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# ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis

**KENG-THYE WOO, YEOW-KOK LAU, KOK-SENG WONG, and GILBERT SHIH-CHEN CHIANG**

*Department of Renal Medicine and Department of Pathology, Singapore General Hospital, Singapore*

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*Background.* It has been postulated that angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ATRA) may decrease proteinuria in patients with glomerulonephritis by its action on the glomerular basement membrane. We therefore studied the relationship between the response of patients with IgA nephritis (IgAN) to ACEI/ATRA therapy by decreasing proteinuria and its effect on the selectivity index (SI) in these patients.

*Methods.* Forty-one patients with biopsy-proven IgAN entered a control trial, with 21 in the treatment group and 20 in the control group. The entry criteria included proteinuria of 1 g or more and/or renal impairment. Patients in the treatment group received ACEI/ATRA or both with three monthly increases in dosage. In the control group, hypertension was treated with atenolol, hydrallazine, or methyldopa. The following tests were performed at three monthly intervals: serum creatinine, total urinary protein, SI, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and low molecular weight (LMW) proteinuria.

*Results.* After a mean duration of therapy of 13 ± 5 months, in the treatment group, there was no significant change in serum creatinine, proteinuria, or SI, but in the control group, serum creatinine deteriorated from 1.8 ± 0.8 to 2.3 ± 1.1 mg/dL ($P < 0.05$). Among the 21 patients in the treatment group, 10 responded to ACEI/ATRA therapy determined as a decrease in proteinuria by 30% (responders), and the other 11 did not respond (nonresponders). Among the responders, SI improved from a mean of 0.26 ± 0.07 to 0.18 ± 0.07 ($P < 0.001$), indicating a tendency toward selective proteinuria. This was associated with an improvement in serum creatinine from mean 1.7 ± 0.6 to 1.5 ± 0.6 mg/dL ($P < 0.02$) and a decrease in proteinuria from a mean of 2.3 ± 1.1 to 0.7 ± 0.5 g/day ($P < 0.001$). After treatment, proteinuria in the treatment group (1.8 ± 1.6 g/day) was significantly less than in the control group (2.9 ± 1.8 g/day, $P < 0.05$). The post-treatment SI in the responder group (0.18 ± 0.07) was better than that of the nonresponder group (0.33 ± 0.11, $P < 0.002$). Eight out of 21 patients in the treatment group who had documented renal impairment had improved renal function compared with two in the control group ($\chi^2 = 4.4$, $P < 0.05$). Of the eight patients in the treatment group who improved their renal function, three normalized their renal function compared with one from the control group.

*Conclusion.* Our data suggest that ACEI/ATRA therapy may be beneficial in patients with IgAN with renal impairment and nonselective proteinuria, as such patients may respond to therapy with improvement in protein selectivity, decrease in proteinuria, and improvement in renal function. ACEI/ATRA therapy probably modifies pore size distribution by reducing the radius of large unselective pores, causing the shunt pathway to become less pronounced, resulting in less leakage of protein into the urine.

Patients with IgA nephritis have nonselective proteinuria [1, 2]. It has also been previously reported that the selectivity index (SI) can be used as a prognostic index in IgA nephritis (IgAN) [3, 4]. There is no definitive therapy for IgAN, and many patients run a progressive course of renal deterioration to end-stage renal failure, unlike patients with selective proteinuria like minimal change disease. One of the causes of renal deterioration is now believed to be due to the tubulotoxic effect of proteinuria [5]. In minimal change disease, in contrast to IgAN, although the protein load in the renal tubules is heavier, it is only for a short duration since minimal change disease is responsive to steroids, unlike IgAN, where patients are subject to long-term tubulotoxic effects of proteinuria resulting in gradual loss of renal function.

Angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ATRA) has been employed to treat the majority of patients with chronic progressive renal disease associated with proteinuria in an attempt to retard the progression to renal failure. The theory behind this form of therapy is that ACEI/ATRA causes efferent arteriolar vasodilation of the glomerulus, thereby decreasing the intraglomerular hypertension causing the proteinuria. This is referred to as nonimmunological therapy to reduce hyperfiltration.

