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ORIGINAL ARTICLE

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Histologically advanced IgA nephropathy treated successfully with prednisolone and cyclophosphamide

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Abstract
Background. No definitive therapeutic consensus has been established for progressive immunoglobulin A nephropathy (IgAN).
Methods. We retrospectively investigated 35 patients with histologically advanced IgAN. The patients were divided into two groups: 27 received prednisolone and cyclophosphamide (PSL+CPA group) and 8 received supportive treatment (control group). The initial doses of PSL and CPA were 30 mg/day and 50 mg/day, respectively. PSL was tapered to 2.5 mg/day over 2 years and CPA was discontinued at 6 months.
Results. In the control group, mean follow-up duration was 22.9 months, renal progression rate was -20.9×10^{-3} dl/mg per month, and all patients developed endstage renal disease within 5 years. In the PSL+CPA group, mean follow-up duration was 64.3 months, renal progression rate was -1.5×10^{-3} dl/mg per month, and renal survival at 5 years was 89.8%. Renal prognosis was markedly improved in the PSL+CPA group compared with the control group. The patients in the PSL+CPA group were divided into two subgroups according to baseline serum creatinine (<2 mg/dl or ≥2 mg/dl); renal survival in the two subgroups was similar (84.4% versus 100% at 5 years). Adverse effects of PSL+CPA were minimal and mild.
Conclusions. It is possible that PSL+CPA therapy safely improved the renal prognosis of patients with severe IgAN who would otherwise have required dialysis therapy within 5 years. However, a prospective, multicenter clinical trial is required to prove the effects and safety of this treatment.

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Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of idiopathic glomerulonephritis worldwide.[1–3] Although its clinical course is usually benign, 25%–35% of patients develop endstage renal disease within 20 years of diagnosis.[3,4] Several variables indicating the clinical outcome of IgAN have been suggested, such as the amount of proteinuria and hematuria at diagnosis, the baseline renal function, arterial blood pressure, and histopathologic renal injury. Among these, the most powerful poor prognostic factors are heavy proteinuria, impaired baseline renal function, and severe renal morphologic lesions, including glomerulosclerosis and tubulointerstitial damage.[4–6]

Although IgAN patients with a low risk of progressing to endstage renal disease require no specific treatment, the choice of therapy for patients with poor prognostic factors is a very important problem. However, few published studies, especially randomized controlled trials, on treatment options in progressive IgAN are available. Consequently, there is no definitive international consensus on strategies to preserve renal function in patients with advanced IgAN.[7–11] The consensus in recent articles seems to be that supportive therapy or isolated conventional corticosteroids cannot improve renal survival,[12,13] so more active treatments, including steroid pulse therapy,[14–17] tonsillectomy,[14,16] and immunosuppressive agents[18–28] are needed to treat progressive IgAN. Furthermore, several reports have indicated that patients with impaired renal function, with serum creatinine (SCr) of more than 2–3 mg/dl at baseline, will show irreversible renal deterioration and develop endstage renal disease, even though they have received active treatments.[16,29] This suggests the existence of a "point of no return" in progressive IgAN.

Until 1990–1992, we treated patients with IgAN, including those with advanced disease, with supportive therapy, so

all the patients with advanced disease required dialysis therapy rapidly. In 1990 (complete transition by 1992), however, we initiated combination therapy using prednisolone and cyclophosphamide (PSL+CPA) for the treatment of patients with progressive IgAN, and recognized its efficacy. In 2000, we reported our results from 1985 to 1997, showing that PSL+CPA slowed the progression of moderately advanced IgAN.[18] In this study, we retrospectively evaluated the clinical effects of PSL+CPA, including the effects on renal survival, in patients with severe histological damage and renal impairment.

Patients and methods

Patients

From January 1988 to December 2003, glomerular IgA deposition was confirmed by renal biopsies in 240 patients at our Kidney Center. Thirteen patients with other glomerular diseases or systemic diseases such as Henoch-Schoenlein purpura and systemic lupus erythematosus were excluded, and 217 patients were specified as having isolated primary IgAN. Semiquantitative analysis of renal tissues showed severe histological changes in 35 (16%) of these 217 patients – 16 men and 19 women (mean age, 44.3 years). At biopsy, all 35 patients showed impaired renal function with heavy proteinuria, which had been considered as the most powerful prognostic factor for endstage renal disease. Eight of these patients were treated with supportive therapy during the period from 1988 to 1992. We defined them as the control group. From 1990, we started combination therapy using PSL+CPA for patients with advanced IgAN. During the period from 1992 to 2003, the 27 patients who had been treated with PSL+CPA were defined as the PSL+CPA group. Informed consent was obtained from all patients before the start of treatment.

