Clin Exp Nephrol (2000) 4:241–250

ORIGINAL ARTICLE

Kazuho Honda · Kosaku Nitta · Hideo Kobayashi
Keiko Uchida · Akira Kawashima · Shigeru Horita
Wako Yumura · Hiroshi Nihei

Clinical significance of histological grading and staging for predicting the effectiveness of steroid therapy in IgA nephropathy

Received: August 17, 1999 / Accepted: May 8, 2000

Abstract
Background. A beneficial effect of steroid therapy for IgA nephropathy (IgAN) has been reported. However, precise histological criteria for steroid therapy have not yet been established. The present study was designed to assess the clinical validity of histological grading and staging for predicting the responsiveness to steroid therapy in IgAN.
Methods. We performed a retrospective study of 27 patients with IgAN who underwent steroid therapy. The duration of steroid therapy was 42.9 ± 23.1 months, and the mean follow-up period was 7.5 ± 2.4 years, ranging from 4 to 14 years. Responsiveness to the steroid therapy was evaluated by reduction of urinary protein at 1 year after treatment; more than 50% reduction of initial urinary protein and less than 1.0 g/day. Responsiveness to the therapy was also evaluated by preservation of renal function; i.e., maintenance of serum creatinine level under 2.0 mg/dl during follow-up. The histological grading and staging method (G-S system) proposed by Shigematsu was used to evaluate the histological severity of lesions in renal biopsy specimens. Univariate analyses of clinical and histological parameters, using the logistic regression model or Cox proportional hazards model, were performed to find predictive factors for the effectiveness of steroid therapy.
Results. No clinical parameters at the start of treatment predicted the effectiveness of the steroid therapy. However, some histological parameters – crescent formation rate (%), grade of glomerular extracapillary lesions (Gex) and grades of acute and chronic interstitial inflammation (Gint and Sint) – were predictive for the effectiveness of steroid therapy. To predict reduction of proteinuria at 1 year after steroid therapy, the crescent formation rate, Gex, Gint, and Sint were significant (odds ratio; P value): crescent formation rate per 10% increment (2.91; $P = 0.019$), Gex per 0.1 grade increment (1.56; $P = 0.021$), Gint per one grade increment (0.20; $P = 0.022$), and Sint per one grade increment (0.33; $P = 0.039$). These results indicated that a high crescent formation rate and active extracapillary lesions predicted favorable response, and active and chronic interstitial lesions predicted lower efficacy in proteinuria reduction. To predict deterioration of renal function, Gint and Sint were significant (hazard ratio; P value): Gint per one grade increment (3.30; $P = 0.015$) and Sint per one grade increment (2.99; $P = 0.006$), indicating that high degrees of acute and chronic interstitial inflammation predicted the deterioration of renal function.
Conclusions. The severity of acute glomerular extracapillary lesions predicts the possibility of reduction in proteinuria after steroid therapy, while the severity of interstitial inflammation suggests a lower efficacy for proteinuria reduction and a high risk of renal dysfunction even after steroid therapy in IgAN.

Key words IgA nephropathy · Steroid therapy · Histological grading and staging · Extracapillary lesion · Interstitial inflammation

K. Honda (✉) · K. Nitta · H. Kobayashi · K. Uchida · A. Kawashima · S. Horita · W. Yumura · H. Nihei
Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
Tel. +81-3-3353-8111, ext. 39112-4; Fax +81-3-3356-0293
e-mail: khonda@kc.twmu.ac.jp

Introduction

IgA nephropathy (IgAN) is a slowly progressive glomerulonephritis and often leads to end-stage renal failure after long periods (20–30 years).[1,2] The disease activity of IgAN varies at different stages in each patient. Repeated episodes of acute glomerular inflammation, which manifested as the clinical exacerbation of hematuria and proteinuria, could contribute to glomerular destruction and finally lead to end-stage renal failure.[3,4]

Steroid therapy for IgAN has been employed since the 1970s. It has been considered to be beneficial in reducing the extent of proteinuria and hematuria.[3–6] Although the long-term effects of steroid therapy have not yet been

precisely evaluated, a benefit of steroid therapy for long-term renal survival has been reported recently.[5,6] Kobayashi et al.[6] proposed three criteria for steroid therapy: (1) moderate amount of proteinuria (1–2 g urinary protein/day), (2) preserved renal function (creatinine clearance, more than 70 ml/min), and (3) severe histological changes. They suggested that patients who fulfilled these criteria showed significant improvement of renal function after steroid therapy, and concluded that steroid therapy was beneficial in the early stage of progressive IgAN.

In consideration of these clinical findings, it is necessary to establish more precise clinical and histological evaluations of the disease activity in IgAN patients in order to decide on indications for steroid therapy. For this purpose, we retrospectively analyzed the detailed histological features and the outcome of 27 IgAN patients who received steroid therapy.

To evaluate the severity of IgAN, several histological grading systems have been reported.[7–11] Recently, Shigematsu[12] proposed a new method for the histological evaluation of IgAN, a histological grading and staging system (G-S system). In this method, the severity of acute tissue damage is expressed by the histological grade (G), and the severity of chronic tissue damage is expressed by the histological stage (S). G and S are separately scored in each renal component (glomerular endocapillary, glomerular extracapillary, and interstitium) and the total score for G-S is obtained by adding the scores for each component. In the present study, we adopted the G-S system to evaluate histological activity, and to analyze clinical and histological parameters that would predict a beneficial effect of steroid therapy for IgAN. The results of this study revealed more precise histological criteria for indications for steroid therapy in IgAN.

