 5'-TTT GAG ACG GAG TCT CGC TC-3' together with the same reverse primer above (7). A true DD genotype should give no product at the 409 bp band, whereas ID and II genotypes should.

Statistical analysis
SPSS 10.0 for Windows was used to calculate Pearson's chi-square for comparing categorical data and Student's *t* test for evaluating significance of difference between means of numeric data.

Results

Clinical profile of patients in treatment group
The clinical profiles of the 37 patients in the treatment group together with the data on ACE gene polymorphism were shown in Table 1. The patients are stratified according to their renal outcome, those who continue to have normal renal function (NRF, n = 20), those with impairment renal function (IRF, n = 10) and those with ESRF (n = 7) at the end of the study period. Among NRF patients, there was significant improvement in the mean proteinuria before (2.3 ± 0.8 gm/day) and after (0.8 ± 0.7 gm/day) the trial ($p < 0.001$). Patients with IRF have significant worsening of the renal function, mean serum creatinine 1.84 ± 0.26 mg/dl (before) compared to 2.21 ± 0.53 mg/dl (after), $p < 0.05$, but proteinuria improved (2.0 ± 0.08 to 0.9 ± 0.8 gm/day, $p < 0.01$). For patients with ESRF there was progressive renal deterioration ($p < 0.001$). Five patients with initial renal impairment in the normal renal function group had recovered to normal renal function at the end of the trial (marked with * in Table 1).

Clinical profile of patients in control group
The clinical profiles for 38 untreated patient controls were shown in Table 2. At the end of the trial, there were 6 patients with NRF, 11 with IRF and 21 with ESRF. Among the NRF patients, there was significant improvement in the mean proteinuria before (2.2 ± 1.6 gm/day) and after (0.8 ± 0.6 gm/day) the trial ($p < 0.002$). Patients with IRF had significant worsening in the renal function, mean serum creatinine 1.33 ± 0.36 mg/dl (before) compared to 2.58 ± 0.97 mg/dl (after) ($p < 0.05$) but there was an improvement in proteinuria (2.5 ± 2.0 gm/day before, 1.6 ± 1.0 gm/day after, $p < 0.05$). For those with ESRF there was progresssive renal deterioration ($p < 0.001$). In contrast to the 5 in the treatment group, only 1 patient with initial renal impairment had recovered to normal renal function at the end of the trial in this untreated control group (marked with * in Table 2).

Comparing data between treatment and control group
As shown in Table 3, data were compared between the treatment and untreated control groups at the entry and end points of the trial. At entry, there were no significant differences between the treatment groups and control groups in the various parameters. But at post-trial, the mean serum creatinine in the control group was significantly worse than the treatment group ($p < 0.01$). The post-trial proteinuria in the control group was also worse than that in the treatment group ($p < 0.002$). With regards to renal outcome, there were

Table 1. Clinical profile of 37 patients with IgAN who were treated (Treatment Group)

