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ORIGINAL ARTICLE

The predictive value of attenuated proteinuria at 1 year after steroid therapy for renal survival in patients with IgA nephropathy

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Abstract
Background The relationship between the urinary protein excretion (UPE) initially achieved after steroid therapy and the long-term renal outcome of IgA nephropathy (IgAN) has not been clarified. We investigated the threshold UPE at 1 year after steroid therapy which predicts a favorable renal survival.
Methods We enrolled 141 IgAN patients who received 6 months of steroid therapy. The endpoint was defined as a 50 % increase in serum creatinine from baseline. The spline model was used to define the threshold UPE predicting renal survival.
Results Thirteen patients (9.2 %) reached the endpoint at a median follow-up of 3.8 years. When evaluating the relative hazard ratio (HR) of the UPE at 1 year for the endpoint, we found an inflection point at 0.40 g/day on the spline curve. The multivariate Cox model revealed that, in addition to the *Disappeared* category of UPE (range <0.30 g/day), the *Mild* category (range 0.30–0.39 g/day) was associated with more reduced risk of the endpoint [HR 0.02, 95 % confidence intervals (CI) 0.00–0.29] relative to the *Severe* category (range ≥1.00 g/day), whereas the *Moderate* category (range 0.40–0.99 g/day) was not. The estimated glomerular filtration rate <60 ml/min/1.73 m^2 was also an independent predictor of the endpoint. When renal survival was adjusted with pathological parameters in the Cox model, UPE <0.40 g/day was still an independent favorable predictor (HR 0.08, 95 % CI 0.01–0.45).
Conclusions In IgAN patients receiving 6 months of steroid therapy, the achievement of proteinuria <0.4 g/day at 1 year could be a therapeutic indicator for a favorable renal outcome.

Keywords Corticosteroid therapy · Proteinuria · Threshold · Clinical remission · Endocapillary hypercellularity · Tonsillectomy

Introduction

IgA nephropathy (IgAN), a major component of chronic glomerulonephritis, causes end-stage renal disease in up to 50 % of affected patients [1]. Although proteinuria has been considered one of the most important predictors of renal outcome [2–6], few studies have clarified what degree of proteinuria at an early phase after initial treatment predicts renal survival. Donadio et al. [7] showed a lower amount of proteinuria at 1 year after the introduction of treatment to be associated with a better renal survival. However, they did not define the proteinuria level predicting a favorable renal outcome.

Among the many clinical trials demonstrating the efficacy of steroid therapy for IgAN [8–10], a randomized controlled trial by Pozzi et al. [11, 12] clearly demonstrated that 6 months of steroid therapy significantly reduced the

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risk of a 100 % increase in serum creatinine from the baseline compared to conventional therapy during a 5- or 10-year follow-up. They demonstrated that the steroid therapy induced the lowest level of proteinuria at 1 year of follow-up.

We herein aimed to define the target level of proteinuria at 1 year after initiating steroid therapy to establish a prognostic threshold for a favorable renal survival of IgAN patients.

Subjects and methods

Patients and study design

We collected the medical records from 169 patients with IgAN who received 6 months of steroid therapy between 2004 and 2010 in four affiliated hospitals of Jikei University School of Medicine, employing a historical cohort design. Four patients followed for <1 year after the introduction of steroid therapy were excluded. Another 24 patients who were recruited into a prospective randomized controlled trial were also excluded. Finally, the data obtained from 141 patients were analyzed to elucidate the renal outcome. The patients were followed up until April 2012 or the last day of serum creatinine measurement before April 2012. The cohort study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Ethics Committee of Jikei University School of Medicine.

Definitions

The endpoint was defined as a 50 % increase in serum creatinine from baseline. Disappeared proteinuria or hematuria was defined as a urinary protein excretion (UPE) <0.3 g/day or having urinary sediment of red blood cells (U-RBC) <5/high power field (hpf). Clinical remission was defined as the disappearance of both proteinuria and hematuria. The estimated glomerular filtration rate (eGFR) was calculated by the Japanese eGFR equation based on age, sex and serum creatinine [13]. Uncontrolled hypertension was defined as arterial blood pressure (BP) ≥130/80 mmHg [14]. Smoking status was defined according to a report by Yamamoto et al. [15].

Treatment

The 6-month steroid therapy was previously reported by Pozzi et al. [11, 12], and was modified for Japanese patients as follows: the patients received 0.5 g of methylprednisolone intravenously for three consecutive days at the beginning of the steroid course and again 2 and 4 months later; they were also given oral prednisolone at a dose of 0.5 mg/kg every other day for 6 months. Some patients received a tonsillectomy for chronic tonsillitis complicated with IgAN just before the 6 months of steroid therapy. The patients were administered angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (RAAS inhibitors) and antiplatelet agents as needed.

Histology

To examine the impact of pathological changes on renal survival, renal biopsy data were obtained if a biopsy was performed within 1 year before corticosteroid therapy. All renal biopsy specimens were processed routinely for light microscopy. Sections were stained with hematoxylin and eosin and periodic acid–Schiff, together with silver methenamine and Masson's trichrome. Pathological variables were evaluated according to the Oxford classification [16]. "Histological grade (HG)" recently reported from the Special Study Group on Progressive Glomerular Disease in Japan was also adopted in this study [17]. Briefly, four histological grades, HG 1, HG 2, HG 3 and HG 4, were established corresponding to <25, 25–49, 50–74 and ≥75 % of glomeruli exhibiting cellular or fibrocellular crescents, global sclerosis, segmental sclerosis or fibrous crescents.

Statistical analyses

Normally distributed variables were expressed as the mean ± standard deviation (SD) and compared using the *t* test or one-way ANOVA. Nonparametric variables were expressed as medians and interquartile ranges (IQRs) and compared using the Mann–Whitney *U* test, Kruskal–Wallis test, Spearman correlation or Friedman test. Categorical variables were expressed in percentages and compared using the chi-squared test.

To identify a threshold UPE at 1 year that predicts a favorable outcome, we first specified the median UPE for each decile. Second, using the highest decile as the referred category, the relative hazard ratios (HRs) adjusted by the baseline eGFR were plotted according to the specified median values of each decile. Third, quadratic splines were fitted to the relative HR with knots. The spline model is considered to be a smooth function that is sensitive to changes in the relationship between a predictor variable and an outcome across the range of the predictor [18]. The UPE was log-transformed for the spline analyses. The result of the threshold analysis was additionally ascertained by a receiver operating curve (ROC) analysis.

Renal survival was analyzed using the Kaplan–Meier method. In addition, it was analyzed in multivariate Cox regression models to explore the independent prognostic value of predictors. The variables with p value <0.1 in the

univariate analysis were selected as predictors for the multivariate model. The start point of follow-up was 1 year after steroid therapy in Cox–hazard models. Different relevant multivariate models were tested, obeying the standard statistical rules. The results were expressed as HR with 95 % confidence intervals (CI).

Values of $p < 0.05$ were considered to be statistically significant. All statistical analyses were performed with IBM SPSS Statistics ver. 19.0 software (Chicago, IL, USA).

Results

Baseline characteristics and outcome

The clinical and pathological characteristics at baseline and the outcomes are presented in Table 1. The median initial proteinuria was 1.00 g/day, and the mean eGFR was 72.8 ml/min/1.73 m^2. During a median follow-up of 3.8 years (IQR 2.5–5.3), 13 patients (9.2 %) reached the endpoint. One hundred and eighteen patients (83.7 %), who underwent a renal biopsy within 1 year before the steroid therapy, had clinical backgrounds similar to the overall patients.