Patients and methods

Patients

From January 1982 to December 1992, 295 patients were diagnosed with IgAN, based on renal biopsy findings, at the Department of Medicine, Kidney Center, Tokyo Women's Medical University. Of these patients, we selected 27 (9 men and 18 women) who were treated with steroid because of persistent proteinuria (usually more than 1.0 g/day) and/or moderate to severe renal histological injury. The mean duration of the steroid therapy was 42.9 ± 23.1 months, ranging from 12 to 96 months. The mean follow-up time was 7.5 ± 2.4 years (mean ± SD), ranging from 4 to 14 years. Of the 27 patients, 4 (14.8%) went into end-stage renal failure and started maintenance hemodialysis or continuous ambulatory peritoneal dialysis.

Protocol of steroid therapy

Prednisolone (PSL) was administered at an initial dose of 40 mg/day (0.8 mg/kg per day) for the first 4 weeks, followed by the gradual tapering of PSL as 40 mg/30 mg, 40 mg/20 mg, 40 mg/10 mg, 30 mg/10 mg on alternate days for the next 4 weeks, with maintenance on 30 mg of PSL on alternate days for the following 6 to 12 months. For the next 1 year, 20 mg of PSL was administered on alternate days. If the treatment was effective, 10–15 mg of PSL on alternate days was continued during the subsequent follow-up period. If it was not effective (decreased renal function and/or persistent proteinuria), PSL was tapered and discontinued. In four patients (patients 3, 4, 5, and 9) the steroid therapy was discontinued within 2 years because their amounts of proteinuria were effectively reduced. In one patient (patient 20), the steroid therapy was discontinued at 18 months because of persistent proteinuria (1.5 g/day). An anti-platelet drug, dipyridamole or dilazep, was administered in combination with PSL in all patients and administration of this drug was continued after completion of the PSL therapy. Three patients (patients 1, 14, and 23) received angiotensin converting enzyme inhibitor (ACEI) during the first year of PSL treatment, and another 7 patients (patients 4, 13, 15, 17, 20, 21, and 27) received ACEI during the follow-up period 1 year after PSL treatment.

Clinical and laboratory data

The clinical and laboratory data of the 27 patients were evaluated in regard to sex, age at onset, age at the start of the steroid therapy, presence of hypertension (defined as systolic blood pressure of more than 150 mmHg and/or diastolic pressure of more than 90 mmHg). The following laboratory findings were also evaluated at the time of the renal biopsy: serum creatinine, creatinine clearance, proteinuria (g/day), and grade of hematuria (grade 0, fewer than 4 red blood cells/high power field (RBC/HPF); grade 1, 5–20 RBC/HPF; grade 2, 21–40 RBC/HPF; grade 3, 41–80 RBC/HPF; grade 4, more than 81 RBC/HPF). At 1 year after the steroid therapy, urinary protein excretion, grade of hematuria, and serum creatinine and creatinine clearance were examined. These laboratory findings were also evaluated at the time of final observation. The outcome of the steroid therapy was evaluated in regard to urinary protein excretion and renal function. Urinary protein reduction was defined as having occurred when the amount of proteinuria at 1 year after the steroid therapy was less than 50% of the initial amount of proteinuria and the amount of urinary protein was also less than 1.0 g/day. Progression of renal dysfunction was defined as having occurred when serum creatinine reached a level of 2.0 mg/dl during the follow-up period.

Histological investigation of renal biopsy specimens

Light microscopic investigation was performed according to the histological grading and staging method for IgAN (G-S system) described by Shigematsu.[12] Briefly, in each biopsy specimen, glomerular (g) and tubulointerstitial (int) lesions

were evaluated semiquantitatively. The glomerular lesions were divided into two components: endocapillary changes (en) and extracapillary changes (ex). In the evaluation of each component, acute and chronic changes were separately estimated. The grade (G) expressed the extent of acute lesions and the stage (S) expressed the extent of chronic lesions. The extent of each histological injury was semiquantitatively evaluated in four grades (0, none; 1, mild; 2, moderate; 3, severe). The extent of each glomerular grading (G) and staging (S) was evaluated in every glomerulus, and the final Gen, Gex, Sen, and Sex values were expressed as sums of numbers divided by the total number of glomeruli. Tubulointerstitial grading (Gint, 0–3) and staging (Sint, 0–3) were also estimated. The glomerular grade (Gg) was the sum of Gen and Gex, and the glomerular stage (Sg) was the sum of Sen and Sex. The total histological grade (G) was the sum of Gg and Gint, and the total histological stage (S) was the sum of Sg and Sint. In addition to the G-S system, we evaluated the percentage of glomeruli that exhibited obsolescence (global hyalinization), crescent formation, and glomerular tuft adhesion to Bowman's capsule. Crescents were divided into two categories; cellular or fibrocellular (active crescents) and fibrous crescents. Thus, the number of active crescents indicates the severity of acute extracapillary lesions and the number of fibrous crescents indicates the severity of chronic extracapillary lesions. Glomeruli counted for with tuft adhesions did not include glomeruli in which crescents were assessed.

Statistical analysis

The prognostic significance of the clinical and histological variables was determined using the univariate logistic regression model or univariate Cox proportional hazards model. We used the univariate logistic regression model to determine the prognostic significance for proteinuria reduction at 1 year after treatment, and the univariate Cox proportional hazards model to determine the prognostic significance for the development of renal dysfunction. Multivariate analysis was attempted, but failed to generate a model because of the small number of patients and events involved. All data were analyzed using SAS System 6.12 (SAS Institute, Cary, NC, USA). Significance was considered to be present at $P < 0.05$ in all analyses.

Results

Clinical profiles and outcome of the patients (Table 1)

Table 1 shows the clinical data of the 27 patients (9 men and 18 women). The age at treatment was 29.2 ± 10.3 years (mean ± SD) and the duration of steroid therapy was 42.9 ± 23.1 months. The follow-up period was 7.5 ± 2.4 years. The pretreatment level of urinary protein was 2.7 ± 1.6 g/day and the urinary RBC grade was 2.9 ± 1.2; the level of serum creatinine was 1.1 ± 0.3 mg/dl and creatinine clearance was 76.4 ± 24.9 ml/min. Clinical data 1 year after treatment and at final observation, and the period when the serum creatinine level of the patient reached more than 2.0 mg/dl are shown in Table 1.

