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Clinical Course of Patients with IgA Nephropathy between Combined Treatment of Immunosuppressive Agents and ACE Inhibitor and ACE Inhibitor alone

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Background : *It has not been clear whether immunosuppressive therapy favorably influences renal function and proteinuria in IgA nephropathy (IgAN). Angiotensin converting enzyme inhibitor (ACEi) has an anti-proteinuric effect in IgAN. A retrospective study was done to see whether the addition of immunosuppressive therapy to ACEi produces a more excellent anti-proteinuric effect and preserves better renal function than ACEi alone.*

Methods : *A total of 49 patients with proteinuria>1.0 g/day and serum creatinine concentrations<1.5 mg/dL were followed-up from at least 1 year to 9 years. Among them, 25 patients were treated with the combination of cyclophosphamide, prednisolone and ACEi while the other 24 were treated with ACEi alone.*

Results : *The combination therapy or ACEi alone both reduced proteinuria with significant value (the combination group: from 5.74 ±5.08 to 2.29 ±2.77 g/day, ACEi group: from 3.85 ±2.54 to 1.68 ±1.91 g/day), while no significant differences in reduction of proteinuria were noticed between the two groups. There was no significant elevation of serum creatinine in both groups during follow-up (the combination group: from 0.91 ±0.20 to 1.03 ±0.38 mg/dL, ACEi group: from 0.93 ±0.27 to 0.99 ±0.37 mg/dL). This study showed no significant differences in the change in slope of 1/serum creatinine levels during the follow-up period between the two groups.*

Conclusion : *We conclude that immunosuppressive therapy may not be beneficial in patients with proteinuric IgAN. ACEi may be a valuable therapeutic agent avoiding serious side effects of immunosuppressive agents.*

Key Words : *Glomerulonephritis, IGA; Prednisolone; Cyclophosphamide; Angiotensin-converting enzyme inhibitors; Proteinuria; Renal function*

INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerular disease and is now recognized as one of the leading glomerular diseases that progress to end-stage renal failure[1]. In long-term follow-up studies of adult patients with IgAN, 20-50% have been found to develop progressive renal insufficiency 20 years after the initial discovery of the disease[2, 3].

Although the etiology or pathogenesis are still unknown, many therapeutic challenges, including corticosteroids or cytotoxic drugs have been tried in the treatment of IgAN, but there is no treatment of proven value for IgAN.

Angiotensin converting enzyme inhibitor (ACEi) has an anti-proteinuric effect and is widely regarded as one of the renoprotective agents[4-6]. Long-term studies have also demonstrated that proteinuria is an independent risk factor for renal function in patients with primary

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renal diseases[7].

Therefore, we observed the effect of ACEi in IgAN patients with proteinuria, and furthermore examined whether the addition of prednisolone and cyclophosphamide to ACEi produces a more excellent anti-proteinuric effect and preserves better renal function than ACEi alone.

MATERIALS AND METHODS

Between 1985 and 1997, 49 biopsy-proven IgAN patients visiting the Division of Nephrology, Kyung-Hee University Hospital were enrolled in the study. The inclusion criteria were proteinuria > 1.0 g/day and serum creatinine concentrations < 1.5 mg/dL.

The patients with HBsAg (+) or Anti-HCV (+) and those who showed histologic findings of minimal change nephrotic syndrome or crescentic glomerulonephritis were excluded from this study.

This study was designed to compare the effects of the combination therapy with prednisolone (30-60 mg/day), cyclophosphamide (1.2-2.0 mg/kg/day), and ACEi to that with ACEi alone on remission of proteinuria and change in renal function.

We defined 1) complete remission (CR) as proteinuria of less than 0.5 g/day, 2) non-nephrotic range proteinuria (NN) as 0.5-3.0 g/day and 3) nephrotic range proteinuria (NP) as over 3.0 g/day. According to the change of renal function, worsening of renal function was defined as an increase in serum creatinine concentration of at least 50% over the baseline value and serum creatinine concentration over 1.5 mg/dL, chronic renal failure (CRF) as serum creatinine concentration over 3.0 mg/dL, and end-stage renal disease as cases in need of renal replacement therapy.

The results were reported as mean±standard deviation of the mean, range and percentage. Comparisons of data were made by Mann-Whitney test. A p value of less than 0.05 was regarded as statistically significant.