Case	Age	Sex	HPT	Drug	Dose	Trial	SCr1	SCr2	SCr3	SCr4	SCr5	SCr6	Tup1	Tup2	ACE
Normal renal function															
1	47	M	Y	Prop, ACEI	80, 10	54[#]	1.35	1.45	1.20	1.38	1.26	1.30	2.1	0.5	DD
2	46	F	N	ATRA	100	54	0.77	0.83	0.88	0.92	0.75	0.74	3.4	0.7	ID
3	35	F	N	ATRA	100	60	0.92	1.09	1.20	1.39	1.38	1.33	2.3	0.9	ID
4	35	F	N	ATRA	50	60	0.93	1.02	0.95	0.78	0.76	0.80	1.1	0.2	II
5	27	M	Y	ATRA	100	66	1.71*	1.66	2.01	1.70	1.56	1.49	1.5	0.3	ID
6	22	F	N	ATRA	100	60	0.88	0.69	0.85	0.76	0.80	0.84	3.1	0.3	II
7	46	F	Y	Am, ATRA	5, 100	66	1.64	1.8	1.63	1.59	1.58	1.53	2.4	1.1	DD
8	41	F	Y	At, ATRA	100, 100	54	0.97	0.83	0.93	0.89	0.75	0.77	2.1	0.1	II
9	46	F	Y	ACEI, ATRA	20, 100	68	1.96*	1.82	1.77	1.61	1.53	1.47	1.6	2.2	ID
10	28	M	N	ATRA	100	70	0.91	1.22	0.80	1.12	0.96	1.01	1.9	0.7	II
11	19	M	N	ATRA	100	64	1.73*	1.60	1.71	1.83	1.42	1.40	3.9	2.7	ID
12	43	M	N	ATRA	100	66	1.82*	1.78	1.69	1.4	1.01	1.14	2.3	0.3	II
13	35	M	N	ATRA	100	60	1.5	1.61	1.43	1.32	1.26	1.27	3	0.3	DD
14	25	M	N	ACEI, ATRA	10, 100	68	1.21	1.41	1.26	1.32	0.92	1.30	2.6	0.2	II
15	20	M	N	ATRA	100	70	1.2	1.12	1.24	1.44	1.34	1.38	1.6	0.2	ID
16	26	F	N	ACEI, ATRA	20, 100	58	1.93	2.1	2.26	2.30	1.91	1.55	2.8	0.8	ID
17	42	M	Y	Am, ATRA	5, 100	62	1.46	1.52	1.70	1.83	1.58	1.49	1.4	0.8	II
18	31	F	Y	At, ATRA	50, 100	64	1.49	1.63	2.03	1.86	1.62	1.51	2.6	0.9	II
19	38	F	N	ATRA	100	57	1.33	1.41	1.23	1.04	0.94	1.12	3.4	0.5	DD
20	11	M	N	ATRA	100	63	1.84*	1.92	2.02	1.60	1.32	1.23	1.3	2.1	II
Mean ± SD	33 ± 11					62 ± 5	1.38 ± 0.39[a,b,r]					1.23 ± 0.27[c, d, r]	2.3 ± 0.8[u]	0.8 ± 0.7[f, u]	
Impaired renal function															
1	40	M	N	ATRA	100	65	1.71	1.89	1.88	2.05	2.44	2.38	3.3	0.5	II
2	40	M	Y	Am, ATRA	5, 100	66	2.29	2.76	3.74	2.29	2.19	2.39	0.4	0.3	II
3	45	M	Y	At, ACEI, ATRA	100, 10, 100	54	1.7	1.53	1.49	1.66	1.62	1.59	1.1	0.3	II
4	42	F	Y	Prop, ATRA	80, 100	60	1.99	2.09	2.17	2.12	2.59	2.58	2.1	1	II
5	18	M	Y	Am, ATRA	10, 100	62	1.72	1.78	2.04	2.34	2.22	2.53	2.5	0.9	ID
6	41	F	N	ACEI	20	60	1.36	1.32	1.63	1.70	1.79	1.75	2.6	1.4	DD
7	59	M	Y	ACEI, ATRA	5, 100	60	1.8	1.64	1.81	1.83	1.95	1.92	1.5	0.4	II
8	37	F	Y	Am, ATRA	5, 100	72	2.13	2.04	1.91	2.31	2.49	3.33	2.3	2.6	ID
9	42	F	Y	ACEI, ATRA	5, 100	64	1.74	1.68	1.44	1.80	1.78	1.74	1.8	0.3	II
10	33	F	Y	ACEI	20	58	2.01	2.16	2.91	2.26	2.11	1.89	1.9	1.6	DD
Mean ± SD	40 ± 10					62 ± 5	1.84 ± 0.26[b, s]					2.21 ± 0.53[d, e, s]	2.0 ± 0.8[v]	0.9 ± 0.8[g,v]	
End-stage renal failure															
1	53	M	Y	ACEI	20	65	2	2.3	2.9	3.5	4.03	5.67	2.6	2.2	DD
2	43	F	Y	ACEI, ATRA	10, 100	66	1.67	1.97	1.84	4.20	4.56	6.13	0.9	3	ID
3	46	F	Y	Am, ATRA	5, 100	54	1.70	2.90	3.43	3.97	5.03	6.27	1.1	1.8	ID
4	36	F	Y	Am, ACEI, ATRA	5, 10, 100	54	1.63	2.25	2.60	3.14	3.71	6.41	2.9	3	DD
5	44	M	N	At, ACEI	50, 15	60	1.71	1.87	2.35	2.75	3.25	5.88	1.5	0.7	ID
6	30	F	Y	Am, ATRA	10, 100	52	1.74	2.39	3.07	4.21	6.12	7.32	1.9	2.3	II
7	19	M	Y	At, ACEI, ATRA	50, 10, 100	60	1.92	1.70	2.81	3.92	4.68	6.32	1.5	1.8	II
Mean ± SD	39 ± 12					59 ± 6	1.77 ± 0.14[a, t]					6.29 ± 0.53[c, e, t]	1.8 ± 0.7	2.1 ± 0.8[f, g]	

[#], trial months; *, denotes patients with renal impairment who normalized their serum creatinine.