The urinary protein excretion in 12 patients (patients 1–11, 19) 1 year after PSL treatment was reduced by more than 50% of the initial amount and was less than 1.0 g/day, while the proteinuria in 15 patients (patients 12–18, and 20–27) was persistent. The serum creatinine levels in 9 patients (patients 19–28) reached more than 2.0 mg/dl during the follow-up period, and 4 patients (patients 21, 23, 26, and 27) went into maintenance dialysis therapy. In the other 18 patients (patients 1–18), renal function was preserved (serum creatinine level under 2.0 mg/dl) until the final observation.

Histological analysis of renal biopsy specimens (Table 2)

Table 2 shows the results of the histological evaluation in each patient. The histological scores were determined by using the G–S system proposed by Shigematsu.[12] The percentages of glomeruli exhibiting obsolescence (global hyalinization), crescent formation, and glomerular tuft adhesion to Bowman's capsule are listed in Table 2. "Crescents" in Table 2 includes all types of crescents; cellular, fibrocellular, and fibrous. "Active crescents" includes cellular and fibrocellular crescents.

Figure 1 shows representative glomerular changes in patient 8. Two glomeruli showed intracapillary and extracapillary inflammation in both acute and chronic stages. In the left-sided glomerulus, fibrocellular crescents with tuft-adhesion to Bowman's capsule, mesangial cell proliferation

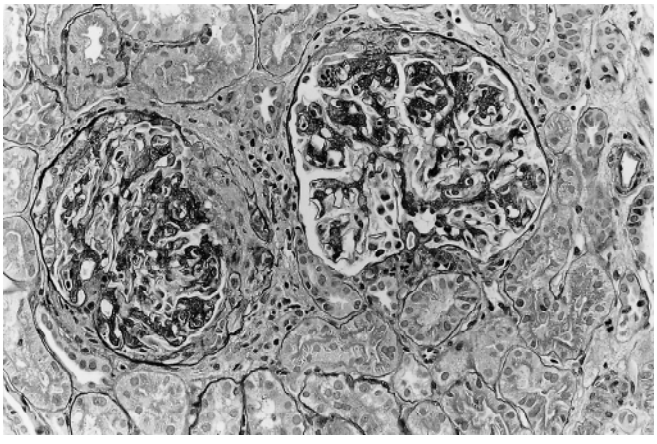

Fig. 1. Glomerular changes in patient 8. Two glomeruli showed intracapillary and extracapillary inflammation in both acute and chronic stages. In the glomerulus on the *left*, fibrocellular crescents with tuft-adhesion to Bowman's capsule, mesangial cell proliferation with matricial increase, and mesangial interposition were observed. The grade and stage were Gen(1), Gex(2), Sen(2), and Sex(2) (see text for explanation). In the glomerulus on the *right*, mild mesangial proliferation with partial mesangial interposition, and small cellular crescents with tuft-adhesion were observed. The grade and stage were Gen(1), Gex(1), Sen(2), and Sex(1). Periodic acid-Schiff, ×65

Table 1. Patient profiles (clinical data)

Patient no.	Age at treatment (years)	Age at onset (years)	Sex	BP	PSL duration (months)	Follow-up period (years)	U-P (pre) (g/day)	U-RBC (pre) (grade)	sCr (pre) (mg/dl)	CCr (pre) (ml/min)	U-P (1 year) (g/day)	U-RBC (1 year) (grade)	sCr (1 year) (mg/dl)	CCr (1 year) (ml/min)	U-P (last) (g/day)	U-RBC (last) (grade)	sCr (last) (mg/dl)	CCr (last) (ml/min)	Period (year) at sCr 2.0	Proteinuria	Function
1	25	23	M	H → N	26	6	1.2	2	1.2	115	0.4	0	1.1	104	0	0	1	ND	No	Reduced	Maintained
2	18	16	F	N	43	6	1.79	4	0.8	98.2	0.53	2	0.7	126	0	0	0.6	139	No	Reduced	Maintained
3	50	50	M	H	19	5	4.6	4	2	40	0.68	0	1.2	78	0.17	0	1.2	95	No	Reduced	Maintained
4	29	25	F	N → H	12	10	3.72	2	0.9	113	0.84	1	0.9	71	0.33	0	0.92	107	No	Reduced	Maintained
5	18	18	F	N	18	7	2.5	4	1	73	0.82	1	0.9	70	0.7	1	1.02	81	No	Reduced	Maintained
6	23	22	F	N	35	5	1.73	4	0.8	67	0.2	1	0.8	80	0.3	1	0.8	78	No	Reduced	Maintained
7	24	23	M	N	64	7	4.5	4	1.5	37	0.9	4	1.2	80	2.1	4	1.3	90	No	Reduced	Maintained
8	47	47	F	N	50	7	4.1	4	0.8	72	0	0	1	76	0	0	0.9	87.5	No	Reduced	Maintained
9	26	20	F	N	18	7	1.4	4	0.8	71	0.52	1	0.9	73.6	0.46	0	0.68	71.6	No	Reduced	Maintained
10	41	40	M	N	34	7	2.8	1	1.1	75.2	0.59	1	1.4	72.8	0.5	1	1.36	77.7	No	Reduced	Maintained
11	20	16	M	N	79	9	1.1	3	1.1	97	0.32	1	1.1	128	0.7	0	1	124	No	Reduced	Maintained
12	34	33	F	N	60	6	3.45	4	0.8	71.5	1.51	2	0.76	77.1	1.25	1	0.79	88.8	No	Persistent	Maintained
13	18	12	M	N	85	7	4.84	3	0.9	109	1.6	1	0.8	108	0.86	1	1.1	87	No	Persistent	Maintained
14	44	43	F	N	26	7	2.56	2	1.2	80	1.25	0	1.2	83	0.74	0	1.16	87	No	Persistent	Maintained
15	25	21	M	N	28	7	3.52	3	1	126	2.13	3	1	123	1.14	1	1.05	116	No	Persistent	Maintained
16	18	18	F	N	30	11	1.37	3	0.9	96.7	0.98	2	0.8	88.8	0.96	1	0.8	112	No	Persistent	Maintained
17	25	23	M	H	26	11	1.12	1	1	111	1.13	1	1	109	0.62	0	0.9	142	No	Persistent	Maintained
18	21	19	F	N	36	4	1.4	4	1.1	53	1.26	4	1.1	57	0.79	4	1.3	60	No	Persistent	Maintained
19	41	38	F	N	51	10	1.8	3	1.1	66	0.86	2	1.3	55	1.34	1	2.98	23.7	7	Reduced	Worse
20	29	20	F	N → H	18	15	3	1	1.3	40	1.5	1	1.2	54	0.16	0	2.01	33.8	15	Persistent	Worse
21	37	35	F	N → H	48	6	3	4	0.8	70	1	2	0.8	ND	3.1	2	6	9.8	5	Persistent	Worse (HD)
22	51	51	F	N → H	72	6	1.35	4	1.6	49.3	1.3	3	1.16	59.9	4.88	1	2.36	39.6	6	Persistent	Worse
23	19	18	F	N → H	54	7	7.9	2	1	61	4.7	3	1.1	62	2.74	1	8.36	6.5	6	Persistent	Worse (PD)
24	27	12	F	H	96	8	3.25	1	1	61.2	2.07	1	1.3	60.4	1.08	0	2.16	32.1	4	Persistent	Worse
25	22	15	M	N	28	6	1.9	1	1.2	76.7	3.06	0	1.1	106	4.3	2	4.3	18.6	6	Persistent	Worse
26	25	17	F	N → H	28	5	3.7	2	1.6	47	4.6	1	1.7	45	2.21	1	15.8	10	3	Persistent	Worse (HD)
27	31	31	F	N → H	73	10	0.48	3	0.8	86.8	0.61	3	0.8	86.8	0.64	0	9.18	4.4	8	Persistent	Worse (HD)
Mean	29.19	26.15			42.85	7.48	2.74	2.85	1.09	76.43	1.31	1.52	1.05	82.09	1.19	0.85	2.63	70.08			
SD	10.32	11.77			23.13	2.39	1.60	1.17	0.30	24.90	1.16	1.19	0.23	23.35	1.27	1.10	3.47	42.30			