Renal biopsy morphology criteria

Renal biopsies were examined by a single renal pathologist who was blinded to the patient information. All renal specimens for light microscopy were stained with hematoxylin and eosin, periodic acid Schiff, and periodic acid methenamine. In each biopsy specimen, we evaluated, semiquantitatively, eight different parameters: mesangial hypercellularity, crescents, tuft adhesion, mesangial sclerosis, global sclerosis, tubular atrophy, interstitial fibrosis, and vascular sclerotic changes, according to the method described by Kobayashi et al.[30] This method was also used for histological evaluation in our previous report. Each parameter was graded from 0 to 3 and the sum of all scores represented the degree of histological renal damage, ranging from 0 to 24. For immunofluorescence studies, another specimen was snap-frozen in n-hexane with dry-ice acetone at –70°C, and was cut at 4 μm on a cryostat. Sections were stained with fluorescein isothiocyanate-conjugated monospecific antisera against human IgG, IgA, IgM, C3, C1q, and fibrinogen (Dako, Glostrup, Denmark).

Treatment protocol

PSL was started at a dose of 30 mg/day and tapered to 2.5 mg/day over a 2-year period (30 mg/day for 1 week, 20 mg/day for 2 weeks, 15 mg/day for 1 month, 10 mg/day for 6–8 months, 5 mg/day for 6–12 months, and 2.5 mg/day for 12 months). CPA was administered for the initial 3 months at 50 mg/day, and at 25 mg/day for another 3 months and then discontinued.

Antiplatelet agents were administered more frequently in the control group compared with the PSL+CPA group (75% versus 7%; $P = 0.0004$), and no patient received fish oil treatment. To control blood pressure (systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg), antihypertensive drugs, including calcium-channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-Is), and/or angiotensin II receptor blockers (ARBs) were used if necessary in both groups. No patient from either group received tonsillectomy before or during the follow-up period.

Assessment of clinical outcome

After discharge from hospital, all patients visited our Kidney Center monthly, and physical examination and laboratory tests were performed, including urinary protein excretion and SCr. If the patients showed stable renal function, they were followed up every 2 or 3 months. Quantitative analysis of proteinuria was assessed by the ratio of urinary protein to urinary creatinine (UP/UCr). This parameter was closely correlated with 24-h urinary protein excretion; we usually measured UP/UCr for the follow-up of outpatients with proteinuria.

The effect of treatment was evaluated by the progression rate (PR) and renal survival rate. PR was defined as the slope of the regression line between the time after renal biopsy and the reciprocal SCr. The development of endstage renal disease during the observation period was considered as the endpoint, and patients who were lost to follow-up or did not reach endstage renal disease at the end of the observation period were classified as censored cases.

Statistical analysis

Data values are expressed as means ± SD. To test for statistically significant differences in clinical variables and PR between the control group and the PSL+CPA group, the Mann-Whitney *U*-test was used. Fisher's exact test was used to compare frequencies. Renal survival rate was plotted using the Kaplan-Meier method, and differences between the two groups were tested by log-rank and Tarone-Ware tests. A P value of less than 0.05 was considered to be statistically significant.

Table 1. Characteristics of the patients

	Control group	PSL+CPA group	*P*
No. of patients	8	27	
Age (years)	39.0 ± 15.1	46.0 ± 14.7	NS
Men/women	5/3	11/16	NS
SBP (mmHg)	146.0 ± 8.2	150.7 ± 3.7	NS
DBP (mmHg)	88.8 ± 4.1	89.0 ± 2.6	NS
SCr at biopsy (mg/dl)	2.5 ± 1.1	1.8 ± 0.5	NS
SCr at last follow-up (mg/dl)	14.8 ± 4.1	4.0 ± 3.7	<0.0001
UP/UCr at biopsy	4.4 ± 2.9	3.0 ± 1.6	NS
UP/UCr at last follow-up	4.6 ± 1.8	1.4 ± 1.1	<0.0005
Follow-up duration (months)	22.9 ± 15.6	64.3 ± 35.2	<0.005
ESRD	8/8 (100%)	6/27 (22%)	<0.0001
CCBs/BBs	6/8 (75%)	22/27 (81%)	NS
ACE-Is/ARBs	3/8 (38%)	23/27 (85%)	NS