Changes in proteinuria during follow-up, and clinical remission rate at 1 year after steroid therapy

As shown in Fig. 1, the median values for UPE were significantly decreased at 6 months, 1 year and the last follow-up. The lowest level of UPE was seen at 1 year, with a 78.2 % (IQR 50.0–88.5 %) reduction of the UPE from baseline. At the 1 year follow-up, 49 patients (34.8 %) had reached clinical remission.

Table 1 Baseline characteristics and outcomes of the 141 patients analyzed in the study

Variables	Overall ($N = 141$)	Patients who received RBx within 1 year before treatment ($N = 118$)
Baseline features		
Age (years)	34 (26–43)	35 (27–43)
Female	72 (51.1)	58 (49.1)
Current smokers	34 (24.1)	27 (22.9)
BP ≥130/80 mmHg	43 (30.5)	40 (33.9)
UPE (g/day)	1.00 (0.65–1.70)	0.94 (0.63–1.67)
U-RBC		
≥30/hpf	77 (54.6)	66 (55.9)
5–29/hpf	58 (41.1)	46 (39.0)
<5/hpf	6 (4.3)	6 (5.1)
eGFR (ml/min/1.73 m^2)	72.8 ± 28.0	71.6 ± 28.7
eGFR <60 ml/min/1.73 m^2	51 (36.2)	45 (38.1)
Concurrent treatments		
Tonsillectomy	68 (48.2)	48 (40.7)
RAAS inhibitors	62 (44.0)	52 (44.1)
Oxford classification		
M1	–	38 (32.2)
E1	–	74 (62.7)
S1	–	96 (81.4)
T0/T1/T2	–	93/20/5 (78.8/16.9/4.2)
Ext, present	–	108 (91.5)
HG[a]		
HG1/HG2/HG3 + 4	–	32/56/30 (27.1/47.5/25.4)
Follow-up		
Period (years)	3.8 (2.5–5.3)	3.8 (2.3–5.3)
Outcome	13 (9.2)	10 (8.5)

Values are presented as numbers (%), medians (IQR) or mean ± SD

RBx renal biopsy, *BP* blood pressure, *UPE* urinary protein excretion, *U-RBC* urinary sediments of red blood cells, *eGFR* estimated glomerular filtration rate, *RAAS* renin–angiotensin–aldosterone system, *M* mesangial hypercellularity, *E* endocapillary hypercellularity, *S* segmental sclerosis, *T* tubulointerstitial atrophy/fibrosis, *Ext* extracapillary lesion, *HG* histological grade

[a] According to Ref. [17]

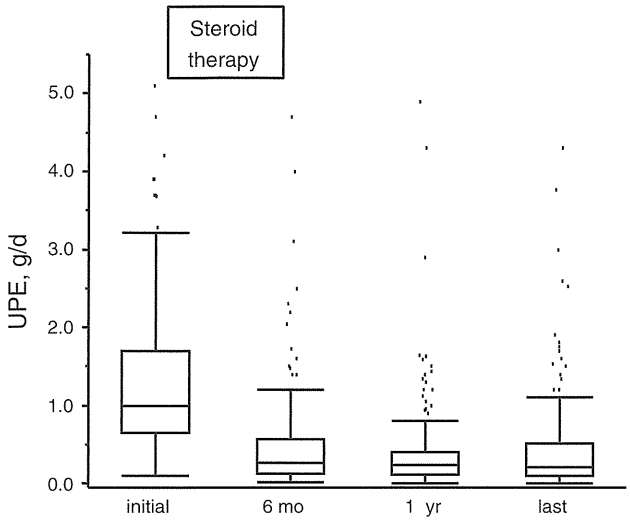

Fig. 1 Changes in proteinuria at baseline, 6 months, 1 year and at the last follow-up. The *lines* in the middle and those delimiting the *boxes* indicate the median, 25th and 75th percentile values, respectively. The *whiskers* at the ends of the boxes are lines that show the distance from the end of the box to the largest and smallest observed values that are <1.5 box-length from either end. *Dots* indicate outliers

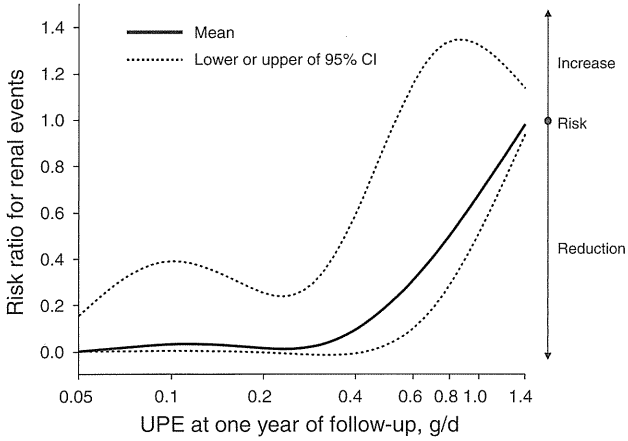

Fig. 2 Risk ratio for the endpoint associated with the UPE at the 1-year follow-up. Plots of the risk ratios and 95 % confidence intervals adjusted for the baseline eGFR for the endpoint using the level of proteinuria at the 1-year follow-up examination as the continuous variable are shown (reference: the highest decile, the median of which was 1.44 g/day). The degree of proteinuria was log transformed

Threshold proteinuria after steroid therapy predicting the renal outcome

We further explored what degree of UPE at 1 year after steroid therapy was associated with renal survival. The spline model of UPE at 1 year was used to predict the relative HR of the endpoint (Fig. 2). The spline curve showed that the relative HRs were equivalent in the range of UPE under 0.4 g/day, but increased as the UPE increased beyond this value, indicating an inflection at approximately 0.40 g/day. Furthermore, the ROC of UPE at 1 year indicated that the optimal cutoff for predicting an unfavorable outcome was 0.40 g/day; the area under the curve and p value were 0.78 and <0.001, respectively.

Categorization of UPE at 1 year after steroid therapy

"Disappeared proteinuria" was previously defined as UPE <0.3 g/day [19] and UPE >1.0 g/day was generally associated with following deterioration of renal function [4–6]. Based on the results from our threshold analysis (0.4 g/day) and the above two values, we divided the UPE at 1 year of follow-up into four categories; *Disappeared* category (<0.30 g/day), *Mild* category (0.30–0.39 g/day), *Moderate* category (0.40–0.99 g/day) and *Severe* category (≥1.00 g/day). The clinical parameters were not significantly different among the four categories, except for the baseline proteinuria (Table 2).

Renal survival according to the UPE category at 1 year by Kaplan–Meier analysis and multivariate Cox model

The results of the univariate time-dependent analyses by the Kaplan–Meier method are shown in Fig. 3. Patients in the *Disappeared* and *Mild*categories showed significantly better renal survival compared to the *Moderate* or *Severe* categories (log-rank, $p < 0.05$ for both strata), whereas there was no such difference between the *Moderate* and *Severe* categories (log-rank, $p > 0.2$).

The clinical predictors for the endpoint in the Cox–hazard model are presented in Table 3. Relative to the *Severe* category in the multivariate model, the *Disappeared* and *Mild* categories were favorable predictors, with risk reduction of approximately 90 and 70 %, respectively, whereas the *Moderate* category was not associated with renal survival. In contrast, eGFR <60 ml/min/1.73 m^2 at baseline was an unfavorable predictor. Clinical remission, as well as a U-RBC <5/hpf at 1 year after steroid therapy, was not associated with renal survival in the univariate model.