Am, amlodipine; At, atenolol; Prop, propranolol; ACEI, angiotensin converting enzyme inhibitor; ATRA, angiotensin receptor antagonist

Inter-group *t* test: [a], $p < 0.002$; [b], $p < 0.005$; [c], $p < 0.001$; [d], $p < 0.001$; [e], $p < 0.001$; [f], $p < 0.001$; [g], $p < 0.01$

Intra-group paired-*t* test: [r], $p < 0.05$; [s], $p < 0.05$; [t], $p < 0.001$; [u], $p < 0.001$; [v], $p < 0.01$

SCr1, serum creatinine at entry of trial; SCr2-5, serum creatinine at end of years 1-4, SCr 6,serum creatinine at end of trial; TUP1, total urinary protein in 24 hours at entry of trial; TUP1, total urinary protein in 24 hours at end of trial.

Table 2. Clinical profile of 38 patients with IgAN who were not treated (Control Group)

Case	Age	SEX	HPT	Drug	Dose	Trial	SCr1	SCr2	SCr3	SCr4	SCr5	SCr6	Tup1	Tup2	ACET
Normal renal function															
1	21	M	Y	At	50	65[#]	0.77	1.10	0.90	0.80	1.1	1.14	2.2	1.2	II
2	54	M	N			58	1.07	1.22	1.48	1.40	1.48	1.37	5.2	0.8	II
3	29	M	N			50	0.96	1.00	1.05	0.94	1.15	1.28	1	0.2	ID
4	20	M	Y	At	50	63	1.11	1.00	1.40	1.60	1.2	1.57	2.6	1.8	DD
5	60	M	Y	Prop, H	80, 120	69	1.92 *	2.26	2.71	2.31	1.72	1.48	1.1	0.5	II
6	44	F	Y	Am	10	60	0.90	0.83	1.10	1.39	1.12	1.01	1.3	0.5	ID
Mean ± SD	38 ± 17					61 ± 7	1.12 ± 0.41[a]					1.31 ± 0.21[c, d]	2.2 ± 1.6	0.8 ± 0.6[f]	
Impaired renal function															
1	48	M	Y	At, H	50, 120	60	1.58	1.75	2.04	2.65	2.56	2.81	3.9	2.5	II
2	48	F	N			48	1.14	1.20	1.39	1.57	1.62	1.69	1.2	0.5	ID
3	25	M	Y	At	50	65	1.57	1.87	1.96	2.05	2.22	2.10	7.8	1.8	ID
4	26	F	Y	Prop	120	49	0.95	1.11	1.96	1.80	1.92	1.98	1.5	1.6	ID
5	44	F	N			60	0.88	0.93	0.79	1.69	1.83	1.95	3.2	1.6	ID
6	34	M	N			61	1.31	1.25	1.38	1.41	1.55	1.71	2.3	1.7	II
7	22	M	N			70	1.83	1.98	3.24	4.73	4.20	4.01	1.9	3.8	DD
8	35	F	N			68	1.32	1.70	1.63	2.02	1.91	2.34	1	1.3	II
9	38	M	N			62	1.2	2.15	2.35	3.22	3.63	3.88	1.3	0.6	II
10	23	F	N			60	0.92	1.63	1.62	4.34	3.83	4.13	1.4	1.8	DD
11	21	M	N			66	1.91	1.55	2.04	1.86	1.56	1.82	2.3	0.6	ID
Mean ± SD	33 ± 10					61 ± 7	1.33 ± 0.36[b,r]					2.58 ± 0.97[c, e, r]	2.5 ± 2	1.6 ± 1[g]	
End-stage renal failure															
1	32	F	Y	Prop	120	66	1.48	1.76	2.10	2.71	3.67	7.63	4.4	3.1	II
2	31	F	Y	At, Am	100, 10	49	1.61	1.67	2.68	4.21	6.66	8.61	1	1.7	ID
3	34	M	N			60	1.57	1.59	1.86	4.51	5.86	7.82	5.2	1.8	II
4	41	F	Y	At	75	38	2.81	4.32	7.14	7.88	8.65	9.2	1.4	2.3	II
5	25	M	Y	At, H	100, 120	64	1.71	2.22	4.69	7.26	7.72	7.6	1.6	2.1	II
6	45	F	Y	Prop, H	120, 120	52	1.75	2.27	2.21	4.28	5.69	7.4	1.2	2.4	II
7	29	M	N			62	1.98	2.38	4.13	3.62	6.85	7.2	0.5	1.8	ID
8	40	F	Y	Am	10	56	1.63	2.06	2.60	3.71	6.28	6.93	6.4	4.7	DD
9	44	F	Y	At, Am	50, 5	49	1.72	2.55	3.10	5.12	6.39	8.33	0.6	3.7	DD
10	47	F	N			58	1.28	1.63	1.90	3.61	6.31	6.45	1.4	2.9	DD
11	36	F	Y	At, Am	100, 10	50	1.48	1.53	2.65	5.57	7.4	8.61	3.1	3.5	DD
12	48	F	Y	At	50	56	1.52	2.20	2.91	3.84	5.62	6.32	1.8	1.9	II
13	19	M	Y	Prop	80	64	1.81	1.91	2.20	3.24	4.84	6.59	3.3	2.1	II
14	24	M	N			68	1.73	1.92	3.89	4.43	4.99	6.26	1.5	1.2	II
15	30	M	N			70	1.64	2.30	3.98	5.11	6.12	6.78	3	1.6	II
16	30	M	N			58	1.80	1.63	3.20	4.6	5.56	6.81	2.3	2.8	DD
17	31	F	Y	At, H	50, 120	69	1.43	1.86	2.67	3.91	4.89	6.3	1.4	1.8	ID
18	17	M	N			60	1.71	2.49	3.86	4.43	6.6	7.44	1.4	2.1	II
19	46	M	Y	At	75	62	1.93	2.12	2.93	4.18	5.93	8.61	1.3	2.4	ID
20	18	M	N			60	2.1	1.63	3.20	5.1	4.83	7.2	1.6	0.9	ID
21	31	M	N			62	1.51	2.60	3.29	4.81	6	7.23	1.2	1.8	DD
Mean ± SD	33 ± 10					59 ± 8	1.72 ± 0.31[a, b, s]					7.4 ± 0.87[d, e, s]	2.17 ± 1.54	2.3 ± 0.9[f, g]	

