FIGURE 3: Patient distribution of the severity of proteinuria during the trial period. The severity of proteinuria was divided into the four grades shown below the figure according to the level of urinary protein (UP) in g/g creatinine (Cr). The patient distribution in the four grades is shown as a percentage. *The rate of the disappearance of proteinuria (UP level of <0.3 g/g Cr) was significantly higher in Group A than in Group B (Pearson's chi-square test).
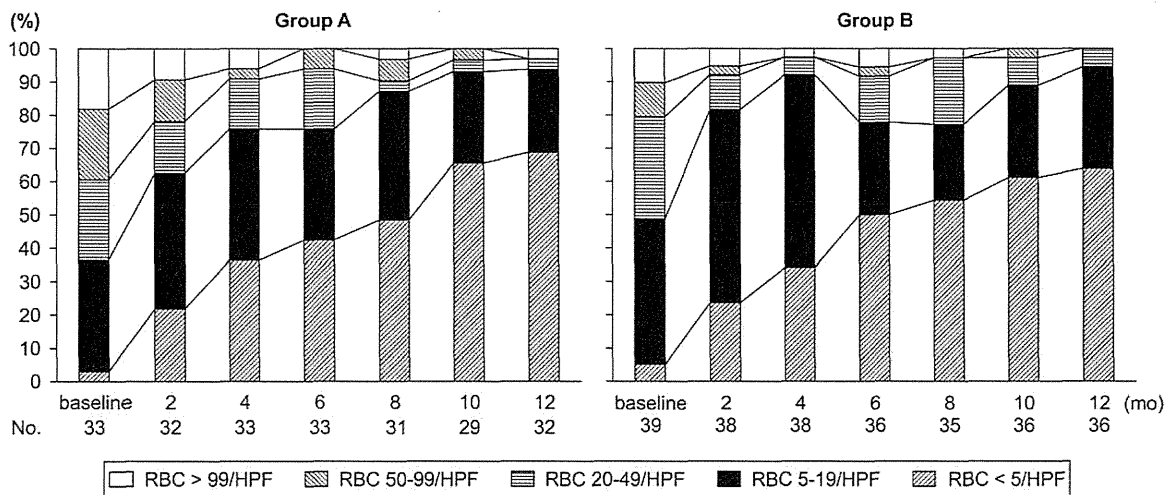

FIGURE 4: Patient distribution of the severity of hematuria during the trial period. The severity of hematuria was divided into the five grades according to the number of red blood cells per high power field (HPF). The patient distribution in the five grades is shown as a percentage. The rate of the disappearance of hematuria, defined as the number of red blood cells <5/HPF, was not different between both groups at any time point (Pearson's chi-square test).

treatment with corticosteroid. At the end of the study, blood sugar levels of all four patients were restored to the normal range without any medications. No patient had a new onset of hypertension.

Logistic regression analysis

Logistic regression analysis was performed to evaluate the impact of multiple covariates on the disappearance of proteinuria or hematuria and the occurrence of clinical remission. Independent variables included the allocated treatment, eGFR, mean blood pressure, urinary protein excretion and the use of RAS inhibitors at baseline (Table 2). Only the allocated

treatment had a significant and independent impact on the disappearance of proteinuria (hazard ratio, 2.98; 95% confidence interval, 1.01–8.83; P = 0.049). No independent factors were identified as achieving the disappearance of hematuria or clinical remission.

Use of RASi during the trial

RAS inhibitors were started after the initiation of treatment in three patients in Group A (losartan 50 mg, telmisartan 40 mg or valsartan 80 mg) and four patients in Group B (aliskiren 150 mg, losartan 50 mg, olmesartan 10 mg or valsartan 80 mg). The disappearance of proteinuria was achieved in two
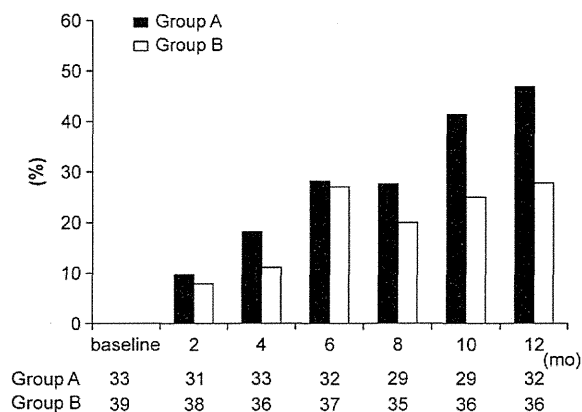
FIGURE 5: Frequency of clinical remission during the trial period. The frequency of patients with clinical remission (i.e. the disappearance of both proteinuria and hematuria) is shown for each time point. The frequency was not significantly higher in Group A than Group B at any time point (Pearson's chi-square test).