Significance of UPE <0.4 g/day as a predictor when the renal survival was adjusted for pathological parameters

The predictive value of UPE <0.4 g/day at 1 year for the outcome when adjusted for pathological parameters in the Oxford classification and "HG" from Japan was examined by the univariate and multivariate models and the data are summarized in Table 4. The univariate analysis revealed that the existence of endocapillary hypercellularity (E1) was significantly associated with a preferable renal survival

Table 2 Baseline characteristics according to the category of proteinuria at 1 year of follow-up

Variables	Category of UPE at 1 year of follow-up (g/day)				*p* value
	Disappeared (<0.3)	*Mild* (0.30–0.39)	*Moderate* (0.40–0.99)	*Severe* (≥1.00)	
Number of patients	80	23	22	16	
Age (years)	35 (26–44)	30 (25–42)	32 (26–36)	35 (26–42)	>0.2
Female	39 (48.8)	11 (47.8)	12 (54.5)	9 (56.3)	>0.2
Current smokers	18 (22.5)	5 (21.7)	6 (27.3)	5 (31.3)	>0.2
BP >130/80 mmHg	25 (31.3)	9 (39.1)	5 (22.7)	4 (25.0)	>0.2
UPE (g/day)	0.82 (0.57–1.28)	0.80 (0.64–2.17)	1.58 (0.97–2.28)	1.90 (1.25–2.80)	<0.001[#]
U-RBC >30/hpf	48 (60.0)	12 (52.2)	8 (36.4)	9 (56.3)	>0.2
eGFR (ml/min/1.73 m^2)	75.1 ± 27.1	73.7 ± 29.1	68.2 ± 29.5	66.3 ± 29.1	>0.2
eGFR <60	25 (31.3)	10 (43.5)	10 (45.5)	6 (37.5)	>0.2
Tonsillectomy	40 (50.0)	10 (43.5)	12 (54.5)	6 (37.5)	>0.2
RAAS inhibitors	35 (43.8)	9 (39.1)	11 (50.0)	7 (43.8)	>0.2

Values are presented as numbers (%), medians (IQR) or mean ± SD

BP blood pressure, *UPE* urinary protein excretion, *U-RBC* urinary sediments of red blood cells, *eGFR* estimated glomerular filtration rate.
[#] $p < 0.05$

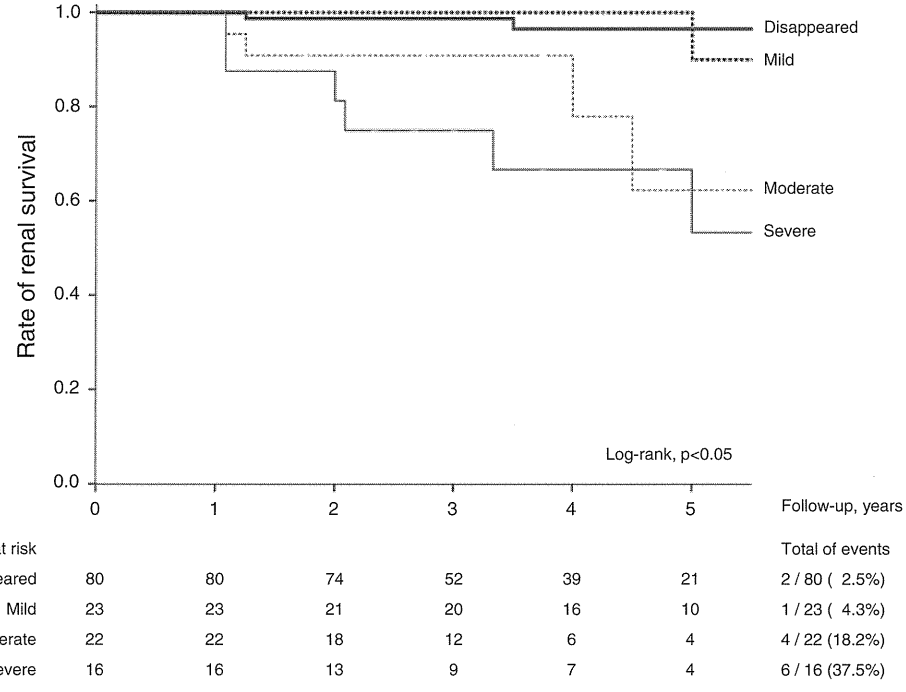

Fig. 3 Renal survival determined by the Kaplan–Meier method, stratified by the category of UPE at 1 year after 6 months of steroid therapy. These unadjusted curves demonstrate that, in addition to the *Disappeared* category, the *Mild* category showed significantly better renal survival compared to that in the *Moderate* or *Severe* categories (log-rank, $p < 0.05$ for both strata)

relative to the absence of endocapillary hypercellularity (E0). T1 or T2 tubular atrophy/interstitial fibrosis was significantly associated with impaired renal survival relative to T0. In addition, HG 2 was significantly associated with favorable renal outcome relative to HG 3 plus HG 4. Although HG 1 was not significantly associated with favorable outcome, no event was observed in 32 patients of HG 1.

The multivariate model A and model B in Table 4 examined the predictive power of UPE <0.4 g/day at 1 year for renal survival after adjusting for pathological predictors in the Oxford classification and HG, respectively. A UPE <0.4 g/day at 1 year was selected as an independent predictor in both model A and model B.

Adverse effects

Serious adverse events were not observed during the study period. Although three patients developed type 2 diabetes during the 6 months of treatment, they showed normal levels of glycosylated HbA1 at 1 year with diet therapy alone. Seven patients developed infections during the

Table 3 Clinical predictors for a 50 % increase in serum creatinine from the baseline level in the Cox–hazard model

Predictors	Univariate model		Multivariate model[a]	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
At 1 year				
Category of proteinuria[b]				
Disappeared[c]	0.07 (0.01–0.33)	0.001[#]	0.06 (0.01–0.57)	0.014[#]
Mild[c]	0.10 (0.12–0.80)	0.030[#]	0.02 (0.00–0.29)	0.003[#]
Moderate[c]	0.55 (0.16–1.98)	>0.2	0.24 (0.04–1.25)	0.089
U-RBC <5/hpf[d]	2.59 (0.71–9.42)	0.148	–	–
Clinical remission[d]	0.35 (0.08–1.57)	0.170	–	–
At baseline				
Age (years)	1.04 (0.99–1.08)	0.092	1.00 (0.94–1.06)	>0.2
Female[d]	1.06 (0.36–3.16)	>0.2	–	–
Current smoking[d]	3.96 (1.33–11.8)	0.013[#]	1.27 (0.28–5.58)	>0.2
BP ≥130/80 mmHg[d]	1.31 (0.36–4.79)	>0.2	–	–
UPE (g/day)	2.09 (1.43–3.07)	<0.001[#]	–[e]	–[e]
U-RBC ≥30/hpf[d]	0.22 (0.06–0.79)	0.021[#]	0.34 (0.06–1.99)	>0.2
eGFR <60 ml/min/1.73 m^2 [d]	11.5 (2.55–52.3)	0.002[#]	24.3 (2.72–217)	0.004[#]
Concurrent treatment				
Tonsillectomy[d]	0.37 (0.11–1.21)	0.099	1.23 (0.27–5.55)	>0.2
RAAS inhibitors[d]	2.06 (0.67–6.29)	>0.2	–	–

HR hazard ratio, *CI* confidence interval, *UPE* urinary protein excretion, *U-RBC* urinary sediments of red blood cells, *NE* not enrolled in the multivariate model, *eGFR* estimated glomerular filtration rate, *RAAS* renin–angiotensin–aldosterone system

[a] If the *p* value of the variable was <0.1 in the univariate model, the predictor was selected for the multivariate model

[b] The category is shown in Table 2

[c] Reference = *Severe* category

[d] Yes versus no

[e] As it was related to category of UPE at 1 year (see Table 2), it was not enrolled in the multivariate model

[#] $p < 0.05$

Table 4 Pathological predictors and UPE <0.4 g/day at 1 year for a 50 % increase in the serum creatinine level from baseline in the Cox model