Values are expressed as means ± SD
PSL, prednisolone; CPA, cyclophosphamide; SBP, systolic blood pressure; DBP, diastolic blood pressure; SCr, serum creatinine; UP/UCr, ratio of urinary protein to urinary creatinine; ESRD, endstage renal disease; CCBs, calcium-channel blockers; BBs, beta-blockers; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers

Results

Baseline characteristics and changes in clinical data

Table 1 shows the clinical characteristics at renal biopsy. Because we treated all patients with advanced IgAN with PSL+CPA from 1992 to 2003 (a period of 11 years), the number of cases in the PSL+CPA group was greater than that in the control group. Distributions of age and sex showed no significant differences, and blood pressure was similar in the two groups. Moderate to severe elevation of the initial SCr in both groups (range, 1.2–4.0 mg/dl) was recognized, and the SCr in the control group (range, 1.4–4.0 mg/dl) tended to be higher than that in the PSL+CPA group (range, 1.2–3.0 mg/dl), but insignificantly. The patients in both groups showed heavy proteinuria (UP/UCr; 1.2–9.5). The control group also showed greater urinary protein excretion than the PSL+CPA group, but the difference between them was not significant.

Because all patients in the control group rapidly lost renal function and reached endstage renal disease, the follow-up period of the control group was significantly shorter than that of the PSL+CPA group. The frequency of patients reaching endstage renal disease during the observation period in the PSL+CPA group was much lower than that in the control group (22% versus 100%). At the last follow-up, SCr in the PSL+CPA group was significantly elevated, but its change was mild compared with that in the control group. Urinary protein excretion at the last follow-up was similar to the baseline in the control group. However, proteinuria was significantly reduced in the PSL+CPA group.

Calcium-channel blockers and/or beta-blockers were needed to control blood pressure in most patients in both groups (75% of the control group and 81% of the PSL+CPA group; $P = 0.65$). ACE-Is or ARBs were used in 3 patients (38%) in the control group and 19 patients (70%) in the PSL+CPA group. The proportion of patients receiving ACE-Is or ARBs in the PSL+CPA group was larger than that in the control group, but there was no significant difference ($P = 0.12$). No patient in either group received combined therapy using ACE-Is and ARBs.

Table 2. Comparison of mean histological scores

	MH	CR	AD	MS	GS	TA	IF	VS	Total
Control	1.4	1.0	1.3	2.0	2.5	2.1	2.1	1.8	14.1
PSL+CPA	1.7	0.7	1.2	1.9	2.7	2.2	2.1	1.3	13.7

PSL, prednisolone; CPA, cyclophosphamide; MH, mesangial hypercellularity; CR, crescent; AD, tuft adhesion; MS, mesangial sclerosis; GS, global sclerosis; TA, tubular atrophy; IF, interstitial fibrosis; VS, vascular sclerotic change

Histological scores for both groups are shown in Table 2. In our previous report, the severity of histological changes was categorized into three grades, mild (score 0–6), moderate (score 7–11), and severe (score 12–24), and "moderate" and "severe" cases were recruited as the study population. In the present study, the entry criterion was limited to patients with a "severe" histological score. The distribution and grade of histological renal damage in the two groups were similar, and the mean total score in each group was higher than that in our previous study (14.1 versus 12.3 in the control group; 13.7 versus 11.2 in the PSL+CPA group).

Clinical outcome

Changes in the reciprocal SCr of all patients in both groups are shown in Fig. 1. All patients in the control group (before 1992) rapidly progressed to endstage renal disease and required dialysis treatment within 5 years. After 1992, the progression of renal failure was not arrested completely, but the rate of decline in the reciprocal SCr in the PSL+CPA group was very slow compared to that in the control group.