	baseline	2	4	6	8	10	12 (mo)
Group A	33	31	33	32	29	29	32
Group B	39	38	36	37	35	36	36

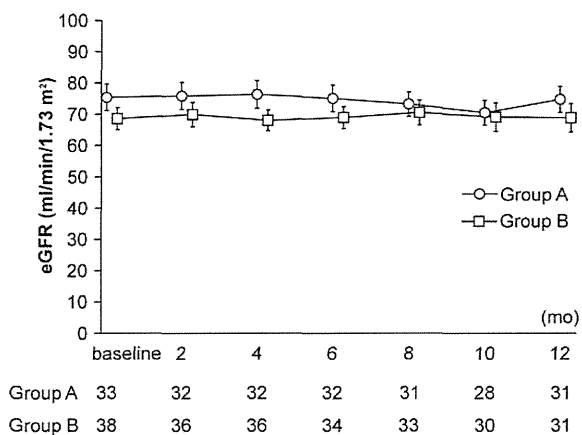|	baseline	2	4	6	8	10	12 (mo)
Group A	33	32	32	32	31	28	31
Group B	38	36	36	34	33	30	31

FIGURE 6: Renal function during the trial period. Mean values and standard errors of the estimated glomerular filtration rate (eGFR) are shown. The value of eGFR remained stable in both groups.

of these patients from each group after 12 months. No patient started other antihypertensive drugs during the period.

DISCUSSION

For the first time, we performed a multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with IgA nephropathy. The findings of the present study indicated that the decrease in urinary protein excretion during follow-up was significantly greater, albeit marginally, in patients receiving tonsillectomy combined with steroid pulse therapy than in those receiving steroid pulse therapy alone, as shown by a mixed effect model and logistic regression analysis. However, 12 months after the initial treatment, the frequency of the disappearance of microscopic hematuria and clinical remission was comparable between the two groups. Thus, we conclude that tonsillectomy has no

Table 2. Logistic regression analysis of the impact of tonsillectomy, renal function, blood pressure and urinary protein excretion at baseline and after disappearance of proteinuria, hematuria or both at study completion

	Odds ratio	95% CI	P-value
Disappearance of proteinuria			
Assigned treatment	2.98	1.01–8.83	0.049
eGFR (baseline)	0.99	0.97–1.02	0.560
Mean blood pressure (baseline)	1.04	0.97–1.11	0.297
Proteinuria (baseline)	0.61	0.33–1.13	0.115
RASi (baseline)	0.51	0.16–1.68	0.270
Disappearance of hematuria			
Assigned treatment	1.23	0.43–3.55	0.697
eGFR (baseline)	0.99	0.97–1.01	0.304
Mean blood pressure (baseline)	0.97	0.91–1.04	0.450
Proteinuria (baseline)	0.91	0.54–1.54	0.737
RASi (baseline)	0.95	0.29–3.13	0.930
Clinical remission			
Assigned treatment	2.24	0.77–6.51	0.140
eGFR (baseline)	0.99	0.97–1.02	0.554
Mean blood pressure (baseline)	1.01	0.94–1.08	0.858
Proteinuria (baseline)	0.75	0.41–1.38	0.348
RASi (baseline)	0.63	0.19–2.06	0.445

Logistic regression analysis was used to determine the association of assigned treatment, eGFR, mean blood pressure or urinary protein excretion at baseline with the disappearance of proteinuria, hematuria or both (clinical remission) after 12 months of treatment with tonsillectomy plus steroid pulse therapy or steroid pulse therapy alone after adjusting for the other covariates.
CI, confidence interval; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitors.

impact on the disappearance of hematuria, but can have a beneficial effect on the decrease in proteinuria of IgAN patients, at least for those clinically comparable to the present patients. However, whether this subtle antiproteinuric effect by tonsillectomy indeed leads to better renal outcome remains to be elucidated.