However, there have been studies to show that ACEI also reduces proteinuria in patients with insulin-dependent diabetes mellitus (IDDM) by reducing the size of

**Key words:** protein selectivity, IgA nephropathy, angiotensin receptor antagonist, ACE inhibitor, renal failure.

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large unselective pores in the glomerular basement membrane (GBM) [6].

Angiotensin-converting enzyme inhibitor in animals and humans reduces the log-normal component of the assumed pore size distribution [7] and more importantly causes the shunt pathway to become less pronounced by reducing the radius of large unselective pores [8].

In the present study, we decided to investigate the effects of ACEI/ATRA therapy in patients with IgA nephritis to see whether ACEI/ATRA therapy could modify the SI of these patients and whether this modification of SI was associated with a change in protein excretion and renal function in these patients.

## METHODS

During the period from December 1997 to December 1999, 41 patients with biopsy-proven primary IgA nephritis entered a randomized controlled trial, with 21 in the treatment group and the other 20 in the control group. Entry criteria included proteinuria of 1 gram or more and or renal impairment defined as serum creatinine >1.4 mg/dL. Those with serum creatinine >5.0 mg/dL were excluded or withdrawn from the trial. In the 21 patients with IgA nephritis on treatment, there were 11 patients with hypertension and 15 with renal impairment. In the control group, there were 9 patients with hypertension and 13 with renal impairment. There were no significant differences in the various parameters between the treatment and control group on entry into the trial. None of the patients were on calcium channel blockers, which may affect proteinuria, and all had well-controlled blood pressure [systolic blood pressure (BP) <150 mm Hg, diastolic BP <90 mm Hg] during the study period. Also, none were on steroids, cyclophosphamide, or cyclosporine A. In the control group, hypertension was treated with atenolol, hydrallazine, or methyldopa. All patients were given advice on a low-salt diet. None of the patients in the control as well as the treatment groups were on treatment with aspirin, warfarin, dipyridamole, steroids, and cytotoxic drugs before and during the study.

The patients in the treatment group were treated with ACEI/ATRA or both and were reviewed at three monthly intervals. The dose of ACEI/ATRA was increased if necessary 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, after three months if proteinuria had not decreased by 30%. The maximum dose we have prescribed in the study for a patient was 10 mg of enalapril plus 100 mg of losartan. The dose of ACEI or ATRA was decreased if a patient complained of giddiness. One patient with normal BP could tolerate the maximum dose of 10 mg ACEI and 100 mg losartan without giddiness or hypotension. Patients who could not tolerate the side effect of cough caused by enalapril were converted to losartan; 5 mg of enalapril are equivalent to 50 mg of losartan. The cost of enalapril locally is half that of losartan, but some of our patients suffer from a dry cough while on enalapril. On entry into the trial, patients were given a choice of either enalapril or losartan after being told of the side effect of enalapril. Patients who could afford losartan tended to choose it. There were eight patients on ACEI alone and eight on ATRA alone, and five patients were on a combination of ACEI and ATRA. A decrease of proteinuria by 30% or more was defined as response to therapy.

Patients had the following investigations performed at three monthly intervals: serum creatinine, total urinary protein (TUP), SI (the ratio of IgG clearance over transferrin clearance), sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and low molecular weight (LMW) proteinuria, namely urinary $\alpha_1$-microglobulin ($\alpha_1$m) and retinol-binding protein (RBP). Assay methodologies have been described previously [4]. Essentially, creatinine was quantitated with alkaline picrate and TUP was quantitated by biuret reagent. SDS-PAGE was performed on the PhastSystem (Pharmacia, Uppsala, Sweden) using precast gel. Measurement of IgG and transferrin in urine and serum was done by radial immunodiffusion (RID) in agarose gel for SI calculation. The following LMW proteins, urinary $\alpha_1$m and RBP were also estimated by RID using a urine with high LMW protein content as standard so that results were expressed in arbitrary units (AU).

### Statistics

*Sample size.* Controlling for type I error of 5% and taking a power of 80% (that is, type II error of 20%), assuming the success will increase from 0 to 40% moving from control to treatment group, 16 patients would need to be recruited in each group. It was decided to recruit around 40 patients to allow for patients who may drop out of the trial.

Results were expressed as mean ± SD. The *t*-test and Pearson's chi-square were used for comparing data between groups. Paired *t*-test was used to compare data obtained before and after treatment.