RESULTS

A total of 49 patients were followed-up periodically from at least 1 year to 9 years. Among them, 25 patients were treated with the combination of cyclophosphamide, prednisolone and ACEi while the other 24 were treated with ACEi alone. The duration of prednisolone treatment was 12.9±13.0 months and that of cyclophosphamide 4.7±3.1 months. The demographic and initial laboratory data of both groups are summarized in Table 1. The mean age of the combination and ACEi groups at the time of diagnosis was 33.5 yrs (range 15 to 66 yrs) and 31.0 yrs (range 16 to 56 yrs), respectively. The amount of urinary protein excretion at the time of diagnosis varied considerably ranging from 1.2 to more than 10.0 g/day. Each group showed a mean value of 5.74±5.08 g/day and 3.85±2.54 g/day, respectively, and there was no significant difference between the two groups.

The level of proteinuria was analyzed in each of the combination and ACEi alone group 6 months after the starting point of treatment and at the end of the follow-up (Table 2). Five of the 25 (20.0%) in the combination group and 5 of the 24 (20.8%) in ACEi alone group showed complete remission 6 months after treatment. At the last follow-up, each group showed complete remission rates of 28.0% and 20.8%, respectively. The percentage of non-nephrotic range proteinuria and nephrotic range proteinuria was not different between the two groups.

Table 1. Characteristics of the patients in the combination and ACEi groups at baseline

	Combination (N=25)	ACEi (N=24)
Age (yrs)	33.5 (15-66)	31.0 6 (16-56)
Sex (Male:Female)	11:14	7:17
Hypertension	4/25	5/24
Serum creatinine (mg/dL)	0.91±0.20	0.93±0.27
Proteinuria (g/day)	5.74±5.08	3.85±2.54
Proteinuria (No. of patients)		
1-2	5	6
2-3	4	6
3-10	12	10
≥10	4	2

Table 2. Remission of proteinuria

	Combination (N=25)		ACEi (N=24)	
	6th Month	Final	6th Month	Final
CR[a]	5 (20.0)*	7 (28.0)	5 (20.8)	5 (20.8)
NN[b]	12 (48.0)	12 (48.0)	16 (66.7)	16 (66.7)
NP[c]	8 (32.0)	6 (24.0)	3 (12.5)	3 (12.5)

* No. of patients (%)

[a] ; Complete remission

[b] ; Non-nephrotic proteinuria

[c] ; Nephrotic range proteinuria

Table 3. Change in proteinuria and renal function

	Combination	ACEi
Proteinuria (g/day)		
Baseline	5.74±5.08	3.85±2.54
Final	2.29±2.77*	1.68±1.91*
-△	3.44±4.17	2.17±2.38
Serum creatinine (mg/dL)		
Baseline	0.91±0.20	0.93±0.27
Final	1.03±0.38	0.99±0.37
1/serum creatinine/month (dL/mg/mo)	-0.0053±0.0171	-0.0024±0.0123
Follow-up (months)	32.0(12-72)	47.5(12-108)

*p<0.05 vs Baseline

Table 3 summarizes the change in renal function and proteinuria during the follow-up period. The mean follow-up duration was 32 months in the combination group and 48 months in ACEi group. Proteinuria decreased significantly in both groups after treatment (the combination group: from 5.74±5.08 to 2.29±2.77 g/day, ACEi only group: from 3.85±2.54 to 1.68±1.91 g/day; p<0.05).

The final serum creatinine levels at the end of follow-up were not different between the two groups (the combination group: 1.03±0.38 mg/dL Vs ACEi group 0.99±0.37 mg/dL). The change in renal function according to the change in slope of 1/serum creatinine levels during the follow-up period showed no significant difference between the two groups. Most of the patients preserved their renal function, but worsening of renal function developed in two in the combination group and one in the ACEi group, and no one showed features of chronic renal failure or end-stage renal disease.

Those showing proteinuric levels over 3 g/day were analyzed separately. Proteinuria decreased significantly in both groups after treatment (the combination group: n=12, from 5.24±1.69 to 2.75±2.66 g/day, ACEi group: n=10, from 4.89±1.43 to 1.38±1.21 g/day).

Finally, there were no significant side effects in combination and ACEi alone group during the follow-up periods.

DISCUSSION

In this study, we observed the effect of ACEi to reduce proteinuria, as reported before. We focused on whether the addition of prednisolone and cyclophosphamide together to ACEi produces a more excellent antiproteinuric effect and preserves renal function more efficiently than treatment with ACEi alone in patients with IgAN. ACEi alone or the combination therapy both reduced proteinuria in patients with IgAN with significant value. This study, however, showed no significant difference in the change of renal function or reduction of proteinuria between the two groups.