Predictors	Univariate model		Multivariate model A		Multivariate model B	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Oxford classification						
M1 versus M0	0.93 (0.24–3.61)	>0.2	–	–	–	–
E1 versus E0	0.23 (0.06–0.89)	0.033[#]	0.44 (0.10–1.91)	>0.2	–	–
S1 versus S0	2.03 (0.26–16.0)	>0.2	–	–	–	–
T1 versus T0	6.97 (1.66–29.2)	0.008[#]	4.35 (1.02–18.5)	0.047[#]	–	–
T2 versus T0	12.8 (2.12–77.1)	0.005[#]	19.1 (2.55–144)	0.004[#]	–	–
Ext, present versus absent	0.44 (0.09–2.06)	>0.2	–	–	–	–
HG						
HG1 versus HG3 + 4	0.00 (0.00–100<)	>0.2	–	–	0.00 (0.00–100<)	>0.2
HG2 versus HG3 + 4	0.24 (0.06–0.92)	0.038[#]	–	–	0.36 (0.08–1.51)	0.161
UPE at 1 year <0.4 g/day[a]	0.10 (0.03–0.36)	<0.001[#]	0.08 (0.01–0.45)	0.004[#]	0.06 (0.01–0.29)	0.001[#]

HR hazard ratio, *CI* confidence interval, *M* mesangial hypercellularity, *E* endocapillary hypercellularity, *S* segmental sclerosis, *T* tubulointerstitial atrophy/fibrosis, *Ext* extracapillary lesion, *HG* histological grade, *UPE* urinary protein excretion volume

[#] $p < 0.05$

[a] Yes versus no

steroid therapy: five bacterial infections (tonsillitis, pharyngitis) and two viral infections (influenza). Two females became pregnant during the follow-up and maintained a stable renal function.

Discussion

The goal of this study was to identify the level of proteinuria after steroid therapy associated with a favorable renal outcome in IgAN patients. Previous studies by Reich et al. [4], Hwang et al. [5], or Le et al. [6] have demonstrated that the average level of proteinuria during the whole period of follow-up (A-P) was significantly associated with the renal outcome, providing a targeted proteinuria during long-term follow-up. In contrast, we identified a therapeutic indicator of a favorable renal outcome as an early response to the steroid therapy, which might be more practical than A-P, whereas it was not analyzed in the previous studies. We adopted 1 year as the time to assess the attenuated proteinuria, since another Cox model in our cohort revealed that the values for proteinuria at 1 year were significantly associated with the outcome, whereas those at baseline or 6 months were not (data not shown).

In this study, the spline model revealed that the threshold UPE predicting the outcome was approximately 0.4 g/day. In addition, a multivariate Cox model including the categorized UPE at 1 year revealed that not only the *Disappeared* category but also the *Mild* category were significantly associated with favorable renal survival relative to the *Severe* category. Therefore, attenuated proteinuria <0.4 g/day at 1 year after treatment can lead to a favorable outcome, as well as the disappearance of proteinuria. The predictive power of UPE <0.4 g/day at 1 year for renal survival was confirmed even after adjusting for pathological predictors determined by the multivariate model (Table 4).

Concerning the impact of clinical remission at an early phase on the renal outcome, Tatematsu et al. [20] showed that clinical remission within 2 years after 6 months of steroid therapy was associated with limiting the eGFR decline. In contrast, clinical remission at 1 year was not significantly associated with the endpoint in our univariate Cox model (Table 3). Although the reasons for the discrepancy between the two studies are unknown, there might be several factors responsible. For example, the timing for assessment of clinical remission was different: during the first 2 years in Tatematsu's study and at 1 year after the intervention in our study. Furthermore, the fact that the incidence of the endpoint in our patients achieving clinical remission at 1 year after the therapy was not significantly different from that in those without clinical remission (4.1 vs. 12.0 %, respectively, $p > 0.2$) may have affected the results shown in Table 3.

Our retrospective study has several limitations. First, we did not include control patients who were followed by supportive therapy alone. Second, the study population and statistical power were small, and the observation period was relatively short to evaluate the outcome in IgAN, leading to the small number of outcomes. Since a limited number of outcomes would generally restrict the number of explanatory variables in multivariate models, we additionally tested the Cox–hazard model for the outcome with two explanatory variables: UPE at 1 year <0.4 g/day and propensity score. The propensity model for UPE at 1 year <0.4 g/day was constructed with the baseline characteristics or pathological parameters. After adjusting the propensity score, we also found the predictive power of UPE at 1 year <0.4 g/day for the outcome (data not shown), suggesting the consistency of the significance of UPE at 1 year <0.4 g/day. Nevertheless, the value of UPE at 1 year <0.4 g/day as a favorable predictor should be ascertained in other studies with longer observation periods and a larger number of outcomes. Third, the role of recurrent proteinuria after 1 year on the progression of IgAN should be examined, since clinical remission was not associated with the endpoint in this study.

In conclusion, the achievement of proteinuria <0.4 g/day at 1 year after 6 months of steroid therapy is an optimal goal for achieving a subsequent favorable renal survival, independent of the baseline renal function or renal pathological changes. Further investigations of the impact of recurrence during follow-up on the endpoint are now in progress.

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Conflict of interest None.

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ORIGINAL ARTICLE

ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes

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Abstract
Background This study was conducted to standardize treatment and determine patient and renal outcome in Japanese anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis/rapidly progressive glomerulonephritis (AAV/RPGN) patients, because the prognosis of AAV/RPGN patients in Japan had been poor compared with that of other countries.
Methods The participants in this retrospective cohort study were 824 ANCA-positive RPGN patients, 705 of whom were only myeloperoxidase (MPO)-ANCA positive.
Results Among the early-years cohort (group A; cases diagnosed between 1988 and 1998), patients frequently died due to opportunistic infection. Therefore, we recommended a reduced dose of prednisolone (oral prednisolone dose <0.8 mg/kg/day) with or without cyclophosphamide for initial treatment of Japanese RPGN patients. After this recommendation, 1-year survival of the patients improved: 75% in group A, 79% in group B (between 1999 and 2002), and 81% in group C (after 2003). During the entire observation period, average serum creatinine level at the start of treatment decreased, and improvement of 1-year renal survival was also found (72% in group A, 83% in group B, and 83% in group C), while the recurrence rate was significantly increased in group C (0.05/patient-year in group A, 0.07/patient-year in group B, and 0.13/patient-year in group C).
Conclusions Oral prednisolone dose <0.8 mg/kg/day with or without cyclophosphamide as an initial treatment could improve patient survival in older Japanese AAV/RPGN patients. However, maintenance treatment avoiding relapse should be established to improve renal outcomes.

Keywords Anti-neutrophil cytoplasmic auto-antibody (ANCA) · Immunosuppression · Prognosis changes · Rapidly progressive glomerulonephritis (RPGN) · Vasculitis

Introduction

Recently, the wider availability of anti-neutrophil cytoplasmic auto-antibody (ANCA) assays, improved recognition of ANCA-associated vasculitis (AAV), and evidence-based treatment for AAV have resulted in longer life expectancy and avoidance of renal replacement therapy (RRT) in patients with AAV. ANCAs have been detected in patients with pauci-immune crescentic glomerulonephritis, microscopic polyangitis (MPA), granulomatosis with polyangitis (Wegener's) (GPA), and other systemic vasculitis syndromes [1, 2]. There are two major subclasses of ANCA: perinuclear (p-)ANCA and cytoplasmic (c-)ANCA [1]. The main epitope of p-ANCA is myeloperoxidase

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(MPO), and that of c-ANCA is proteinase-3 (PR3) [2]. MPO-ANCA is regarded as a useful serum marker for MPA and idiopathic pauci-immune crescentic glomerulonephritis (renal limited form of MPA), and PR3-ANCA is regarded as a serum marker for GPA and MPA [2, 3]. Furthermore, enzyme-linked immunosorbent assay (ELISA)-based serum examination for MPO-ANCA, PR3-ANCA, and anti-glomerular basement membrane (a-GBM) antibody titer tests were available in clinical settings. Several reports have suggested that, compared with PR3-ANCA-positive patients, MPO-ANCA-positive patients were older and showed predominantly chronic sclerotic lesions on histologic analysis [4, 5].