## RESULTS

Table 1 compares the serum creatinine, proteinuria, and SI in the treatment and control group before and after the study. In the treatment group, there was no significant change in serum creatinine, proteinuria, or SI, but in the control group, serum creatinine deteriorated from 1.8 ± 0.8 to 2.3 ± 1.1 mg/dL ($P < 0.05$) with proteinuria increasing from 2.1 ± 1.1 to 2.9 ± 1.8 g/day ($P < 0.02$). There was no significant change in SI. Among

**Table 1.** Data of each patient with IgA nephropathy

| Case no. | Follow-up *years* | Age | Sex *F/M* | Hypertension *Y/N* | Drug | Dosage *mg* | Trial duration *months* | Serum creatinine *mg/dL* Before | Serum creatinine *mg/dL* After | Urinary protein *g/day* Before | Urinary protein *g/day* After | Selectivity index Before | Selectivity index After |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control group | | | | | | | | | | | | | |
| 1 | 16 | 34 | M | N | — | — | 9 | 2.4 | 3.1 | 2.3 | 2.7 | 0.19 | 0.32 |
| 2 | 7 | 32 | F | N | — | — | 12 | 2.4 | 1.0[a] | 2.6 | 2.1 | 0.34 | 0.14 |
| 3 | 8 | 36 | M | Y | A | 100 | 9 | 4.5 | 2.9[a] | 1.4 | 3.6 | 0.23 | 0.26 |
| 4 | 9 | 36 | F | Y | P, M | 80, 120 | 12 | 1.9 | 3.6 | 1.1 | 2.4 | 0.47 | 0.51 |
| 5 | 14 | 44 | M | Y | A | 50 | 12 | 1.6 | 2.6 | 1.5 | 1.9 | 0.14 | 0.24 |
| 6 | 10 | 29 | M | Y | A | 50 | 9 | 2.2 | 2.6 | 1.0 | 2.8 | 0.27 | 0.30 |
| 7 | 16 | 40 | M | Y | P | 80 | 12 | 1.9 | 3.2 | 1.0 | 1.8 | 0.25 | 0.32 |
| 8 | 14 | 37 | M | N | — | — | 12 | 1.5 | 3.0 | 4.4 | 8.8 | 0.21 | 0.26 |
| 9 | 13 | 32 | M | N | — | — | 15 | 1.6 | 1.7 | 1.1 | 2.0 | 0.21 | 0.20 |
| 10 | 5 | 36 | M | Y | M | 750 | 9 | 1.6 | 2.2 | 1.6 | 3.2 | 0.19 | 0.24 |
| 11 | 14 | 34 | M | N | — | — | 6 | 1.4 | 1.5 | 4.5 | 5.4 | 0.22 | 0.13 |
| 12 | 11 | 27 | M | N | — | — | 6 | 1.0 | 1.0 | 2.6 | 2.3 | 0.16 | 0.37 |
| 13 | 10 | 49 | M | Y | P, H | 120, 120 | 12 | 2.1 | 4.4 | 1.2 | 3.2 | 0.13 | 0.22 |
| 14 | 9 | 38 | M | N | — | — | 15 | 2.2 | 3.2 | 4.2 | 3.6 | 0.15 | 0.12 |
| 15 | 7 | 38 | M | N | — | — | 18 | 1.4 | 1.5 | 2.5 | 1.5 | 0.29 | 0.21 |
| 16 | 12 | 50 | M | Y | A, H | 50, 120 | 15 | 2.0 | 3.5 | 2.4 | 2.7 | 0.22 | 0.34 |
| 17 | 7 | 28 | F | N | — | — | 18 | 0.9 | 0.8 | 1.3 | 1.7 | 0.29 | 0.19 |
| 18 | 10 | 45 | F | N | — | — | 18 | 1.1 | 1.0 | 1.5 | 0.4 | 0.31 | 0.10 |
| 19 | 9 | 43 | M | N | — | — | 21 | 1.4 | 1.4 | 1.2 | 1.6 | 0.37 | 0.22 |