BP, Blood pressure; N, normotensive; H, hypertensive; PSL, prednisolone; U-P, urinary protein; U-RBC, urinary red blood cell; sCr, serum creatinine; CCr, creatinine clearance; (pre), pre-treatment; (1 year), 1 year after treatment; (last), at the last observation; ND, not done; HD, hemodialysis; PD, peritoneal dialysis

Table 2. Histological analysis of renal biopsy specimens

Patient no.	Proteinuria	Function	Obsolescence (%)	Crescents (%)	Active crescents (%)	Fibrous crescents (%)	Adhesion (%)	Gen (grade)	Gex (grade)	Gg (grade)	Sen (grade)	Sex (grade)	Sg (grade)	Gint (grade)	Sint (grade)	G (grade)	S (grade)
1	Reduced	Maintained	0	7.7	7.7	0	30.8	1.38	0.54	1.92	0.92	0.46	1.38	0	0	1.92	1.38
2	Reduced	Maintained	0	18.2	18.2	0	18.2	0.91	0.64	1.55	0.91	0.64	1.55	0	0	1.55	1.55
3	Reduced	Maintained	10	25	20	5	15	0.95	0.95	1.9	1	0.75	1.75	1	1	2.9	2.75
4	Reduced	Maintained	25	16.7	16.7	0	16.6	0.75	0.42	1.17	1.67	0.42	2.09	0	0	1.17	2.09
5	Reduced	Maintained	0	25	25	0	25	1.13	0.88	2	0.75	0.5	1.25	0	0	2	1.25
6	Reduced	Maintained	0	42.9	42.9	0	14.2	1.43	0.57	2	1.29	0.57	1.86	0	0	2	1.86
7	Reduced	Maintained	16.7	16.7	16.7	0	0	1.17	0.5	1.67	1	0.5	1.5	0	0	1.67	1.5
8	Reduced	Maintained	0	25	25	0	16.7	1	0.58	1.58	0.67	0.25	0.92	0	0	1.58	0.92
9	Reduced	Maintained	0	23.1	23.1	0	15.4	0.85	1	1.85	0.77	0.15	0.92	0	0	1.85	0.92
10	Reduced	Maintained	15.8	26.3	21.1	5.2	42.1	1	0.68	1.68	1.26	0.84	2.1	1	2	2.68	4.1
11	Reduced	Maintained	4	8	4	4	8	0.76	0.32	1.08	0.4	0.32	0.72	1	1	2.08	1.72
12	Persistent	Maintained	33.3	16.7	16.7	0	16.6	0.83	0.83	1.66	2	0.66	2.66	1	1	2.66	3.66
13	Persistent	Maintained	0	37.5	25	12.5	12.5	1.38	0.5	1.88	1.62	0.38	2	1	1	2.88	3
14	Persistent	Maintained	30	0	0	0	20	0.3	0.2	0.5	1.6	0.5	2.1	1	2	1.5	4.2
15	Persistent	Maintained	0	0	0	0	22.2	1	0.44	1.44	1.33	0.11	1.44	0	0	1.44	1.44
16	Persistent	Maintained	0	0	0	0	0	0.45	0	0.45	0.85	0	0.85	0	0	0.45	0.85
17	Persistent	Maintained	25	0	0	0	12.5	0.62	0.12	0.75	1.25	0.62	1.88	0	0	0.75	1.88
18	Persistent	Maintained	5.6	16.7	8.3	8.4	16.6	0.75	0.47	1.22	0.64	0.5	1.14	1	1	2.22	2.14
19	Reduced	Worse	5.6	11.1	11.1	0	27.8	0.83	0.94	1.77	0.94	0.28	1.22	1	2	2.77	3.22
20	Persistent	Worse	50	0	0	0	12.5	0.88	0.38	1.26	2.25	0.38	2.63	2	2	3.26	4.63
21	Persistent	Worse (HD)	23.1	23.1	23.1	0	0	1.08	0.54	1.62	1.15	0.46	1.61	1	2	2.62	3.61
22	Persistent	Worse	20	6.7	0	6.7	6.6	0.93	0	0.93	1.47	0.8	2.27	1	1	1.93	3.27
23	Persistent	Worse (PD)	33.3	16.7	16.7	0	16.6	1.33	0.67	2	2.17	1.17	3.34	2	3	4	6.34
24	Persistent	Worse	20.8	0	0	0	37.5	1.5	0.42	1.92	1.83	0.46	2.29	2	2	3.92	4.29
25	Persistent	Worse	0	0	0	0	0	1	0	1	0.67	0	0.67	0	1	1	1.67
26	Persistent	Worse (HD)	7.1	7.1	7.1	0	35.8	1.43	0.86	2.29	1.07	0.29	1.36	2	2	4.29	3.36
27	Persistent	Worse (HD)	0	0	0	0	0	0.33	0	0.33	0.5	0	0.5	2	1	2.33	1.5
Mean			12.05	13.71	12.16	1.55	16.27	0.96	0.50	1.46	1.18	0.44	1.63	0.74	0.93	2.20	2.56
SD			13.97	12.20	11.43	3.25	11.62	0.32	0.31	0.53	0.50	0.27	0.68	0.76	0.92	0.96	1.38