To improve the outcome of rapidly progressive glomerulonephritis (RPGN) patients in Japan, we conducted a nationwide survey of RPGN including AAV from 1998, by sending a questionnaire to 351 nephrology departments. From this survey, we concluded that 64.7% of Japanese RPGN patients had ANCAs, and among ANCA-positive patients, approximately 90% had MPO-ANCA [6].

In this study, we report the changes in treatment and outcome of Japanese AAV/RPGN patients during the last 20 years. Furthermore, we discuss the differences in clinical characteristics of ANCA subgroups in our AAV/RPGN patients.

Subjects and methods

Subjects

We retrospectively collected records of patients with RPGN from 1989 to 1998 and prospectively collected the clinical records of RPGN patients from 1999 to 2007 by sending a questionnaire annually by post to 351 nephrology departments of tertiary hospitals in Japan. This study was approved by the medical ethics committee at the Graduate School of Comprehensive Human Sciences, University of Tsukuba, in accordance with the guidelines for epidemiological research by the Ministry of Health, Labor, and Welfare of Japan. The definition of RPGN was based on clinical findings of rapidly progressing renal failure over several weeks to a few months, accompanied by the following nephritic urinary abnormalities: hematuria (mostly microscopic hematuria, but occasionally gross hematuria), proteinuria, and red blood cell cast or granular cast in urine sediment. In total, 171 nephrology departments responded and presented 1772 RPGN cases for this study. During the study period, the Japanese government decided that the PR3-ANCA test was covered by medical insurance in 1993, the MPO-ANCA test in 1998, and the a-GBM antibody test in 1999 for diagnosis of RPGN and vasculitis. Among the RPGN patients, although 1203 patients (67.9%) had ANCA [6], 824 patients received all three serological tests and presented outcome data. To analyze the effect of ANCA subclasses on patient outcomes, we selected these 824 patients for further analysis.

We evaluated AAV cases by stratifying patients into three periods depending on the year of diagnosis of AAV as previously described. Briefly, patients who were diagnosed between 1989 and 1998 were classified as group A, and data were collected retrospectively. Patients diagnosed between 1999 and 2001 were classified as group B, when we had started the analysis of Japanese cases of RPGN and part of the results had been announced in Japan during this period. Patients diagnosed between 2002 and 2007, after we had published the Japanese guideline for RPGN in 2002 [6, 7], were classified as group C.

Clinical evaluation and treatment methods

Baseline characteristics including age, sex, comorbid conditions, features of prodromal illness, and clinical, biochemical, serological, and urinary features at presentation were obtained from clinical records. Follow-up clinical data including serum creatinine level, ANCA subclasses, C-reactive protein (CRP), recurrence and survival outcome, dialysis dependence (after 1, 2, 3, 6, 12, and 24 months), start date of dialysis therapy, final follow-up date, and cause of death were also recorded. Relapse was defined as an increase in creatinine concentration with nephritic sediment and other signs or symptoms of vasculitis. The initial dose of oral prednisolone, the duration of the initial dose, and immunosuppressive treatment were also recorded.

Statistical analysis

Unpaired Student's t test was used, after a symmetrical distribution was confirmed, to determine differences in the continuous variables between groups. Otherwise, the Mann–Whitney U test was used. We used the chi-square test to analyze the frequencies of categorical variables. Both renal and patient survival rates were estimated by the Kaplan–Meier method. Prognostic factors were determined by the chi-square test, and then hazard ratios of patient outcome were estimated by the Cox regression model after confirming the proportionality in each model. To evaluate prognostic factors among the subjects at the start of treatment, we selected age, renal function (serum creatinine, urinary volume), glomerular damage (hematuria, proteinuria, cast formation), general status (serum albumin, serum total protein, hemoglobin), systemic inflammation (CRP, erythrocyte sedimentation rate, white blood cell count), and extrarenal complications (blood pressure, presence of lung involvement). Lung involvement indicates the existence of

chest X-ray abnormality, interstitial pneumonitis, or lung bleeding. We used two sets of models for analysis. The first set included age, gender, serum creatinine level at start of treatment, CRP, presence of lung involvement, and ANCA subclass. For the second set, we added initial dosage of prednisolone and cyclophosphamide usage in addition to the above variables. A p value <0.05 was considered significant. Parts of the statistical analyses were performed using SPSS software 17.0.

Results

Differences among ANCA subclasses

The study participants were 824 ANCA-positive patients, and 94.6% of the subjects had MPO-ANCA. During the last 20 years, 705 AAV patients were only MPO-ANCA positive, 34 patients were only PR3-ANCA positive, 37 patients were both MPO- and PR3-ANCA positive, 44 patients had both MPO-ANCA and a-GBM antibody, and four patients had both PR3-ANCA and a-GBM antibody. Table 1 presents the number of patients, their age, and the male-to-female ratio. Patients with only PR3-ANCA were significantly younger than those with only MPO-ANCA, and both ANCAs and a-GBM. Patients with PR3-ANCA only were predominantly male; however, patients with both ANCAs and a-GBM were predominantly female.

Table 1 Patient profile and ANCA type

ANCA type	n	Mean age (years)[a,b]	Male[a,b,c] (%)
MPO-ANCA only	705	64.4	42.6
PR3-ANCA only	34	53.6	70.6
Both ANCA	37	61.5	54.1
ANCA + a-GBM	48	65.3	29.2

[a] Statistically significant between MPO-ANCA only and PR3-ANCA only

[b] Statistically significant between PR3-ANCA only and ANCA + a-GBM

[c] Statistically significant between both-ANCA only and ANCA + a-GBM

Patients with PR3-ANCA had significantly more affected organs than both patients with MPO-ANCA and patients with both ANCAs. In particular, 65.7% of PR3-ANCA patients had ear, nose, and throat lesions, 34.3% had gut lesions, and 34.3% had skin lesions, and these involvement rates were significantly higher than in patients with MPO-ANCA. Serum creatinine levels at presentation were significantly higher in patients with both ANCAs and a-GBM antibody than for other patients (MPO-ANCA only 4.67 ± 2.84 mg/dl, PR3-ANCA only 4.51 ± 2.74 mg/dl, both ANCAs 5.08 ± 2.96 mg/dl, both ANCAs and a-GBM antibody 6.96 ± 4.08 mg/dl). CRP concentration at presentation was significantly higher in patients with PR3-ANCA only than in those with MPO-ANCA only (MPO-ANCA only 6.30 ± 6.56 mg/dl, PR3-ANCA only 9.11 ± 7.69 mg/dl, both ANCAs 6.65 ± 8.70 mg/dl, both ANCAs and a-GBM antibody 8.30 ± 8.52 mg/dl). Crescent formation rate was calculated from renal biopsy samples; patients with both ANCA and a-GBM antibody had a significantly higher crescent formation rate than patients with other types of AAV (MPO-ANCA only 57.9 ± 32.6%, PR3-ANCA only 54.4 ± 29.8%, both ANCAs 57.7 ± 28.7%, both ANCAs and a-GBM antibody 77.6 ± 22.3%).

Among the patients who were diagnosed from 1989 to 1998 (group A), from 1999 to 2002 (group B), or after 2003 (group C), ANCA subclass patterns and the proportion of patients with lung involvement were similar. The average age of the patients in both groups B and C was significantly higher than that of group A patients, and the serum creatinine level of group C patients was significantly lower than that of group A patients (Table 2).