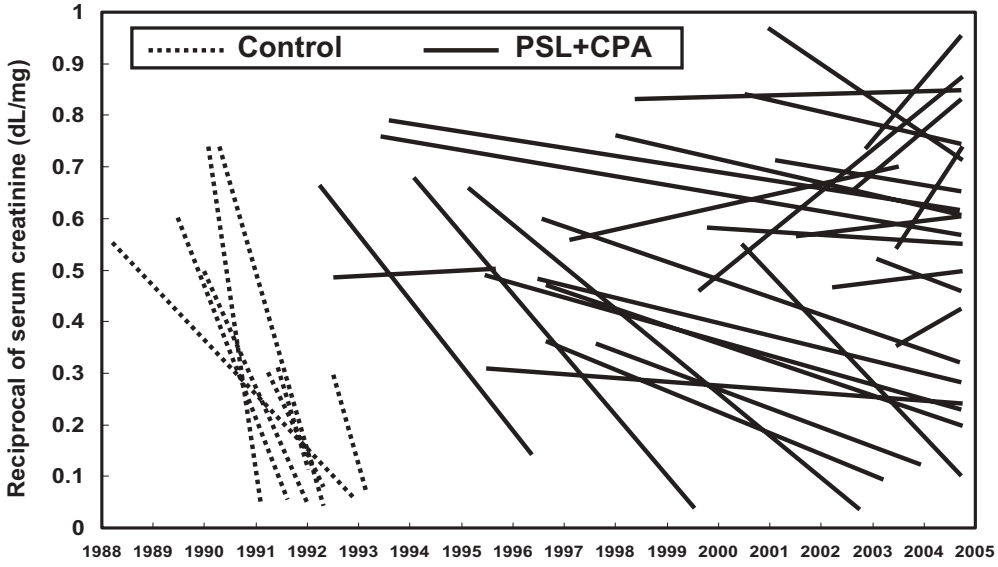

Fig. 1. Changes in the reciprocal of serum creatinine in all patients in both the control group and the prednisolone + cyclophosphamide (*PSL+CPA*) group

Table 3. Comparison of progression rates in patients with and without ACE-I/ARB treatment

	Progression rate ($\times 10^{-3}$ dl/mg per month)		*P*
	Without ACE-Is/ARBs	With ACE-Is/ARBs	
Control group	–18.2 ± 7.5 (*n* = 5)	–25.3 ± 8.9 (*n* = 3)	0.18
PSL+CPA group	–1.8 ± 4.9 (*n* = 8)	–1.3 ± 4.2 (*n* = 19)	0.75

Values are expressed as means ± SD
PSL, prednisolone; CPA, cyclophosphamide; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers

Fifteen patients (56%) were free from endstage renal disease over the 5-year period, including 2 patients without dialysis treatment over a period of 10 years. Furthermore, 10 patients (37%) in the PSL+CPA group showed an improvement in renal function. Six patients (22%) in the PSL+CPA group reached endstage renal disease during the follow-up period, but the time from renal biopsy to the initiation of dialysis treatment in the PSL+CPA group was significantly longer than that in the control group (66.5 months versus 22.9 months; $P = 0.0045$). The mean PR in the PSL+CPA group was markedly lower than that in the control group ($-1.5 \pm 4.3 \times 10^{-3}$ dl/mg per month versus $-20.9 \pm 8.3 \times 10^{-3}$ dl/mg per month; $P < 0.0001$). Additionally, to estimate the influence of ACE-Is/ARBs, we compared the PRs of patients receiving them with the PRs of those that did not (Table 3). There was no significant difference between the mean PRs of patients receiving ACE-Is/ARBs and those that did not, in either group. Independently of ACE-I/ARB treatment, PR was significantly reduced in the PSL+CPA group.

A comparison of renal survival in the two groups by Kaplan-Meier analysis is shown in Fig. 2. Renal survival in the PSL+CPA group was markedly high compared with that in the control group (95.5% versus 12.5% at 3 years, 89.8% versus 0% at 5 years, and 56.9% versus 0% at 8 and 10 years; $P < 0.0001$ by log-rank and Tarone-Ware tests).