Our patients had urinary protein excretion ranging from 1.0 to 3.5 g/day, and most patients showed moderate to severe histological damage (i.e. relatively poor prognosis or poor prognosis; Table 1), indicating that the present study excluded patients with mild IgAN. In view of the possible effectiveness of steroid pulses alone, as revealed in the present and previous studies [14, 15], a question remains as to whether the advantage of tonsillectomy seen in the present study is relevant to patients with milder IgAN than those in the present patients. Moreover, based on the randomized controlled trial by Pozzi et al. [15] demonstrating an ~10% incidence in the disappearance of proteinuria following steroid pulses, it can be speculated that only a few patients with advanced IgAN, such as those with serum creatinine of >1.5 mg/dL, can achieve the disappearance of proteinuria following steroid pulses alone. In this regard, tonsillectomy combined with steroid pulse therapy can be more effective in patients with advanced IgAN, as suggested by a previous report [30], which found that renal outcome was better with tonsillectomy plus steroid pulses in IgAN patients, particularly in patients with serum creatinine of 1.5–2.0 mg/dL. Further studies are necessary to clarify the profiles of IgAN patients suited for treatment with tonsillectomy plus steroid pulses.

This study had several limitations. First, the follow-up period was too short to be able to assess several long-term

outcomes, i.e. renal function, incidence of relapse/recurrence of proteinuria, frequency of patients who need additional therapies, etc. Indeed, none of the patients were found to reach the end points. In this regard, the secondary end points established in this trial appeared inadequate in view of a short follow-up period. The primary end points used in this study (e.g. the disappearance of proteinuria and/or hematuria after 12 months) were surrogate markers, since the real hard end points should have represented long-term renal survival, such as the progression of renal disease or the development of ESRD. Nevertheless, many previous studies indicate that a marked reduction of proteinuria as an early response to the initial treatment ensures stable renal function after the cessation of treatment [14, 15, 17, 31, 32]. In addition to those studies that examined the relationship between the level of proteinuria after 12 months and the final renal outcome, Hirano et al. recently reported that, in the IgAN patients receiving 6 months of steroid therapy (Pozzi's protocol), the achievement of proteinuria <0.4 g/day after 12 months could be a therapeutic indicator for a favorable renal outcome [27]. Therefore, a superior antiproteinuric effect of tonsillectomy plus steroid pulses compared with steroid pulses alone could lead to better preservation of renal function in the long-term. Since it is crucially important whether tonsillectomy can protect IgAN patients from the progressive deterioration of renal function or the relapse/recurrence of proteinuria during a long-term follow-up, we are now in the process of a study to follow-up the present patients for 3 years.

Second, the incidence of the disappearance of proteinuria and/or hematuria after 12 months was not significantly different between the two groups. In our study, the disappearance of proteinuria with steroid pulses alone was more frequent than that extrapolated from the results of the previous reports [14, 15, 26]. This unexpectedly high incidence may have resulted in the failure to find statistical difference between the two groups. More patients should be included for a more definitive conclusion. Third, the pattern in the decrease of urinary protein excretion could not be analyzed using repeated ANOVA, because the data available at some time points were insufficient for analysis. Fourth, a few of the enrolled patients had to be excluded from the analysis, which may have reduced the effectiveness of randomization. Nevertheless, all the parameters at baseline were comparable between the two groups. This notion is supported by the results of the logistic regression analysis. Fifth, RAS inhibitors were administered only in nearly half of the patients in both groups at baseline. Therefore, some patients could show proteinuria <1 g/day at baseline, if all the patients were given RAS inhibitors prior to the trial. The mixed effect model revealed that a significantly greater antiproteinuric effect of tonsillectomy plus steroid pulses was independent from the use of RAS inhibitors at baseline. Nevertheless, the differential use of RAS inhibitors by different investigators could have potentially biased the results. Moreover, the impact of RAS inhibitors on patients who started RAS inhibitors during the trial was not clear. Finally, the study lacks sufficient information for the removed tonsil, such as, the frequency of presence of tonsils with infection as assessed by the presence of crypt abscesses or bacterial

colonies in tonsillar tissues by macroscopic or microscopic inspection. It has been reported that the efficacy of tonsillectomy is difficult to predict on the basis of the appearance of tonsils or clinical episodes of recurrent tonsillitis [33]; thus, the relationship between the condition of removed tonsils and the outcome of proteinuria remains elusive.