Table 2 Patient profile by treatment period

n	ANCA subclass MPO:PR3:both:+a-GBM	Mean age (years)*#	Lung involvement (%)	Mean serum creatinine (mg/dl)#	Recurrence (n)/patient (year)#$	Initial prednisolone dose (mg/kg/day)*#$	Cyclophosphamide usage (%)
Group A							
347	284:15:27:21	60.56	50.70	5.11	0.05	0.85	41.69
Group B							
136	116:5:6:9	65.01	55.00	4.52	0.07	0.79	45.16
Group C							
341	305:14:4:18	66.88	58.80	4.19	0.13	0.71	33.67

* $p < 0.05$ between groups A and B

# $p < 0.05$ between groups A and C

$ $p < 0.05$ between groups B and C

Renal and patient survival

Cumulative patient survival rate and renal survival rate by Kaplan–Meier analysis are shown in Fig. 1. The median follow-up duration was 19.1 months (range 0–211.8 months). Cumulative patient survival rate at 12 months was 79.1%, and cumulative renal survival at 12 months was 78.4%. We further analyzed both patient survival rate and renal survival rate separated by treatment period by Kaplan–Meier analysis (Fig. 2). The median follow-up durations were 42.9, 33.2, and 10.3 months in groups A, B, and C, respectively. Patient survival rate in group C was significantly improved compared with that in group A (6-month cumulative patient survival rate: group A 77.5%, group B 81.0%, group C 85.1%; 12-month cumulative patient survival rate: group A 75.0%, group B 79.3%, group C 81.3%; $p < 0.05$). Cumulative renal survival rates in groups B and C were significantly higher than that in group A (6-month renal survival rate: group A 73.3%, group B 84.3%, group C 83.9%; 12-month renal survival rate: group A 71.7%, group B 83.3%, group C 82.8%; $p < 0.05$). Patient survival rate was slightly improved in group B compared with group C; however, renal survival was slightly exacerbated. Furthermore, the recurrence rates were 0.05, 0.07, and 0.13/patient-year in groups A, B, and C, respectively (Table 3).

Table 4 presents multivariate analysis for patient survival and renal survival. Age, lung involvement (as interstitial pneumonitis or lung bleeding), renal function, and CRP level were predictors of mortality in AAV patients. ANCA subclass did not affect patient survival. Serum creatinine level at presentation was the best predictor of renal survival; in addition, age between 60 and 69 years, and a-GBM antibody positivity among AAV patients were predictors of reduced renal survival.

Treatment methods and outcome changes

As shown in Table 4, renal function was the best predictor of renal survival; we compared renal outcome according to renal function at the start of treatment. Renal outcome in patients with serum creatinine levels <3 mg/dl showed a significant improvement in groups B and C, compared with group A. However, renal outcome in patients with serum creatinine levels of 3–6 mg/dl was similar during the entire study period. Patients with serum creatinine levels >6 mg/dl showed a tendency toward poor renal outcome in group C compared with group B (Fig. 3). Figure 4 shows the initial prednisolone dosage and cyclophosphamide usage according to both renal function and treatment period. In patients with serum creatinine levels <3 mg/dl, the initial prednisolone dosage in both groups B and C was significantly lower than that in group A. In patients with serum creatinine levels of 3–6 mg/dl, the initial prednisolone dosage in group C was significantly lower than that in group A. In patients with serum creatinine levels >6 mg/dl, the initial prednisolone dosage in group C was significantly lower than that in either group A or B. The proportion of initial cyclophosphamide usage was similar among groups A, B, and C in patients with serum creatinine levels <3 and >6 mg/dl. The proportion of initial cyclophosphamide usage in group C was significantly lower than that in group A in patients with serum creatinine levels of 3–6 mg/dl.

As shown in Table 2, the initial prednisolone dosage was significantly reduced recently (group C). We further analyzed the initial dosage of prednisolone and the proportion of cyclophosphamide usage, in addition to the above variables, by forward selection methods of

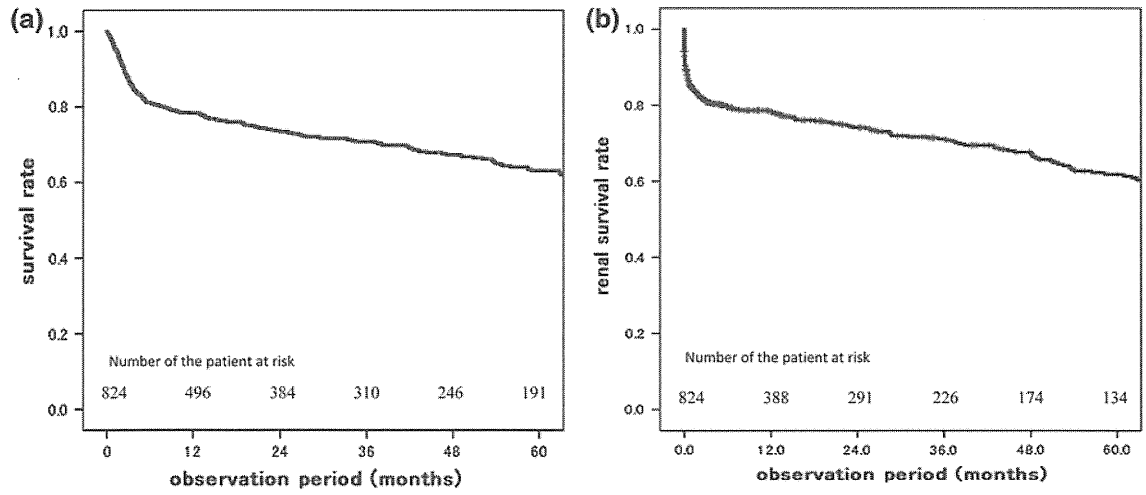

Fig. 1 Cumulative patient survival and renal survival by Kaplan–Meier analysis. **a** Patient survival: 6-month, 12-month, and 5-year cumulative patient survival rates were 81.8%, 79.1%, and 63.6%, respectively. **b** Renal survival: the 6-month, 12-month, and 5-year cumulative renal survival rates were 79.7%, 78.4%, and 62.0%, respectively