Active crescents mean both cellular and fibrocellular crescents
See text for explanation of Gen, Gex, Gg, Sen Sex, Sg, Gint, Sint, G, and S

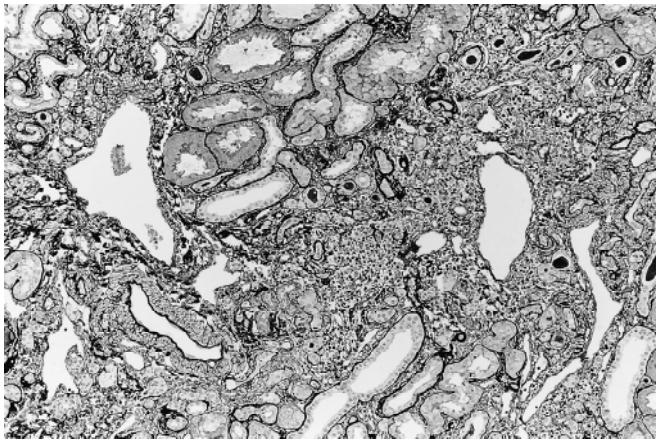

Fig. 2. Advanced tubulointerstitial changes in patient 24. A moderate grade mononuclear cell infiltration, and interstitial fibrosis with tubular atrophy were observed. The grade and stage were Gint(2) and Sint(2). (Periodic acid-methenamine silver, ×33

with matricial increase, and mesangial interposition were observed. The grade and stage were expressed as Gen(1), Gex(2), Sen(2), and Sex(2). In the right-sided glomerulus, mild mesangial proliferation with partial mesangial interposition, and small cellular crescents with tuft-adhesion were observed. The grade and stage were expressed as Gen(1), Gex(1), Sen(2), and Sex(1).

Figure 2 shows advanced tubulointerstitial changes, in patient 24. A moderate grade of mononuclear cell infiltration and interstitial fibrosis with tubular atrophy were observed. The grade and stage were expressed as Gint(2) and Sint(2).

Clinical and histological predictors of proteinuria reduction (univariate logistic regression analysis)

Table 3 summarizes the results of the univariate logistic regression analysis to determine the clinical and histological predictors for proteinuria reduction after steroid therapy. None of the clinical factors at treatment was significant for the prediction of proteinuria reduction.

Concerning the histological factors, the following factors were significant predictors of proteinuria reduction; percentages of all crescents (odds ratio per 10% increment: 2.91; $P = 0.019$), active crescents (odds ratio per 10% increment: 3.98; $P = 0.009$), and Gex (odds ratio per 0.1 grade increment: 1.56; $P = 0.021$). On the other hand, an increase in Gint and Sint predicted proteinuria persistence, i.e., predicted a lower possibility of proteinuria reduction (odds ratio of Gint per one grade increment: 0.20; $P = 0.022$, and odds ratio of Sint per one grade increment: 0.33, $P = 0.039$). The score of S was also significant (odds ratio per one grade increment: 0.46; $P = 0.048$); therefore, this predicted a lower possibility of proteinuria reduction. This possibility was ascribed to the strong correlation between S and Sint ($R = 0.899$; $P < 0.0001$).

Clinical and histological predictors of progressive renal dysfunction (univariate Cox proportional hazards analysis)

Table 4 summarizes the results of the univariate Cox proportional hazards analysis to determine the clinical and histological predictors of progression of renal dysfunction after steroid therapy. None of the clinical factors at treatment was significant for the prediction of progressive renal dysfunction. The duration of the steroid therapy also had no influence on the outcome of renal function after treatment. However, urinary protein and serum creatinine 1 year after treatment were predictors of progressive renal dysfunction (hazard ratio of urinary protein at 1 year per 1.0 g/day increment was 2.04; $P = 0.003$, and that of serum creatinine at 1 year per 0.1 mg/dl increment was 1.46; $P = 0.041$).