In conclusion, tonsillectomy combined with steroid pulses had no additional benefit over steroid pulses alone in the disappearance of hematuria or the achievement of clinical remission. Although the antiproteinuric effect was significantly larger in the treatment with tonsillectomy plus steroid pulses than in steroid pulses alone, the difference was very subtle. Whether this marginal antiproteinuric effect improves renal outcome remains to be clarified.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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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 m² 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.

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) $\geq 130/80$ 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 $\geq$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		
$\geq$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
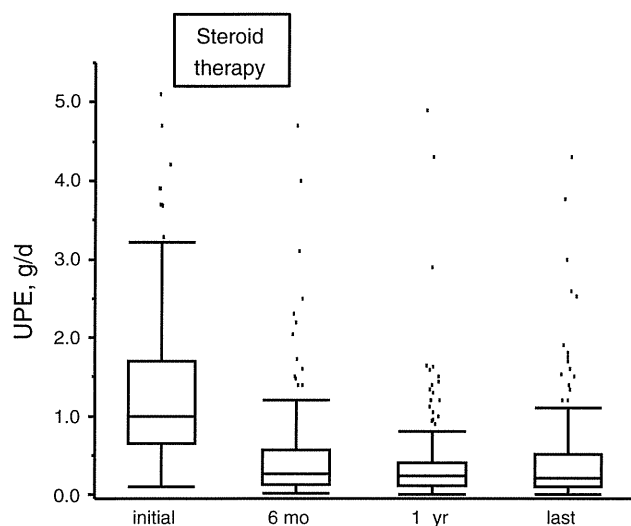
[a] According to Ref. [17]

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
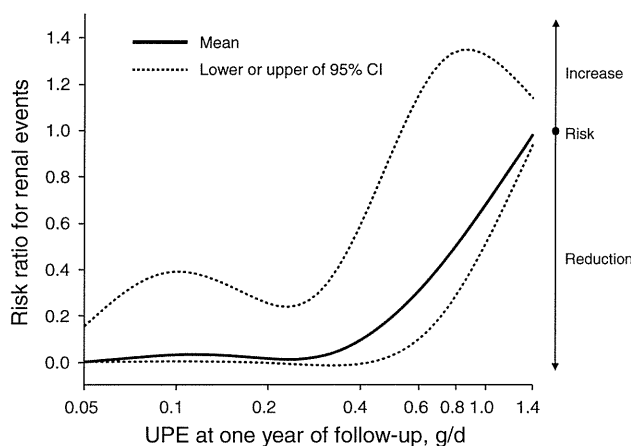

Fig. 2 Risk ratio for the endpoint associated with the UPE at the 1-year follow-up. Plots of the risk ratios and 95 % confidence intervals adjusted for the baseline eGFR for the endpoint using the level of proteinuria at the 1-year follow-up examination as the continuous variable are shown (reference: 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
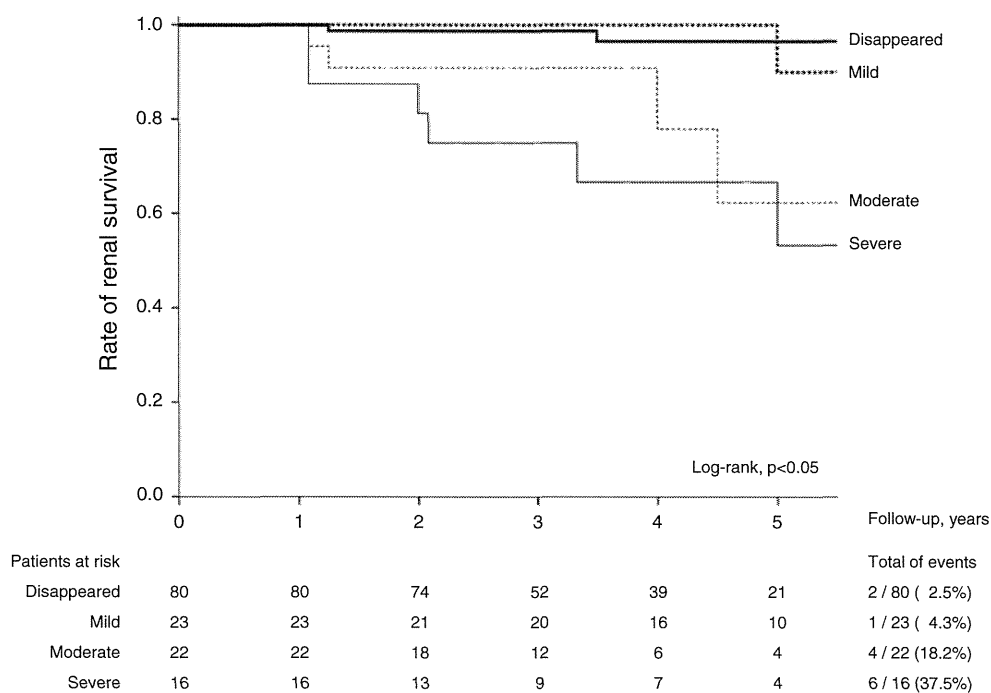
Table 2 Baseline characteristics according to the category of proteinuria at 1 year of follow-up