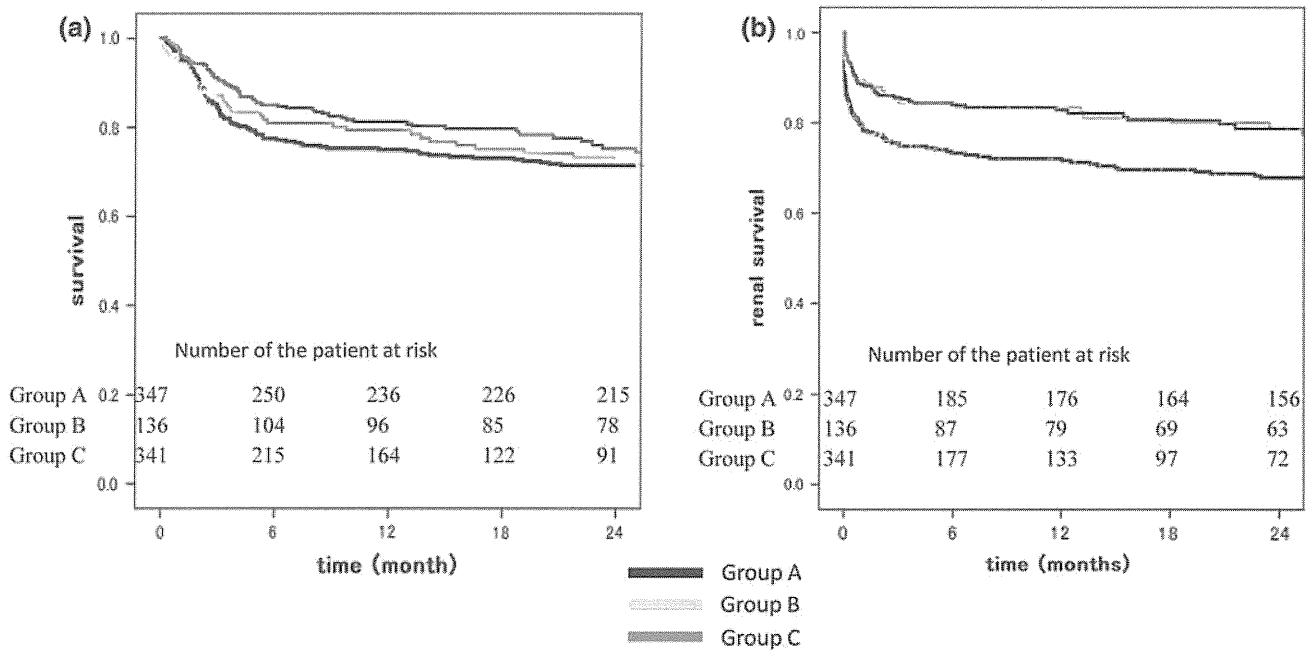

Fig. 2 Patient survival and renal survival by treatment period. **a** Patient survival: patient survival rate in group C was significantly higher than that in group A. **b** Renal survival: renal survival in groups B and C was significantly higher than that in group A. Comparing group B with group C, patient survival rate was slightly improved; however, there was no improvement in renal survival

Table 3 Multivariate Cox proportional regression analysis on predictor of death and ESRD

Factors	Death		ESRD	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (ref. <59 years)				
60–69 years	2.20 (1.54–3.16)	0.000	1.38 (0.99–1.92)	0.056
>70 years	3.32 (2.35–4.68)	0.000	1.20 (0.85–1.68)	0.301
Sex (ref. male)	1.14 (0.91–1.42)	0.265	0.92 (0.71–1.19)	0.536
Lung involvement (ref. negative)	1.94 (1.51–2.48)	0.000	0.83 (0.63–1.10)	0.199
Number of affected organs	0.98 (0.90–1.07)	0.621	0.98 (0.89–1.08)	0.725
Serum creatinine (ref. <3 mg/dl)				
3–6 mg/dl	1.85 (1.39–2.47)	0.000	3.26 (2.17–4.90)	0.000
>6 mg/dl	2.53 (1.88–3.38)	0.000	11.77 (7.96–17.40)	0.000
CRP (ref. <2.6 mg/dl)				
2.6–10 mg/dl	0.95 (0.73–1.24)	0.717	0.72 (0.53–0.98)	0.036
>10 mg/dl	1.46 (1.10–1.95)	0.010	1.22 (0.88–1.69)	0.243
ANCA subclass (ref. PR3-ANCA only)				
MPO-ANCA only	0.69 (0.42–1.14)	0.144	1.50 (0.79–2.83)	0.214
Both ANCA	0.59 (0.29–1.18)	0.135	1.72 (0.74–3.96)	0.205
ANCA + a-GBM	0.61 (0.30–1.24)	0.173	3.27 (1.50–7.11)	0.003

ESRD end-stage renal disease, *CI* confidence interval, *HR* hazard ratio

multivariate stepwise Cox proportional hazard analysis. An increase in the oral prednisolone dosage significantly reduced patient survival. The initial prednisolone dosage did not affect renal survival; however, cyclophosphamide use significantly improved renal outcome (Table 4).

Discussion

We began this survey of AAV/RPGN cases in Japan in 1998 to determine patient outcome, evaluate standard treatment patterns, and enable us to propose suitable

Table 4 Multivariate stepwise Cox proportional hazard analysis on predictor of death and ESRD (forward selection method, critical $F_{in} = 0.05/F_{out} = 0.1$)

	HR (95% CI)	*p*
Death		
Age (ref. <59 years)		
60–69 years	2.284 (1.383–3.772)	0.001
>70 years	4.286 (2.649–6.936)	0.000
CRP (ref. <2.6 mg/dl)		
2.6–10 mg/dl	0.776 (0.538–1.120)	0.176
>10 mg/dl	1.315 (0.886–1.951)	0.175
Lung involvement (ref. negative)	2.169 (1.508–3.119)	0.000
Serum creatinine (ref. <3 mg/dl)		
3–6 mg/dl	2.250 (1.474–3.434)	0.000
>6 mg/dl	2.492 (1.636–3.797)	0.000
Initial prednisolone dose (ref. <0.6 mg/kg/day)		
0.6–0.8 mg/kg/day	1.555 (0.996–2.429)	0.052
0.8–1.0 mg/kg/day	1.645 (1.005–2.692)	0.048
>1.0 mg/kg/day	2.132 (1.296–3.506)	0.003
Other variables considered: gender, ANCA subclass, cyclophosphamide usage		
ESRD		
Serum creatinine (ref. <3 mg/dl)		
3–6 mg/dl	2.811 (1.595–4.957)	0.000
>6 mg/dl	11.513 (6.827–19.416)	0.000
ANCA subclass (ref. PR3-ANCA only)		
Both ANCA	2.891 (0.788–10.611)	0.110
MPO-ANCA only	2.224 (0.699–7.077)	0.176
ANCA + a-GBM	5.403 (1.474–19.806)	0.011
Cyclophosphamide usage (ref. none)		
CYC	0.683 (0.474–0.986)	0.042

Other variables considered: age, gender, CRP, lung involvement, initial prednisolone dose

treatment guidelines for Japanese AAV/RPGN patients. During the early years of this study, we considered that the prognosis of AAV/RPGN patients in Japan was very poor compared with that of patients of different races and countries. A 1-year survival rate in AAV patients of 89% was reported in the USA [8], and 84% was reported in Europe [9], whereas the rate was 75% in our cohort during the same period (group A). We analyzed the etiology of these differences. We found that more than 90% of Japanese AAV patients had MPO-ANCA, the average age of Japanese AAV patients was high, and the most frequent cause of death was infectious complications. The standard treatment for AAV/RPGN in Europe and the USA was a combination of 1 mg/kg prednisolone and 100–200 mg cyclophosphamide [10, 11]. However, the prognosis of patients treated with high-dose prednisolone was significantly worse than that of patients treated with an oral prednisolone dose <0.8 mg/kg/day in our cohort. Furthermore, 95% of our AAV patients had MPO-ANCA (85.5% of patients were only MPO-ANCA positive), and the average age was 64.4 years. Gayraud et al. [9] reported that MPA patients above 65 years of age showed poorer outcome with use of cyclophosphamide. Based on our analysis of patients with group A and published reports, we proposed treatment guidelines for Japanese RPGN patients in 2002 [7] (Fig. 5). The guidelines emphasized the need for reduced immunosuppressive treatment, such as an initial oral prednisolone dose reduction with or without immunosuppressant, for Japanese MPO-ANCA-positive AAV/RPGN patients. With this treatment recommendation, the oral dose of prednisolone was significantly reduced and the number of patients using cyclophosphamide as an immunosuppressant was decreased.

Patient age was one of the prognostic factors for AAV/RPGN patients, and the average age of our patients was significantly increased with time; however, patient survival was significantly improved. There were several possible reasons for this. First, serum creatinine level at start of treatment was a good predictor of patient survival, and was also the strongest predictor of renal survival. Serum creatinine level at start of treatment was gradually decreased by early diagnosis and early treatment start during our observation period. Second, prophylaxis with trimethoprim/sulfamethoxazole combinations or other agents was generally used to avoid pneumocystis pneumonia in AAV/RPGN patients using immunosuppressant [12]. This prophylactic treatment was recommended in the Japanese RPGN/AAV treatment guideline [7], and was effective in reducing opportunistic infection in our most recent cohort (group C). Third, a significant reduction in prednisolone dosage and selective usage of cyclophosphamide according to treatment guideline for Japanese RPGN patients resulted in increased patient survival [6].