Of the histological factors, the hazard ratios of Gint and Sint were significant predictors of renal dysfunction (Gint per one grade increment: 3.30; $P = 0.015$; for Sint per one grade increment: 2.29; $P = 0.006$). G and S were also significant, because of their strong correlation to Gint and Sint, respectively. (Gint vs G, $R = 0.833$; $P < 0.0001$; Sint vs S, $R = 0.899$; $P < 0.0001$) None of the glomerular indexes (Gen, Gex, Gg, Sen, Sex, Sg) or the percentages for glomerular obsolescence, crescents, and adhesion were significant for the prediction of progressive renal dysfunction.

Discussion

To establish factors predictive of the effectiveness of steroid therapy in IgAN, we first analyzed the clinical parameters at the start of therapy, but we failed to find any clinical factors that were predictive of the response. The reason why no initial clinical parameter predicted the outcome in this study was likely that the steroid therapy modified the disease activity and the natural course of IgAN. Therefore, initial clinical factors do not predict the outcome of IgAN when a therapeutic intervention such as the use of steroid was employed for the patients. On the other hand, proteinuria and serum creatinine 1 year after treatment predicted the development of renal dysfunction to some extent. This result coincided with previous studies suggesting that the amount of proteinuria and renal function at the time of renal biopsy predicted progressive renal failure.[8,13–15]

Histological factors that predict the outcome of renal function have been investigated by many authors.[8,13–19] Bogenscuetz et al.[18] suggested, in their multivariate analysis of 239 IgAN patients, that interstitial fibrosis was the only histological predictor of renal failure. Other reports also indicated interstitial fibrosis as one of the significant histological predictors of renal failure.[8,13,14,19] In the present study, we analyzed predictors of renal dysfunction, using the univariate Cox proportional hazards model; we found that high degrees of both acute and chronic inflammation in interstitium (Gint and Sint) predicted the deterioration of renal function after steroid therapy (hazard ratio per one

Table 3. Clinical and histological predictors of proteinuria reduction (univariate logistic regression analysis)

	No. of patients (n = 27)	U-P reduced (n = 12)	Odds ratio (95% CI)	P Value
Treatment age (years)				
10 unit	27		1.19 (0.56–2.52)	NS (P = 0.654)
Onset age (years)				
10 unit	27		1.32 (0.68–2.56)	NS (P = 0.421)
Sex				
Female	18	7 (38.9%)	1.00	
Male	9	5 (55.6%)	1.96 (0.39–9.93)	NS (P = 0.414)
BP (pre)				
Normotensive	22	10 (45.5%)	1.00	
Hypertensive	5	2 (40.0%)	0.80 (0.11–5.77)	NS (P = 0.825)
U-P (pre) (g/day)				
1 unit	27		0.90 (0.55–1.48)	NS (P = 0.680)
U-RBC (pre) (grade)				
1	5	1 (20.0%)	1.00	
2	5	2 (40.0%)	1.81 (0.86–3.80)	
3	6	2 (33.3%)	3.27 (0.74–14.41)	
4	11	7 (63.6%)	5.90 (0.64–54.70)	NS (P = 0.118)
sCr (pre) (mg/dl)				
1 unit	27		1.14 (0.09–15.04)	NS (P = 0.918)
CCr (pre) (ml/min)				
10 unit	27		1.02 (0.75–1.39)	NS (P = 0.909)
Sclerosis (%)				
10 unit	27		0.52 (0.25–1.07)	NS (P = 0.074)
Crescents (%)				
10 unit	27		2.91 (1.19–7.11)	P = 0.019
Active crescents (%)				
10 unit	27		3.98 (1.41–11.26)	P = 0.009
Fibrous crescents (%)				
10 unit	27		0.51 (0.04–6.34)	NS (P = 0.600)
Adhesion (%)				
10 unit	27		1.51 (0.75–3.08)	NS (P = 0.251)
Gen (grade)				
0.1 unit	27		1.10 (0.86–1.41)	NS (P = 0.454)
Gex (grade)				
0.1 unit	27		1.56 (1.07–2.28)	P = 0.021
Gg (grade)				
0.1 unit	27		1.19 (0.99–1.43)	NS (P = 0.067)
Sen (grade)				
0.1 unit	27		0.82 (0.68–1.00)	NS (P = 0.056)
Sex (grade)				
0.1 unit	27		1.07 (0.81–1.43)	NS (P = 0.624)
Sg (grade)				
0.1 unit	27		0.92 (0.81–1.04)	NS (P = 0.198)
Gint (grade)				
0	12	8 (66.7%)	1.00	
1	10	4 (40.0%)	0.20 (0.05–0.79)	
2	5	0 (0.0%)	0.04 (0.00–0.62)	P = 0.022
Sint (grade)				
0	11	8 (72.7%)	1.00	
1	8	4 (50.0%)	0.33 (0.11–0.95)	
2	7	2 (28.6%)	0.11 (0.01–0.90)	
3	1	0 (0.0%)	0.04 (0.00–0.85)	P = 0.039
G (grade)				
1 unit	27		0.67 (0.29–1.58)	NS (P = 0.363)
S (grade)				
1 unit	27		0.46 (0.22–0.99)	P = 0.048

Active crescents mean both cellular and fibrocellular crescents; CI, confidence interval; BP, Blood pressure; U-P, urinary protein; U-RBC, urinary red blood cell; sCr, serum creatinine; CCr, creatinine clearance; pre, pre-treatment; NS, not significant

grade increment of Gint: 3.30; P = 0.015; for Sint: 2.99; P = 0.006).