| 20 | 9 | 34 | F | Y | A | 50 | 6 | 0.7 | 0.9 | 2.7 | 3.5 | 0.23 | 0.09 |
| mean | 11 | 37 | | | | | 12 | 1.8 | 2.3 | 2.1 | 2.9 | 0.24 | 0.24 |
| ±SD | 3 | 6 | | | | | 4 | 0.8 | 1.1 | 1.1 | 1.8 | 0.08 | 0.10 |
| Treatment groups | | | | | | | | | | | | | |
| Responders (>30% TUP reduction, $N = 10$) | | | | | | | | | | | | | |
| 1 | 9 | 30 | M | N | ATRA | 50 | 6 | 1.1 | 1.1 | 1.0 | 0.1 | 0.14 | 0.10 |
| 2 | 9 | 47 | M | Y | ACEI | 5 | 9 | 1.9 | 1.3[a] | 1.2 | 0.6 | 0.22 | 0.11 |
| 3 | 11 | 40 | M | Y | ATRA | 150 | 18 | 2.3 | 2.2 | 3.6 | 1.1 | 0.35 | 0.26 |
| 4 | 16 | 39 | F | Y | ACEI/ATRA | 10/100 | 18 | 1.6 | 1.1[a] | 1.6 | 1.0 | 0.31 | 0.24 |
| 5 | 10 | 27 | M | Y | ATRA | 50 | 21 | 2.0 | 1.7[a] | 1.9 | 0.1 | 0.25 | 0.20 |
| 6 | 11 | 42 | F | Y | ATRA | 50 | 12 | 2.9 | 2.6[a] | 3.1 | 1.2 | 0.28 | 0.18 |
| 7 | 3 | 29 | F | N | ATRA | 50 | 12 | 0.9 | 0.8 | 1.4 | 0.3 | 0.27 | 0.09 |
| 8 | 3 | 38 | M | N | ACEI | 15 | 9 | 1.7 | 1.6 | 4.1 | 1.7 | 0.21 | 0.16 |
| 9 | 3 | 38 | F | N | ATRA[b] | 100 | 12 | 1.4 | 1.3 | 3.2 | 0.5 | 0.38 | 0.31 |
| 10 | 16 | 48 | F | N | ATRA[b] | 50 | 6 | 1.0 | 1.0 | 2.2 | 0.6 | 0.22 | 0.12 |
| mean | 9 | 38 | | | | | 12 | 1.7 | 1.5 | 2.3 | 0.7 | 0.26 | 0.18 |
| ±SD | 5 | 7 | | | | | 5 | 0.6 | 0.6 | 1.1 | 0.5 | 0.07 | 0.07 |
| Nonresponders (<30% TUP reduction, $N = 11$) | | | | | | | | | | | | | |
| 1 | 33 | 53 | M | Y | ATRA | 50 | 18 | 4.2 | 5.9 | 5.5 | 4.6 | 0.46 | 0.46 |
| 2 | 13 | 43 | F | Y | ACEI/ATRA | 5/100 | 15 | 1.9 | 3.0 | 1.4 | 6.4 | 0.36 | 0.44 |
| 3 | 19 | 55 | F | N | ACEI | 10 | 6 | 1.4 | 1.4 | 1.3 | 1.7 | 0.21 | 0.41 |
| 4 | 5 | 35 | F | N | ACEI | 10 | 12 | 1.3 | 0.8 | 1.8 | 1.9 | 0.16 | 0.19 |
| 5 | 20 | 40 | M | Y | ACEI | 10 | 12 | 2.2 | 2.0[a] | 1.5 | 1.4 | 0.33 | 0.20 |
| 6 | 20 | 45 | M | Y | ACEI | 10 | 6 | 1.8 | 1.5[a] | 1.5 | 1.6 | 0.40 | 0.37 |
| 7 | 15 | 30 | M | Y | ACEI/ATRA | 10/100 | 21 | 1.7 | 2.7 | 1.0 | 2.7 | 0.27 | 0.24 |
| 8 | 5 | 26 | M | N | ACEI | 10 | 6 | 3.9 | 4.9 | 2.0 | 2.6 | 0.18 | 0.19 |
| 9 | 10 | 46 | F | Y | ACEI/ATRA | 10/100 | 18 | 1.8 | 1.3[a] | 4.2 | 4.7 | 0.35 | 0.32 |
| 10 | 4 | 18 | M | N | ACEI | 10 | 12 | 2.3 | 1.5[a] | 1.3 | 1.3 | 0.33 | 0.43 |
| 11 | 16 | 59 | M | N | ACEI/ATRA | 10/100 | 15 | 2.3 | 2.3 | 1.5 | 1.4 | 0.32 | 0.38 |
| mean | 15 | 41 | | | | | 13 | 2.3 | 2.5 | 2.1 | 2.8 | 0.31 | 0.33 |
| ±SD | 9 | 13 | | | | | 5 | 0.9 | 1.6 | 1.4 | 1.7 | 0.09 | 0.11 |