Furthermore, we performed two subgroup analyses within the PSL+CPA group. Firstly, the patients in the PSL+CPA group were divided into those with an SCr of less than 2 mg/dl at baseline (subgroup A, SCr range 1.2–1.9 mg/dl, mean follow-up period 64.7 ± 36.1 months; $n = 17$) and those with an SCr of 2 mg/dl or more at baseline (subgroup B, SCr range 2.0–3.0 mg/dl, mean follow-up period 63.5 ± 35.5 months; $n = 10$; Fig. 3). There was no significant difference in renal survival between subgroup A and B, based on the Kaplan-Meier analysis (92.9% versus 100% at 3 years, 84.4% versus 100% at 5 years, and 52.8% versus 60.0% at 8 and 10 years; $P = 0.754$ by log-rank and $P = 0.696$ by Tarone-Ware tests). The mean PR was also similar in the two subgroups (-1.9×10^{-3} dl/mg per month in subgroup A versus -0.7×10^{-3} dl/mg per month in subgroup B; $P = 0.861$). Secondly, the patients in the PSL+CPA group were divided into three subgroups based on clinical responses, and we compared their clinical characteristics (Table 4). Subgroup I included the patients who showed an improvement of renal function (PR ≥ 0). Subgroup II included the patients who showed a decline of renal function (PR < 0) but did not develop endstage renal disease. Subgroup III included the patients who developed endstage renal disease. Age, SCr level, and proteinuria at baseline in subgroup III tended to be higher than those in the other two subgroups, but insignificantly.

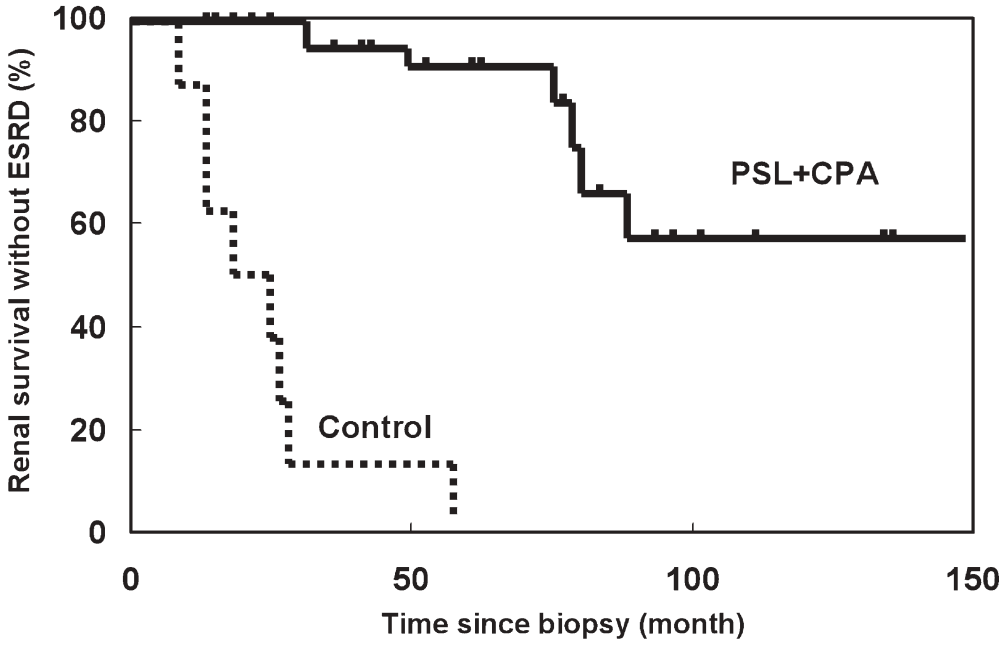

Fig. 2. Comparison of renal survival between the control group and the PSL+CPA group. *ESRD*, endstage renal disease