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)

Patients at risk							Total of events
Disappeared	80	80	74	52	39	21	2 / 80 (2.5%)
Mild	23	23	21	20	16	10	1 / 23 (4.3%)
Moderate	22	22	18	12	6	4	4 / 22 (18.2%)
Severe	16	16	13	9	7	4	6 / 16 (37.5%)

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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REVIEW ARTICLE

Clinical findings on ANCA-associated renal vasculitis from the Japan RPGN registry obtained via a questionnaire survey

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Abstract Renal involvement with significant organ damage is common in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). As a result, it is independently referred to ANCA-associated renal vasculitis. Clinically, ANCA-associated renal vasculitis is characterized by rapidly progressive glomerulonephritis. Pathologically, it is defined by pauci-immune type necrotizing and crescentic glomerulonephritis. According to previous reports from all over the world, the etiology, prevalence, and prognosis of RPGN including ANCA-associated renal vasculitis varies among races and periods. To elucidate the clinical characteristics of Japanese RPGN patients, a registry derived from a questionnaire survey was

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established in 1999 and maintained until 2006. As a result, 1,772 cases were collected, analyzed, and reported previously. In this mini-review, we outline the characteristic clinical findings of Japanese patients (Asian) with ANCA-associated renal vasculitis, based on the registry data.

Clinical findings of ANCA-associated renal vasculitis and RPGN in Japan

The frequency of renal involvement and rapidly progressive glomerulonephritis (RPGN) in Japanese patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is still unclear. A Japan RPGN registry derived from a questionnaire survey was established in

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Table 1 Number of patients with RPGN. This table was prepared with partial modification [1]

Diagnosis	Classification	Total RPGN cases	
		n	%
Primary			
Crescentic GN	Anti-GBM antibody-associated crescentic GN	81	4.6
	Immune-complex-associated crescentic GN	35	2.0
	Renal-limited vasculitis	745	42.0
	Overlapped crescentic GN	31	1.7
	Undifferentiated primary crescentic GN	28	1.6
Primary GN with crescents	Mesangioproliferative glomerulonephritis	15	0.8
	Membranous nephropathy	5	0.3
	IgA nephropathy	43	2.4
	Non-IgA mesangial proliferative GN	8	0.5
	Other primary GN	3	0.2
Systemic disease-associated			
	Goodpasture's syndrome	27	1.5
	Systemic lupus erythematosus	66	3.7
	Granulomatosis with polyangiitis (Wegener's)	46	2.6
	Microscopic polyangiitis	344	19.4
	Other necrotizing vasculitis	15	0.8
	Purpura nephritis	36	2.0
	Cryoglobulinemia	12	0.7
	Rheumatoid arthritis	24	1.4
	Malignant neoplasm	3	0.2
	Other systemic diseases	40	2.3
Infection-associated			
	Poststreptococcal acute glomerulonephritis	10	0.6
	Abscess	6	0.3
	Hepatitis C virus	2	0.1
	Other infectious diseases	20	1.1
Drug-associated		10	0.6
Others		17	1.0
Unknown		100	5.6
Total		1772	100.0