Abbreviations are: A, atenolol; P, propanolol; H, hydrallazine; M, methyldopa; ACEI, ACE inhibitor; ATRA, angiotensin receptor antagonist.
[a] Those who had an improved renal function
[b] Only 2 patients in study who converted from ACEI to ATRA

the 21 patients with IgAN in the treatment group, 10 responded to ACEI/ATRA therapy determined as a decrease in proteinuria by 30% (responders), and the other 11 did not (nonresponders). Table 1 also compares the results of therapy in the responders and nonresponders after a mean duration of therapy for 13 ± 5 months. Among the responders, the SI improved from a mean of 0.26 ± 0.07 to 0.18 ± 0.07 ($P < 0.001$), indicating a tendency toward selective proteinuria. This was associated with an improvement in serum creatinine from a mean of 1.7 ± 0.6 to 1.5 ± 0.6 mg/dL ($P < 0.02$), a decrease in proteinuria from a mean of 2.3 ± 1.1 to 0.7 ±

**Table 2.** Comparing data between groups

| | Control ($N = 20$) | Treatment ($N = 21$) | Treatment Responders ($N = 10$) | Treatment Nonresponders ($N = 11$) |
|---|---|---|---|---|
| Sex *M:F* | 15:5 | 12:9 | 5:5 | 7:4 |
| Age *years* | 37 ± 6 | 39 ± 10 | 38 ± 7 | 41 ± 13 |
| Follow-up *years* | 11 ± 3 | 12 ± 7 | 9 ± 5 | 15 ± 9 |
| Trial duration *months* | 12 ± 4 | 13 ± 5 | 12 ± 5 | 13 ± 5 |
| Hypertension *Yes*:*No* | 9:11 | 11:10 | 5:5 | 6:5 |
| Before treatment | | | | |
| Serum creatinine *mg/dL* | 1.8 ± 0.8 | 2.0 ± 0.8 | 1.7 ± 0.6 | 2.3 ± 0.9 |
| Urinary protein *g/day* | 2.1 ± 1.1 | 2.2 ± 1.2 | 2.3 ± 1.1 | 2.1 ± 1.4 |
| Selectivity index | 0.24 ± 0.08 | 0.29 ± 0.08 | 0.26 ± 0.07 | 0.31 ± 0.09 |
| After treatment | | | | |
| Serum creatinine *mg/dL* | 2.3 ± 1.1[f] | 2.0 ± 1.3 | 1.5 ± 0.6[e,f] | 2.5 ± 1.6[e] |
| Urinary protein *g/day* | 2.9 ± 1.8[a,b] | 1.8 ± 1.6[a] | 0.7 ± 0.5[b,d] | 2.8 ± 1.7[d] |
| Selectivity index | 0.24 ± 0.10[g] | 0.26 ± 0.12 | 0.18 ± 0.07[c] | 0.33 ± 0.11[c,g] |

Quantitative data are expressed as means ± standard deviation. The *t*-test and Pearson's $\chi^2$ are used for comparing data between groups.
[a] $P < 0.05$
[b] $P < 0.002$
[c] $P < 0.002$
[d] $P < 0.005$
[e] NS ($P = 0.073$)
[f] $P < 0.05$
[g] $P < 0.05$

0.5 g/day ($P < 0.001$). LMW proteinuria ($\alpha_1$m) also decreased significantly (91 ± 55 to 33 ± 30 AU/day, $P < 0.01$). Among the 11 nonresponders, there was no change in the SI, proteinuria, or serum creatinine.