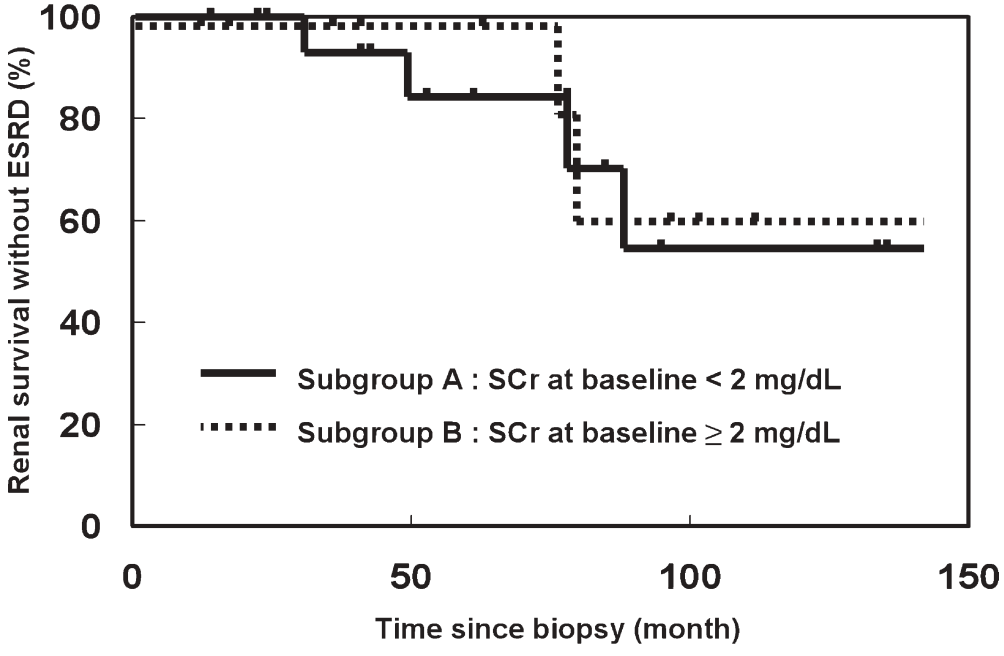

Fig. 3. Comparison of renal survival between subgroup A (SCr < 2 mg/dl at baseline) and subgroup B (SCr ≥ 2 mg/dl at baseline). *SCr*, serum creatinine

Adverse effects of treatment

In the PSL+CPA group, only two patients developed adverse effects that were probably related to the treatment. Gastric ulcer was observed in one patient (a 33-year-old man) and this was well controlled with an oral anti-H_2 blocker. One patient (a 31-year-old woman) developed diabetes mellitus 44 months after the start of PSL+CPA. Although she required insulin therapy, her blood sugar was well controlled. No specific adverse effects were observed in the control group.

Discussion

We previously reported the effect of the PSL+CPA combination therapy in patients with moderately advanced IgAN, and showed that using PSL+CPA slowed the deterioration of renal function.[18] In the present study, we reported outcomes in patients with advanced histological changes, who were a minor stratum characterized by heavy proteinuria and impaired renal function and who developed endstage renal disease rapidly. All patients in the control group

Table 4. Subgroup analysis of characteristics based on clinical responses in the PSL+CPA group

	Subgroup I	Subgroup II	Subgroup III	*P*
No. of patients	9	12	6	
Age (years)	47.3 ± 17.2	42.4 ± 13.8	53.2 ± 10.5	NS
Men/women	4/5	3/9	4/2	NS
SCr at biopsy (mg/dl)	1.8 ± 0.5	1.7 ± 0.4	2.1 ± 0.7	NS
UP/UCr at biopsy	3.0 ± 2.0	2.7 ± 1.4	3.3 ± 1.5	NS
Histological score	14.3 ± 3.3	13.2 ± 3.0	14.0 ± 1.7	NS
ACE-Is/ARBs	8/9 (89%)	7/12 (58%)	4/6 (67%)	NS
PR ($\times 10^{-3}$ dl/mg per month)	2.7 ± 3.0	−1.8 ± 0.9	−7.0 ± 3.4	<0.0001

Values are expressed as means ± SD. Subgroup I consisted of patients who showed an improvement of renal function (PR ≥ 0). Subgroup II consisted of patients who showed a decline of renal function (PR < 0), but did not develop endstage renal disease. Subgroup III consisted of patients who developed endstage renal disease

SCr, serum creatinine; UP/UCr, ratio of urinary protein to urinary creatinine; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; PR, progression rate

required dialysis therapy within 5 years. By contrast, the PSL+CPA combination therapy apparently reduced the incidence of endstage renal disease and elevated the renal survival at 5 years to almost 90%.