1999 and maintained until 2006. As a result, 1772 cases were collected, analyzed and reported [1, 2]. The clinical entity of RPGN is shown in Table 1 [1, 2]. Pauci-immune-type renal-limited vasculitis was the most frequently observed clinical entity of RPGN (42.0 %). Among patients with renal-limited vasculitis (RLV), myeloperoxidase (MPO)-ANCA-associated cases made up 88.1 % and proteinase 3 (PR3)-ANCA-associated cases made up 7.4 %. Among cases of microscopic polyangiitis (MPA), which was the second most common clinical entity of RPGN (19.4 %), MPO-ANCA-associated cases made up 91.8 % and PR3-ANCA-associated cases made up 6.1 %. By contrast, in cases of granulomatosis with polyangiitis (Wegener's) occurring among Japanese individuals with RPGN (2.6 %), MPO-ANCA-associated cases made up 22.7 % and PR3-ANCA-associated cases made up 71.1 %. That is, most Japanese patients with AAV and RPGN were estimated to be positive for MPO-ANCA. Additionally, the age distribution of Japanese RPGN was a characteristic finding [1]. Among all RPGN subjects, the mean age at presentation significantly increased during the observation period. The main reason for this secular change was a significant increase in the mean age of subjects with RLV (61.85–67.28 years), MPA (64.60–68.77 years), and anti-GBM antibody-mediated RPGN (52.05–61.59 years) in recent years. This increase in the age of the onset of RPGN seems to reflect the longevity of the Japanese population and the aging of Japanese society.

Next, the speed of renal deterioration in this RPGN survey was also examined. Because RPGN is a loosely-defined term

Table 2 The clinical grading system for predicting RPGN patient prognosis [1]

Clinical score	Serum creatinine (mg/dl)	Age (years)	Lung involvement	Serum CRP (mg/dl)
0	<3	≤59	Negative	<2.6
1	3–6	60–69		2.6–10.0
2	≥6	≥70	Positive	>10.0
3	Dialysis			
Clinical grade				
I				0–2
II				3–5
III				6–7
IV				8–9

Fig. 1 Clinical grading system for predicting patient prognosis. A clinical grading system was applied to all RPGN patients. This figure was prepared with partial modification [1]

and is challenging to define, we need to provide specific data for an established definition. Seventy-eight cases in which diffuse crescentic glomerulonephritis was confirmed on renal biopsy were selected and analyzed. In cases with RPGN, the average speed of the increase in the serum creatinine level was 1.03 mg/dl per week and the decrease in the estimated glomerular filtration rate (GFR) was 4.6 ml/min/1.73 m² (18.5 %) per week. Moreover, in 52 cases with MPO-ANCA-associated RPGN, the average speed of the increase in the serum creatinine level was 0.80 mg/dl per week, and the decrease in the estimated GFR was 3.6 ml/min/1.73 m² (16.6 %) per week. The Birmingham Vasculitis Activity Score (BVAS), a popular vasculitis activity score, has adopted the following assessment criteria of renal impairment, as specified by professional opinion: an increase in serum creatinine of more than 30 % or a decrease in creatinine clearance of more than 25 % within 4 weeks (personal communication with Professor RA Luqmani) [3]. The definition of RPGN varies among different countries of the world, and a universal standard definition of RPGN should be established in the future.

The first version of the clinical guidelines for Japanese RPGN was published in 2002, and the second version was published in 2011; these were based on the Japan RPGN registry established using a questionnaire survey (articles in Japanese). A clinical degree of severity that was calculated using four items, namely serum creatinine level, age, lung involvement, and serum C-reactive protein level, was defined in these clinical guidelines (Table 2). This was well correlated with the life prognosis of all patients with RPGN and MPO-ANCA-associated RPGN (Fig. 1). Moreover, a therapeutic algorithm for ANCA-associated RPGN based on the clinical degree of severity was suggested (Fig. 2) [2]. This clinical grading system was able to estimate the prognosis in cases of ANCA-associated RPGN and provided an approach to the classification of the treatment choices. In a recent report, the authors named this
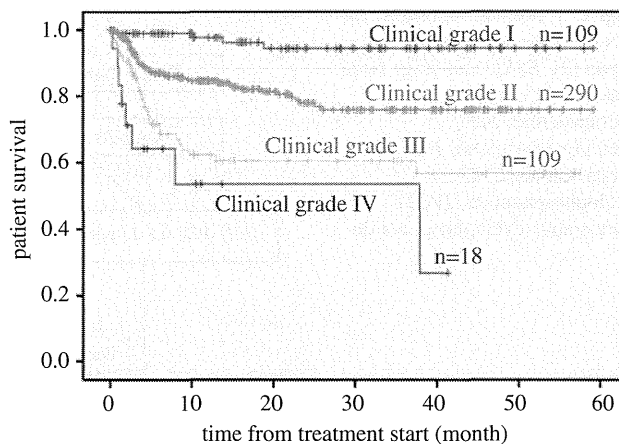
algorithm the Japanese Vasculitis Activity Score (JVAS), and it was found to be useful as a method of grading activity in cases of AAV in comparison with BVAS [4]. It was positively correlated with BVAS. However, at this time, the clinical degree of severity is consistently used as an index of life prognosis in ANCA-associated RPGN. If this clinical grading system is to be applied to the vasculitis activity score, additional investigations are needed.