Table 2 compares the data between the various groups. After treatment, proteinuria in the treatment group (1.8 ± 1.6 g/day) was significantly less than the control group (2.9 ± 1.8 g/day, $P < 0.05$). It was also less in the responder group (0.7 ± 0.5 g/day) compared with the control group (2.9 ± 1.8 g/day, $P < 0.002$). The post-treatment SI in the responder group (0.18 ± 0.07) was better than that of the nonresponder group (0.33 ± 0.11, $P < 0.002$). The post-treatment proteinuria in the responder group (0.7 ± 0.5 g/day) was also less than the nonresponder group (2.8 ± 1.7 g/day, $P < 0.005$). Serum creatinine was not different (1.5 ± 0.6 vs. 2.5 ± 1.6 mg/dL, $P$ = NS).

Figure 1 shows the serum creatinine in the treatment ($N = 21$) and control group ($N = 20$) before and after trial. The renal function in the treatment group remained stable, while that in the control group deteriorated ($P < 0.05$). Figure 2 compares the serum creatinine in the responder ($N = 11$) and nonresponder group ($N = 10$) before and after the trial. The responder group had improvement in renal function ($P < 0.02$), while there was no change in the nonresponder group. Table 3 shows the serial serum creatinine during the trial in eight patients in the treatment group and two patients in the control group who had improvement in their renal function after the trial. There were significantly more patients in the treatment group compared with the control group who had improvement in renal function (improved:not improved, 8:13 vs. 2:18, $\chi^2 = 4.4$, $P < 0.05$). Of the eight patients with improvement in renal function in the treatment group, four were from the responder, and the other four were from the nonresponder group.

## DISCUSSION

Improvement in proteinuria in patients treated with ACEI varies from 30 to 50% according to various series [9–12]. We adopted a reduction of proteinuria of 30% as some patients were on a relatively short period of treatment of six months and on a small dose of either 5 mg ACEI or 50 mg of ATRA. Based on this criterion, we studied a group of patients with IgAN, compared with a control group. About 50% of patients responded to therapy after a mean duration of 12 months. Patients in the treatment group had stabilization of renal function, while renal function deteriorated in the control group. Among patients in the treatment group, the responders not only had a decrease in proteinuria, but there was improvement in SI and renal function in contrast to those who showed no response to ACEI/ATRA therapy.

Hitherto, studies in relationship to ACEI therapy have reported improvement in proteinuria associated with retardation of the progression of renal failure [13, 14]. Ruggenenti et al documented normalization of renal function in 8 out of 74 patients, and these patients continued to have normal renal function over 36 months of follow-up [15]. In our study, we had 8 out of 21 patients who already had documented renal impairment of at least one year before starting therapy, and their renal function improved after treatment (4 from the responder group and 4 from the nonresponder group), suggesting that even though proteinuria may not improve, renal

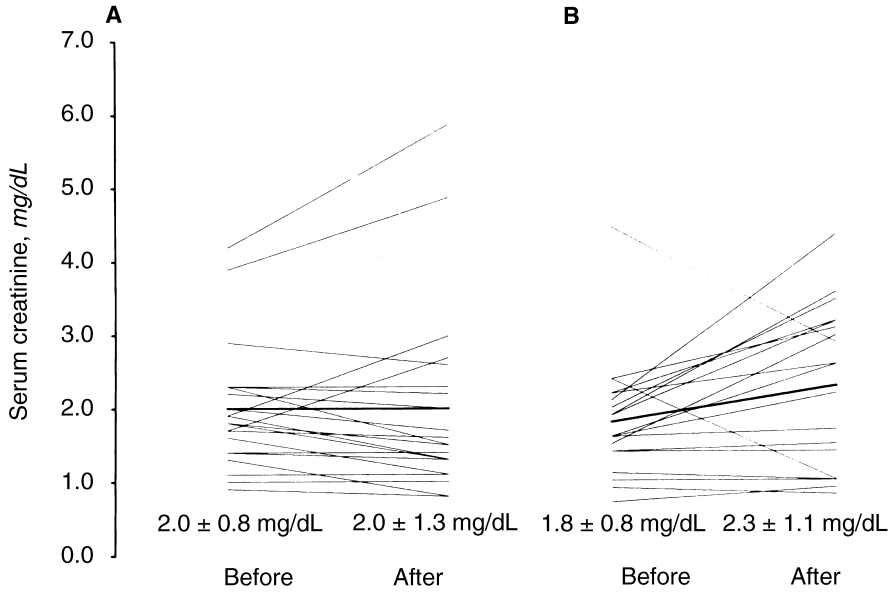


**Fig. 1. Comparison of the serum creatinine before and after the trial among the patients in the treatment (left; $N = 21$; $P$ = NS) and control (right; $N = 20$; $P < 0.05$) groups using the paired $t$-test.**