Beneficial effects of corticosteroids in patients with progressive IgAN have been reported since the 1980s. Kobayashi et al.[31] reported that the 10-year renal survival rate was 80% in the steroid-treated group compared with 34% in the nonsteroid-treated group. Recently, Pozzi et al.[17] showed that the 10-year renal survival in the steroid-treated group was significantly better than that in the supportive treatment group (97% versus 53%). However, patients with renal impairment were excluded in both reports, so the effectiveness of corticosteroids in patients with advanced IgAN is unclear. Katafuchi et al.[12] reported that low-dose prednisolone reduced the amount of urinary protein excretion, but could not improve renal survival compared with supportive treatments. This report made an important suggestion, that additional immunosuppressive agents would be needed to prevent the progression of advanced IgAN, with minimal side effects of the corticosteroids.

The efficacy of treatment in IgAN patients with renal impairment remains controversial and, unfortunately, there have only been a few trials.[7–11] Hotta et al.[14] reported that steroid pulse therapy and tonsillectomy contributed to clinical remission, but ACE-Is, conventional steroid therapy, and CPA did not. Following that study, Sato et al.[16] reported that steroid pulse therapy combined with tonsillectomy was found to improve renal survival much better than conventional steroid therapy (82.8% versus 51.0% at 8 years), and there was no difference between conventional steroid therapy and supportive therapy (51.0% versus 45.1% at 8 years). However, even combination therapy with tonsillectomy and steroid pulse therapy could not improve renal survival compared with supportive therapy in patients with a baseline SCr level of more than 2 mg/dl, and these authors concluded that a baseline SCr of 2 mg/dl would be a possible criterion for the stabilization of renal function; that is "the point of no return." On the other hand, in our present study, there was no difference between the renal survival of patients with a baseline SCr of 2 mg/dl or more and that of patients with a baseline SCr of less than 2 mg/dl. In our present study, the renal survival of patients with an SCr of 2 mg/dl or more at baseline was almost the same as the results in the reports of Sato et al.[16] until about 8 years after biopsy, but the renal survival at 10 years in the present study was higher than that reported by Sato et al.[16] (60% versus about 30%).

There have been only six randomized controlled trials of immunosuppressive agents in patients with IgAN, including one trial of azathioprine,[23] one of cyclophosphamide followed by azathioprine,[20] and four of mycophenolate mofetil.[25–28] Among these studies, only the study by Ballardie and Roberts,[20] who used corticosteroids and cyclophosphamide, showed an improvement in renal progression in patients at high risk of endstage renal disease. In that trial, patients with impaired renal function (SCr > 1.5 mg/dl) were included. The PRs of patients without treatment were −12.5 to -13.9×10^{-3} dl/mg per month (−4.85 to -5.19×10^{-6} l/μmol per day), and all patients in the control group developed endstage renal disease within 5 years. These patients were very much like those in our control group, as regards PRs and renal survival. Additionally, it is noteworthy that the side effects of CPA were minimal in that trial. The side effects of treatment in the present study were also minimal (7%), and they were all mild cases.

Following our first report in 2000,[18] which described the benefits of PSL+CPA therapy in patients with advanced IgAN, we still use PSL+CPA for the treatment of patients with progressive disease. Therefore, we could follow up more patients for longer observation periods than that in our previous study and analyze the accumulated outcomes in IgAN patients limited to those with advanced disease. Comparing the results of our previous report and those of the present study, the PRs of patients in the PSL+CPA group were -4.5×10^{-3} dl/mg per month (−0.054 dl/mg per year) and -1.5×10^{-3} dl/mg per month, and the scores for histological renal damage were 11.2 and 13.7, respectively. Interestingly, even though the renal damage in the patients in the present study was more severe than that in the patients in the previous study, the renal prognosis of the patients in the present study was better with similar treat-

ments. The reason for this might be that the number of patients showing improvement in their renal function was increased by the prolonged observation period. From the viewpoint of clinical responses, the patients in PSL+CPA group in the present study were broadly divided into "responders" and "nonresponders." So we performed subgroup analysis, but could not find the prognostic factors associated with "responders" and "nonresponders."

In conclusion, it is possible that combination therapy using PSL+CPA *is* able to prevent rapid progression to endstage renal disease in patients with histologically advanced IgAN, especially those showing severe renal impairment beyond "the point of no return," and our treatment protocol of PSL+CPA is considered to be safe with regard to side effects. To prove the effects and safety of this treatment, however, a prospective, multicenter clinical trial is required.

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