Because of the publication of the clinical guidelines for Japanese RPGN in 2002, the prognosis for Japanese RPGN including AAV was markedly improved recently [1]. Standard induction therapy consisted of both corticosteroids and cyclophosphamide in Europe, but the clinical guidelines for Japanese RPGN adopted an independent therapeutic algorithm for ANCA-associated RPGN because of the high prevalence of elderly patients as mentioned above. According to the analysis of the Japan RPGN registry, infection was a major cause of death [1]. During the observation period, 31.8 % of patients died within 0–98.8 months. In recent years, the mortality rate decreased from 38.7 % (between 1989 and 1998) to 18.0 % (between 2002 and 2007). By contrast, the rate of infection as a cause of death was not decreased, from 48.1 % (between 1989 and 1998) to 55.9 % (between 2002 and 2007). Infection as the cause of death was frequent in the early phase of treatment. Therefore, the avoidance of severe adverse effects including infections became a priority in Japan, and milder treatment was chosen in the therapeutic regimen. As a result of this change, the life prognosis and renal survival of all RPGN patients were undoubtedly improved [2]. Additionally, the life prognosis and renal survival of patients with MPO-ANCA-associated RPGN were also improved. In contrast, the reduction in the use of immunosuppressant reagents increased the rate of relapse in patients with MPO-ANCA-associated RPGN.

Fig. 2 Treatment algorithm for ANCA-associated RPGN in Japan [2]. *ESRD* end-stage renal disease, *OCS* oral corticosteroid, *MP* methylprednisolone, *PSL* prednisolone, *CYC* cyclophosphamide, *IVCYC* intravenous cyclophosphamide
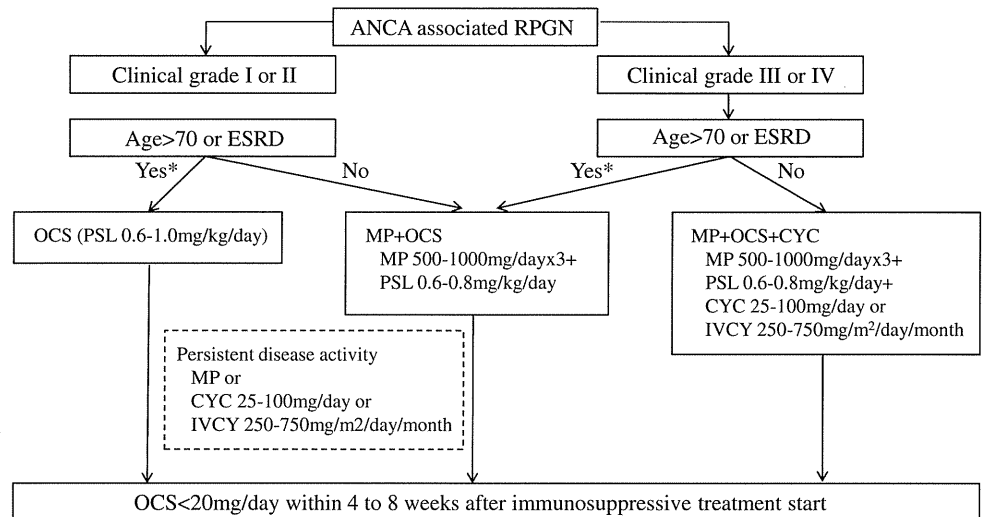
*Older patients often suffered from opportunistic infection. Milder treatment (less dose of PSL, without MP or CYC were recommended.