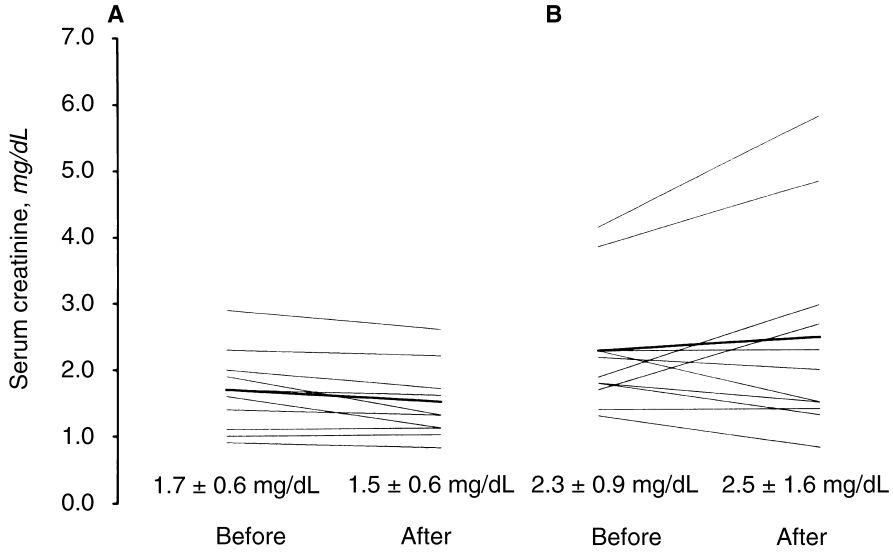


**Fig. 2. Comparison of the serum creatinine before and after the trial among the responders (left; $N = 10$; $P < 0.02$) and nonresponders (right; $N = 11$; $P$ = NS) in the treatment group using paired $t$-test.**

function may improve as in four patients in the nonresponder group, in the absence of any acute reversible elements like the nephrotic state, sepsis, dehydration, uncontrolled hypertension, or exposure to nephrotoxic drugs. Of the eight patients who improved their renal function, three normalized their renal function (2 from the responder group and 1 from the nonresponder group).

Therapy with ACEI/ATRA probably decreases the quantity of proteinuria in responsive patients by decreasing the shunt pathway through improvement of size selectivity [16–18]. Morelli et al, analyzing glomerular sieving coefficients of neutral test macromolecules, reported that in patients with IDDM, studied early in the course of the disease, ACEI reduced proteinuria by reducing the size of large unselective pores on the GBM [6]. A reduction of the protein excretion rate is associated with a slower rate of glomerular filtration rate decline in patients with IDDM with overt nephropathy [19]. ACEI, in addition to BP control, reduces proteinuria and prevents renal injury and progression to end-stage renal failure [20].

Recent studies have also demonstrated that ACEI, apart from remodeling the GBM (the improvement in pore selectivity being one of the end results), may also have beneficial effects on the mesangial cells by decreasing transforming growth factor-β (TGF-β) production, thereby decreasing mesangial matrix production, hence ameliorating the disease process in IgAN where there is mesangial cell proliferation [21]. In addition, ATRA has