Although IgAN is regarded as an immune-complex mediated glomerular disease, there still remains controversy as to the effects of immunosuppressive therapy. Also, there is no consensus as to which patients with IgAN should be treated. The previous studies revealed risk factors of IgAN for progression, such as proteinuria, hypertension and renal insufficiency at the time of diagnosis. We enrolled IgAN patients with proteinuria > 1.0 g/day and normal renal function.

Prednisolone therapy has had variable results in IgAN. In a controlled study, daily steroids for 18 months showed a protective effect on renal function and a reduction in proteinuria 10 years after therapy in patients with early stage of progressive IgAN[9]. Another multicenter randomized controlled trial showed that a 6-months steroid treatment, including methylprednisolone pulse therapy, protected against deterioration of renal function of IgAN[9]. Recently, it was reported that early treatment with corticosteroid for one year ameliorated proteinuria and mesangial proliferative lesions in adult patients with IgAN who had mild proteinuria (mean 754.6 mg/day)[10]. On the other hand, contradictory outcomes have been reported. In a prospective randomized controlled trial for alternative-day prednisolone treatment for IgAN patients with clinical features suggesting a poor prognosis, steroid-treated group has not shown benefit on renal function or proteinuria[11]. A prospective randomized control trial showed that 4 months of prednisone treatment resulted in a high rate of remission of nephrotic syndrome, but had no significant effect on renal function[12]. Furthermore, it has been suggested that short-term, low-dose steroid therapy does not exert any particular benefit, whereas a large dose over a long period of therapy may preserve the renal function in progressive IgAN[9].

We treated our combination group with prednisolone and cyclophophamide in addition to ACEi. The combination therapy reduced proteinuria with significant value, but failed to have an additional effect on renal function and a reduction in proteinuria compared to ACEi alone. It is still controversial whether cytotoxic drugs, such as cyclophosphamide or azathioprine may

be effective in the treatment of IgAN. One study showed combined therapy, including prednisolone and azathioprine, reduced proteinuria and glomerulosclerosis in children with severe IgAN[2]. The therapy, using the combination of cyclophosphamide, dipyridamole and warfarin, provided reduction of proteinuria but no difference in renal function was noticed between the treatment and control groups[13, 14]. A retrospective study showed beneficial effects of the combination of prednisolone and azathioprine in slowing the progression of IgAN in patients with renal impairment, but not in reducing proteinuria[15].

Our study showed ACEi therapy significantly reduced proteinuria in the patients with IgAN. The rate of decline of renal function was also not different between ACEi alone and the combination therapy. ACEi alone therapy had no serious side effect compared to the combination therapy with immunosuppressive drugs and ACEi. In a placebo-controlled study with patients who showed normal range blood pressure and normal renal function, a significant reduction in proteinuria was noticed in the ACEi group, compared to the placebo group[16]. The antiproteinuric effect of ACEi has been mainly attributed to 1) a decrease in glomerular capillary hydraulic pressure through hemodynamic dilatation of efferent arterioles or 2) an increase in basement membrane barrier permselectivity[16, 17]. However, controversy exists as to whether ACEi may be useful in preserving renal function, compared to placebo or other treatment. A prospective study in hypertensive patients with IgAN showed no difference on the rate of decline of renal function between ACEi and nifedipine groups, whereas ACEi had a favorable effect on proteinuria[18]. Other studies showed that ACEi therapy is superior to other antihypertensive agents, such as beta blocker, in preserving renal function and reducing proteinuria in patients with IgAN[5, 19].

On the other hand, there is a suggestion that the rate of decline of renal function in the ACEi-treated patients was greater than that in the fish oil-treated patients[20]. In our study, most of the patients preserved their renal function, but worsening of renal function developed in two in the combination group and one in the ACEi group, and no one showed the features of chronic renal failure during the follow-up period.

There are some limitations in our study. One significant limitation is that this is not a prospective double-blind study. IgAN is a slowly progressive disease, so further long-term follow-up observation will be necessary to reach final conclusions. Another limitation of our study is the lack of evaluation of histological findings.

According to our results, ACEi may be a valuable therapeutic agent due to its effectiveness in severe proteinuric adult patients with IgAN. And the addition of immunosuppressive drugs may have no additional therapeutic effect compared with ACEi alone.

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