[#], trial months; *, denotes patients with renal impairment who normalized their serum creatinine.

Am, Amlodipine; At, Atenolol; H, Hydrallazine; Prop, Propranolol.

Inter-group *t* test: [a], $p < 0.002$; [b], $p < 0.005$; [c], $p < 0.01$; [d], $p < 0.001$; [e], $p < 0.001$; [f], $p < 0.002$; [g], $p < 0.05$.

Intra-group paired-*t* test: [r], $p < 0.005$; [s], $p < 0.001$.

SCr1, serum creatinine at entry of trial; SCr2-5, serum creatinine at end of years 1-4, SCr 6,serum creatinine at end of trial; TUP1, total urinary protein in 24 hours at entry of trial; TUP1, total urinary protein in 24 hours at end of trial.

Table 3. Comparing between treatment and control groups

	Treatment	Control	*p* values
Sex (M:F)	18 : 19	22 : 16	ns
Age (years)	36 ± 11	34 ± 11	ns
Trial duration (months)	62 ± 5	60 ± 7	ns
Hypertension (Yes/No)	21 : 16	19 : 19	ns
Serum creatinine (mg/dl)			
Before	1.6 ± 0.4	1.5 ± 0.4	ns
After	2.4 ± 2.0	5.0 ± 2.8	< 0.001
Urinary protein (g/day)			
Before	2.1 ± 0.8	2.3 ± 1.6	ns
After	1.1 ± 0.9	1.9 ± 1.0	< 0.002
Blood pressure			
Systolic (before)	135 ± 12	132 ± 12	ns
Diastolic (before)	85 ± 7	86 ± 6	ns
Systolic (after)	131 ± 11	129 ± 12	ns
Diastolic (after)	85 ± 6	83 ± 7	ns
ACE Alu I/D (genotype)			
II	17	17	
ID	12	12	ns
DD	8	9	
Outcome			
Normal	20	6	
Impaired	10	11	< 0.002
ESRF	7	21	

21 patients with ESRF in the control group compared to only 7 in the treatment group ($p < 0.005$). There were fewer patients in the treatment group progressing to ESRF.

Impact of ACE ID genotype on disease progression

As shown in Table 4, impact of ACE ID genotype on disease progression was analyzed. For those with genotype II, there were significantly less patients with ESRF in the treatment group when compared to untreated control patients ($p < 0.02$). For those with ID and DD genotype, there was no significant difference in renal outcome between the treated and untreated patients.