Although patient survival was improved with time, renal outcome of the Japanese AAV/RPGN patients was not improved. Although patients with both ANCAs and anti-GBM showed significantly poorer renal outcomes than other ANCA-positive patients, the proportion of patients with both ANCAs and anti-GBM was the same throughout our observation period. As shown in Fig. 3, renal outcome was improved by an initial serum creatinine level below 3 mg/dl; however, renal outcome was the same in the three groups in patients with serum creatinine levels of 3–6 mg/dl, and was worse in group C than in group B in those with a serum creatinine level >6 mg/dl. As shown in Fig. 5, a significant reduction in the initial prednisolone dosage resulted in a reduction in early mortality, but poorer renal outcome. de Lind van Wijngaarden et al. [13] reported a 1-year survival rate of 75% in dialysis-dependent AAV patients, and Day et al. [14] reported a rate of

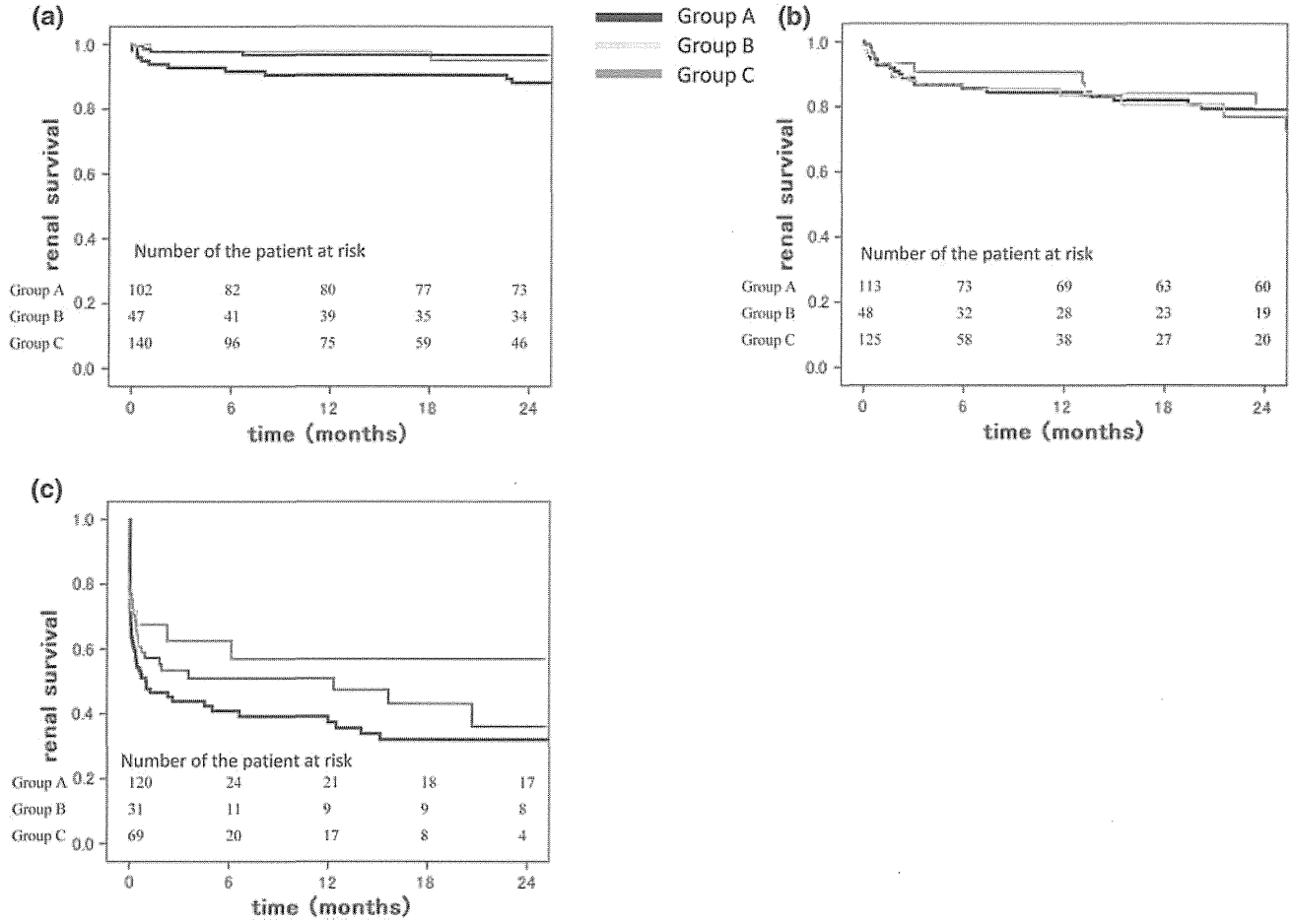

Fig. 3 Renal survival by renal function at start of treatment. Renal outcome in patients with serum creatinine levels <3 mg/dl showed a significant improvement in groups B and C, compared with group A (6-month cumulative renal survival rate: group A 91.6%, group B 97.8%, group C 97.7%; 12-month cumulative renal survival rate: group A 90.5%, group B 97.8%, group C 96.7%; $p < 0.05$). However, renal outcome in patients with serum creatinine levels of 3–6 mg/dl was not statistically different throughout the study period (6-month cumulative renal survival rate: group A 85.6%, group B 90.7%, group C 85.5%; 12-month cumulative renal survival rate: group A 84.4%, group B 90.7%, group C 83.3%; not significant). Patients with serum creatinine levels above 6 mg/dl showed a tendency toward poor renal outcome in group C compared with group B (6-month cumulative renal survival rate: group A 40.9%, group B 62.7%, group C 52.6%; 12-month cumulative renal survival rate: group A 37.4%, group B 57.0%, group C 52.6%; not significant). **a** Serum creatinine <3 mg/dl at treatment start, **b** serum creatinine 3–6 mg/dl at treatment start, **c** serum creatinine <6 mg/dl at treatment start

77% in AAV patients with an average serum creatinine level of 3.9 mg/dl, whereas in our group C patients with serum creatinine level >6 mg/dl, the 1-year survival rate was 71% and was similar in the other two cohorts. However, in our patients with serum creatinine levels >6 mg/dl in group C, the 1-year renal survival rate was 51%. Thus, renal outcome in our cohort was worse or equal to that of previously reported cohorts [13, 14, 15]. It is possible that recent patient survival improvement resulted in longer life expectancy in patients with advanced renal insufficiency, and those patients may have progressed to end-stage renal disease (ESRD). However, it is also possible that a significant reduction in prednisolone dosage in our group C patients with serum creatinine levels >6 mg/dl might result in insufficient treatment to restore their renal function.

It was reported that the recurrence rate of patients with MPO-ANCA was lower than that of patients with PR3-ANCA [3]. However, recently the selective usage of cyclophosphamide according to treatment guidelines for Japanese RPGN patients resulted in a 1.5-fold increase in the recurrence rate in Japanese AAV/RPGN patients. For treatment of active renal vasculitis, to avoid relapses, and to improve long-term renal outcomes, treatment with cyclophosphamide may be recommended; however, prolonged immunosuppression with a safer immunosuppressive agent, such as azathioprine [16], mycophenolate mofetil [17], or mizoribine [18], should be considered. We conducted a prospective randomized controlled trial with and without mizoribine for maintenance treatment of MPO-ANCA-positive RPGN (UMIN000000708). From