In addition to interstitial lesions, the severity of glomerular lesions was also considered to be a significant predictor of prognosis in several studies.[13,14,16] D'Amico et al.[14] reported that the extent of glomerular obsolescence and the presence of IgA deposits in peripheral capillary loop were independent predictors of poor prognosis. Alamartine et al.[16] and Radford et al., using multivariate analysis,[13] concluded that the total histological score (the

Table 4. Clinical and histological predictors of progressive renal dysfunction (univariate Cox proportional hazards analysis)

	No. of patients (n = 27)	RF worse (n = 9)	Hazard ratio (95% CI)	P Value
Treatment age (years)				
10 unit	27		1.34 (0.69–2.62)	NS (P = 0.386)
Onset age (years)				
10 unit	27		1.10 (0.59–2.06)	NS (P = 0.747)
Sex				
Female	18	7 (38.9%)	1.00	
Male	9	5 (55.6%)	0.25 (0.03–2.01)	NS (P = 0.191)
BP (pre)				
Normotensive	22	10 (45.5%)	1.00	
Hypertensive	5	2 (40.0%)	0.75 (0.09–6.15)	NS (P = 0.792)
U-P (pre) (g/day)				
1 unit	27		1.14 (0.76–1.69)	NS (P = 0.531)
U-RBC (pre) (grade)				
1	5	1 (20.0%)	1.00	
2	5	2 (40.0%)	0.83 (0.45–1.54)	
3	6	2 (33.3%)	0.69 (0.20–2.37)	
4	11	7 (63.6%)	0.57 (0.09–3.64)	NS (P = 0.553)
sCr (pre) (mg/dl)				
1 unit	27		3.54 (0.33–38.49)	NS (P =0.300)
CCr (pre) (ml/min)				
10 unit	27		0.75 (0.56–1.01)	NS (P = 0.057)
U-P (1 year) (g/day)				
1 unit	27		2.04 (1.28–3.24)	P = 0.003
U-RBC (1 year) (grade)				
0	5	1 (20.0%)	1.00	
1	11	3 (27.3%)	1.33 (0.73–2.40)	
2	5	2 (40.0%)	1.76 (0.54–5.77)	
3	4	3 (75.0%)	2.34 (0.40–13.88)	
4	2	0 (0.0%)	3.11 (0.29–33.34)	NS (P = 0.348)
sCr (1 year) (mg/dl)				
1 unit	27		1.46 (1.02–2.11)	P = 0.041
CCr (1 year) (ml/min)				
10 unit	27		0.61 (0.37–1.00)	NS (P = 0.052)
PSL duration (year)				
1 unit	27		1.02 (0.99–1.05)	NS (P = 0.168)
Sclerosis (%)				
10 unit	27		1.04 (0.66–1.63)	NS (P = 0.856)
Crescent (%)				
10 unit	27		0.71 (0.35–1.44)	NS (P = 0.337)
Active crescents (%)				
10 unit	27		0.71 (0.33–1.49)	NS (P = 0.362)
Fibrous cresecents (%)				
10 unit	27		0.49 (0.03–9.69)	NS (P = 0.642)
Adhesion (%)				
10 uinit	27		1.10 (0.57–2.12)	NS (P = 0.771)
Gen (grade)				
0.1 unit	27		1.28 (0.97–1.68)	NS (P = 0.083)
Gex (grade)				
0.1 unit	27		0.99 (0.78–1.25)	NS (P = 0.916)
Gg (grade)				
0.1 unit	27		1.08 (0.92–1.27)	NS (P = 0.348)
Sen (grade)				
0.1 unit	27		1.02 (0.90–1.16)	NS (P = 0.793)
Sex (grade)				
0.1 unit	27		1.03 (0.80–1.33)	NS (P = 0.801)
Sg (grade)				
0.1 unit	27		1.02 (0.92–1.12)	NS (P = 0.772)
Gint (grade)				
0	12	1 (8.3%)	1.00	
1	10	3 (30.0%)	3.30 (1.26–8.64)	
2	5	5 (100%)	10.88 (1.59–74.60)	P = 0.015
Sint (grade)				
0	11	0 (0.0%)	1.00	
1	8	3 (37.5)	2.99 (1.37–6.53)	
2	7	5 (71.4%)	8.92 (1.86–42.67)	
3	1	1 (100%)	26.62 (2.54–278.7)	P = 0.006
G (grade)				
1 unit	27		3.07 (1.36–6.92)	P = 0.007
S (grade)				
1 unit	27		1.54 (1.01–2.34)	P = 0.045

Active crescents mean both cellular and fibrocellular crescents; CI, confidence interval;
BP, Blood pressure; U-P, urinary protein; U-RBC, urinary red blood cell; sCr, serum creatinine; CCr, creatinine clearance; pre, pre-treatment; 1 year, at 1 year after treatment; PSL, prednisolone; RF, renal function; NS, not significant

sum of the score of each component) could be a significant predictor of poor prognosis. In the present study, we could not demonstrate any glomerular factors that predicted progressive renal failure. These results suggested that the severity of glomerular lesions could be modified by the steroid therapy, and, thus, the initial glomerular changes could not always predict the prognosis after steroid therapy.

Finally, we analyzed histological parameters that predict a reduction of proteinuria after steroid therapy. Univariate logistic regression analysis indicated that the severity of acute inflammation in the glomerular extracapillary region (Gex) predicted the possibility of proteinuria reduction after steroid therapy (odds ratio per 0.1 grade increment: 1.56; $P = 0.021$). The formation rate of glomerular crescents, especially of active crescents (cellular and fibrocellular crescents) also predicted the possibility of protecinuria reduction (odds ratio per 10% increment of all crescents: 2.91, $P = 0.019$, active crescents: 3.98; $P = 0.009$). These results suggested that glomerular extracapillary lesions could be a useful indicator for predicting the effectiveness of steroid therapy. Yamamoto et al.[17] suggested the significance of extracapillary changes for prediction of the effectiveness of steroid therapy in their analysis of 24 IgAN patients. Furthermore, we also found that the scores for both acute and chronic interstitial inflammation (Gint and Sint) were indicators of lack of proteinuria reduction after steroid therapy (odds ratio per one grade increment of Gint: 0.20; $P = 0.022$, and odds ratio per one grade increment of Sint: 0.33; $P = 0.039$). These results suggested that patients with high degrees of interstitial changes had a low possibility of proteinuria reduction by steroid therapy.