Discussion

Anderson et al. first demonstrated that an ACE inhibitor reduced proteinuria and limited glomerular damage in rats with experimental reduction of renal mass (8). Subsequently, there were numerous reports of similar effectiveness of ACEI therapy for arresting progression of renal dysfunction in humans with various renal diseases (9, 10) including IgAN (11). Our data confirmed the benefits of ACEI/ATRA therapy in IgAN patients with significant reduction of proteinuria and significantly less patients progressing to ESRF when compared to untreated IgAN patients.

Table 4. Impact of ACE ID genotype on disease progression

	Renal Function			*p* value
	End-stage	Impaired	Normal	
Genotype II				
control	10	4	3	< 0.02
treated	2	6	9	
Genotype ID				
control	5	5	2	ns
treated	3	2	7	
Genotype DD				
control	6	2	1	ns
treated	2	2	4	

Suzuki et al. had reported that insertion/deletion polymorphism in ACE gene is not associated with renal progression in Japanese patients with IgAN (12). In a recent article Dillon (13) concluded that polymorphism of the ACE gene may have so far failed to predict either susceptibility to or progression of IgA nephropathy, but the D allele could predict a favourable response to renin-angiotensin blockade. However in our present study, we found that only patients with genotype II seem to respond better to treatment with significantly less patients progressing to ESRF ($p < 0.02$) at the end of the trial (Table 4). So far the beneficial effects of II genotype have only been reported in studies with diabetic nephropathy (DN). Ng et al. in a meta analysis of 14,724 diabetic patients reported a similar protective role of II genotype for Asian patients with Type II DN whereby there was a reduction in the number with ESRF from 1994 to 2004, when they were treated with ACEI/ATRA (14). In contrast those patients with D allele had a deleterious outcome in terms of ESRF. It is believed that the differential drug responses could be explained by the ACE gene profile of the patients. So et al. studying 2,089 Chinese patients with Type II diabetes reported similarly good renal outcome for those with II genotype in contrast to those with DD genotype (15). Seki et al. had reported a similar renoprotective effect of 18 Asian patients with II genotype with Type II Diabetes Mellitus when treated with ACEI/ATRA, in contrast to those with ID and DD genotypes (16).

The ACE I/D polymorphism accounted for half the variance of serum enzyme levels with subjects carrying II genotype having lower levels of enzyme, while DD genotype carriers have higher levels and ID heterozygotes have levels in-between (17). Thus the mechanism for better prognosis for the I allele is similar to that of ACEI/ATRA therapy, primarily lower levels of ACE. The lower enzyme levels led to reduction in glomerular pressure, proteinuria, tubular damage and scarring, resulting in retardation of disease progression to ESRF. Another mechanism to achieve better disease management and less ESRF outcome in II genotype patients may be in the control of TGF-β level. Data from Seki et al. in a recent study of 18 diabetic patients showed that only patients with II genotype treated with ATRA had reduced plasma transforming growth factor (TGF)-β,

probably *via* effects on the angiotensin II type 2 receptor (16). Mimicking glomerular hypertension *in vitro*, cyclic stretching force had also been demonstrated to selectively up-regulate TGF-β isoforms in cultured rat mesangial cells (18). TGF-β is therefore an important cytokine that contributes to progression in DN by stimulating production of the extracellular matrix and induction of glomerular sclerosis (19). These are at best partial explanations as the product of ACE activity, angiotensin II has emerged as a multifunctional factor exhibiting diverse actions. Besides influencing renal haemodynamics and tubular transport, it acts as a growth factor, a profibrogenic cytokine and even having inflammatory properties (20). Its role in the progression of renal disease has gone beyond haemodynamics (21).

IgAN is a very common kidney disease world wide like diabetic nephropathy. In both IgAN and DN, the mesangial cell proliferation is a key step in the pathogenesis. So far the studies reporting a reno-protective effect of the II genotype has been on diabetics in both Caucasians and Asians. Our present data showing that IgAN patients with II genotype respond better to ACEI/ATRA therapy and are protected from ESRF are consistent with the findings in patients with type II DN. We postulate that in both diseases, the ACE gene may play a crucial role in the response of these patients to ACEI/ATRA therapy. The mechanism is probably through lowering levels of ACE and TGF-β, reducing glomerular pressure and decreasing proteinuria. The resulting reduction in renal damage may account for the retardation of progression to ESRF.

In summary, ACEI/ATRA therapy was found effective in retarding disease progression in IgAN with years to ESRF significantly extended at all levels of renal function, including patients whose outcome was ESRF. However treatment significantly reduced the incidence of ESRF only in patients with genotype II but not in those with ID or DD genotypes.

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