**Table 3.** Treatment with ACEI/ATRA to improve renal function

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | Trial duration |
|---|---|---|---|---|---|---|---|---|---|
| | months | | | | | | | | |
| Treatment group ($N = 20$) | | | | | | | | | |
| Responders no. | | | | | | | | | |
| 2[a] | 1.9 | 1.5 | 1.3 | 1.3 | | | | | 9 |
| 4[a] | 1.6 | 1.5 | 1.5 | 1.4 | 1.1 | 1.1 | 1.1 | | 18 |
| 5 | 2.0 | 2.3 | 2.7 | 1.8 | 1.9 | 1.9 | 1.6 | 1.7 | 21 |
| 6 | 2.9 | 2.6 | 3.5 | 2.5 | 2.6 | | | | 12 |
| Nonresponders no. | | | | | | | | | |
| 5 | 2.2 | 2.0 | 2.2 | 2.0 | 2.0 | | | | 12 |
| 6 | 1.8 | 1.5 | 1.5 | | | | | | 6 |
| 9[a] | 1.8 | 1.5 | 1.8 | 1.6 | 1.7 | 1.2 | 1.3 | | 18 |
| 10 | 2.3 | 1.7 | 1.7 | 1.7 | 1.5 | | | | 12 |
| Control group ($N = 21$) | | | | | | | | | |
| 2[a] | 2.4 | 2.2 | 1.6 | 1.6 | 1.0 | | | | 12 |
| 3 | 4.5 | 3.2 | 3.1 | 2.9 | | | | | 9 |
| | Improved | | Not improved | | | | | | |
| Treatment group | 8 | | 13 | | | | | | |
| Control group | 2 | | 18 | | | | | | |
| Chi-square = 4.4 | $P < 0.05$ | | | | | | | | |

Data shown are serial measurement of serum creatinine (mg/dL).
[a] Patients who regained normal renal function

been shown to exert an antiproliferative effect on mesangial proliferative glomerulonephritis [22]. This could help to explain further the improvement in renal function in patients with IgAN on ACEI/ATRA therapy. In order for this to occur, the injury must be still at the stage in which it is possible for amelioration of the renal lesions and possibly remodeling of the renal architecture. Patients with more advanced renal disease with glomerulosclerosis and thickening of the GBM are less likely to respond to therapy with improvement in SI and serum creatinine. In this respect, we found that patients with serum creatinine exceeding 3 mg/dL are less likely to recover renal function though therapy with ACEI/ATRA may retard their long-term progression to end-stage renal failure.

Low molecular weight proteinuria has been reported as a bad prognostic index in IgA nephritis [23–25]. ACEI/ATRA therapy, apart from decreasing proteinuria, probably modifies the composition of the urinary protein, thus improving the SI and decreasing the LMW proteinuria. This may explain the beneficial effects of therapy with ACEI/ATRA in preserving renal function in patients with proteinuria since proteinuria contributes to worsening renal function [5] and LMW proteinuria is associated with a poor prognosis [23, 25].

Individual antiproteinuric response to ACEI varies depending on *ACE* gene polymorphism as those with the D-allele of the *ACE* gene polymorphism respond better to the antiproteinuric effect of ACEI therapy [11, 26]. The antiproteinuric effect of ATRA is the same as that of ACEI. One study compared the effect of ACEI and ATRA on blood pressure, proteinuria, renal blood flow, glomerular filtration rate, plasma renin activity, and plasma angiotensin II levels and did not demonstrate any significant differences. The antiproteinuric effect therefore appears to be dependent primarily on $AT_1$ receptor-mediated pathway [27].

While ACEI has been previously reported to be beneficial in retarding the progression of renal failure in patients with IgAN [13, 14], we now show that ATRA is just as effective and that in patients with renal impairment, there is also the possibility of normalizing renal function in some patients. Furthermore, we have documented that a decrease in proteinuria is due to improvement in glomerular permselectivity. Finally, even if ACEI/ATRA does not decrease proteinuria, there is still the benefit of improvement in renal function in those with renal impairment because ACEI/ATRA may have other beneficial effects on the kidneys that are not related to decrease in proteinuria alone [21, 22].

Recently, Russo et al, in a study of eight patients with IgAN, demonstrated that the combined antiproteinuric effect of converting-enzyme inhibitor (CEI) and losartan was superior to that of CEI alone or losartan alone [28]. We examined the results of ACEI alone ($N = 8$), ATRA alone ($N = 8$), and combination therapy with ACEI/ATRA ($N = 5$) in our treated patients and found that there was no statistical difference in the results.

In conclusion, our data suggest that therapy with ACEI/ATRA may be beneficial in patients with IgA nephritis with renal impairment and nonselective proteinuria, as such patients may respond to therapy with improvement in glomerular permselectivity, decrease of proteinuria, including LMW proteinuria and improvement in renal function.

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*Reprint requests to Dr. Keng-Thye Woo, Department of Renal Medicine, Singapore General Hospital, Outram Road, Singapore 169608. E-mail: grmwkt@sgh.gov.sg*

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