As an anti-platelet drug was administered in combination with PSL in this study, we must consider the influences of this drug on the outcome of the patients. However, the anti-platelet drug alone could not usually reduce the amount of proteinuria to the extent of our standard in this study (50% reduction and less than 1.0 g/day); thus, we should consider that PSL played a major role in the effect of proteinuria reduction. In addition, an ACEI was also administered in combination with PSL in some patients. Although it remains possible that the ACEI participated in the effect of the steroid therapy, we could not elucidate any significant effect of the ACEI on the treatment for IgAN in this study. Another extensive investigation is required to evaluate the effect of ACEI in combination with steroid therapy.

As a consequence of the present study, the following histological criteria seem to be appropriate for initiating steroid therapy for IgAN: (1) frequent crescent formation, (2) active extracapillary lesions; rupture of glomerular basement membrane, exudation and inflammatory cell infiltration into Bowman's space and cellular crescent formation, (3) no or mild interstitial inflammation. In addition, our investigation suggested that the new histological grading method (grading and staging system) proposed by Shigematsu[12] could be useful to evaluate disease activity and to decide on the therapeutic regimen in IgAN patients.

In conclusion, a retrospective study of 27 IgAN patients who received steroid therapy revealed that the clinical findings obtained at the start of therapy could not predict responsiveness to the steroid therapy for IgAN. However, urinary protein excretion and serum creatinine level 1 year after the treatment predicted the deterioration of renal function even after the steroid treatment. The precise evaluation of renal histology, in regard to activity and chronicity of the lesions in each renal component, gives us useful information to assess responsiveness to steroid therapy. The grade of acute glomerular extracapillary lesions, including crescent formation, was a useful parameter for predicting the effect of steroid therapy on proteinuria. On the other hand, the severity of interstitial inflammation was an index of unfavorable outcome for renal function even after the steroid therapy.

Acknowledgments We wish to express our appreciation to Ms. Mayuko Kawashima and Mr. Hideki Nakayama for their excellent technical assistance. We also thank Dr. Katsunori Shimada (Department of Biostatistics, STATZ, Tokyo) for his critical support concerning statistical analysis. This work was, in part, supported by grants from the Ministry of Health and Welfare of Japan.

References

1. D'Amico G. Clinical features and natural history in adults with IgA nephropathy. Am J Kidney Dis 1988;12:353–7.
2. Chaurean D. Follow-up evaluation of the first patients with IgA nephropathy described at the Necker Hospital. Contr Nephrol 1993;104:1–5.
3. Mustonen J, Pasternack A, Rantala I. The nephrotic syndrome in IgA glomerulonephritis: response to corticosteroid therapy. Clin Nephrol 1983;20:172–6.
4. Lai KN, Lai FM, Ho CP, Chan KW. Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. Clin Nephrol 1986;26:174–80.
5. Waldo FB, Alexander R, Wyatt RJ, Kohaut EC. Alternate-day prednisone therapy in children with IgA-associated nephritis. Am J Kidney Dis 1989;13:55–60.
6. Kobayashi Y, Hiki Y, Kokubo T, Tateno S. Steroid therapy during the early stage of progressive IgA nephropathy. Nephron 1996;72:237–42.
7. Lee SMK, Rao VM, Franklin WA, Schiffer MS, Aronson AJ, Spargo BH, Katz AI. IgA nephropathy: morphologic predictors of progressive renal disease. Hum Pathol 1982;13:314–22.
8. Kobayashi Y, Tateno S, Hiki Y, Shigematsu H. IgA nephropathy: prognostic significance of proteinuria and histological alterations. Nephron 1983;34:146–53.
9. Andreoli SP, Yum MN, Bergstein JM. IgA nephropathy in children: significance of glomerular basement membrane deposition of IgA. Am J Nephrol 1986;6:28–33.
10. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathological study of 244 cases. Am J Kidney Dis 1997;29:829–42.
11. Southwest Pediatric Nephrology Study Group. A multicenter study of IgA nephropathy in children. A report of the Southwest Pediatric Nephrology Study Group. Kidney Int 1982;22:643–52.
12. Shigematsu H. Histological grading and staging of IgA nephropathy. Pathol Int 1997;47:194–220.
13. Radford MG Jr, Donadio JV Jr, Bergstralh EJ, Grande JP. Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol 1997;8:199–207.
14. D'Amico G, Minetti L, Ponticelli C, Fellin G, Ferrario F, Barbiano di Belgioioso G, Prognostic indicators of idiopathic IgA mesangial nephropathy. Q J Med 1986;59:363–78.
15. Hogg RJ, Silva FG, Wyatt RJ, Reisch JS, Argyle JC, Savino DA. Prognostic indicators in children with IgA nephropathy. Report of

Southwest Pediatric Nephrology Study Group. Pediatr Nephrol 1994;8:15–20.
16. Alamartine E, Sabatier JC, Guerin C, Berliet JM, Berthoux F. Prognostic factors in mesangial IgA glomerulonephritis: an extensive study with univariate and multivariate analyses. Am J Kidney Dis 1991;18:12–19.
17. Yamamoto S, Iesato K, Yoshida H, Hori J, Hasegawa R, Ohta Y, et al. Study on a predictive marker for evaluating the effectiveness of steroid therapy in IgA nephropathy. Significance of extracapillary changes. Jpn J Nephrol 1996;38:74–83.
18. Bogenscuetz O, Bohle A, Batz C, Wehrmann M, Pressler H, Kendziorra H, Gaertner HV. IgA nephritis: on the importance of morphological and clinical parameters in the long-term prognosis of 239 patients. Am J Nephrol 1990;10:137–47.
19. Freese P, Norden G, Nyberg G. Morphologic high-risk factors in IgA nephropathy. Nephron 1998;79:420–5.