Therefore, it became important to establish maintenance therapy for MPO-ANCA-associated RPGN as quickly as possible. In Japan, a randomized controlled trial of a maintenance therapy using a milder immunosuppressant drug, mizoribine, for MPO-ANCA-associated RPGN is currently underway [Mizoribine for ANCA RPGN Relapse-Prevention Study (MARPGN study)]. A total of 44 cases had been enrolled as of December, 2011, at which point the entry of new patients into the study was ended. The rate of relapse and the effectiveness of mizoribine for maintenance therapy are expected to be determined in this study.

In the present article, we reviewed the clinical findings of ANCA-associated renal vasculitis in Japan. The Japan RPGN registry, based on a questionnaire survey, and the establishment of independent clinical guidelines have definitely improved the medical practice involved in the treatment of Japanese patients with AAV. A comparative discussion regarding the Japanese clinical guidelines and global guidelines is now needed.

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Evaluation of the newly proposed simplified histological classification in Japanese cohorts of myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in comparison with other Asian and European cohorts

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Abstract The prognostic value of renal biopsy in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis is widely recognized; however, there is no consensus regarding its pathological classification. Berden et al. proposed a new classification of glomerulonephritis in ANCA-associated vasculitis (AAV) categorized into focal, crescentic, mixed, and sclerotic classes and showed its prognostic value in 100 international multicenter cohorts for 1- and 5-year renal outcomes. In order to evaluate whether this new classification has predictive value and reproducibility in Japanese AAV cases, 87 cohorts with only microscopic polyangiitis in 3 limited centers in Japan were analyzed. In addition, those from Japan, Europe (Berden's cohorts) and China were compared in a recent report.

Keywords Anti-neutrophil cytoplasmic antibody · Vasculitis · Renal histology · Glomerulonephritis · Classification · Microscopic polyangiitis · Japan

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Introduction

We recently proposed pathological parameters of renal lesions observed in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients [1]. The purpose of this proposal was (1) standardization of pathological findings in AAV should be authorized in Japan; (2) comparison with the European Vasculitis Study Group (EUVAS) standardization should be available; and (3) pathological parameters correlated with specific clinical findings should be evaluated (Table 1). As a result, the pathological parameters selected were almost compatible with those selected by EUVAS except for the collapse of glomeruli as the chronicity parameter; however, further evaluation using these parameters to investigate potential markers for the probability of end-stage renal disease (ESRD) is needed.

Among the parameters listed above, the number of normal or sclerotic glomeruli was proved substantially to be a prognostic indicator of renal outcome in accordance with basal renal function [2–4]; however, no sufficient consensus exists regarding the pathological classification. Recently, using some of the glomerular parameters, an international working group of renal pathologists proposed a new histopathological classification of glomerulonephritis (GN) in

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Table 1 Pathological parameters nominated for evaluation of active and chronic lesion in ANCA-related vasculitis in Japan (comparable with EUVAS)

Glomerular lesion	
No. of normal glomeruli	
Active lesion	Chronicity lesion
Mesangial proliferation	Sclerotic lesion
Endocapillary hypercellularity	Global sclerosis
Tuft necrosis	Segmental sclerosis
Cellular, fibrocellular crescent formation	Fibrous crescent
<50 %	<50 %
>50 %	>50 %
Rupture of Bowman's capsule	Adhesion
	Collapse[a]
Tubulointerstitial lesion	
Active lesion	Chronicity lesion
Tubulitis	Atrophic tubule
Disruption of tubular basement membrane	Interstitial fibrosis
Interstitial cell infiltration	
Granulomatous lesion	
Peritubular capillaritis[a]	
Vascular lesions	
Active lesion	Chronicity lesion
Necrotizing	Arteriosclerosis
Endoarteritis	
Cell infiltration	
Thromboembolism	
Granulomatous lesion	

[a] Parameter not nominated in EUVAS

AAV with four categories (focal, crescentic, mixed and sclerotic), corresponding to the severity of renal function loss in this order during a 5-year follow-up [5]. As the evaluation was performed in 100 cases, consisting of 39 cases of granulomatosis with polyangiitis (GPA) and 61 cases of microscopic polyangiitis (MPA) in 32 centers in 9 European counties, the influence of the relatively mixed races and disease types could not be excluded. In Japan, >90 % of ANCA-positive GN is diagnosed as MPA, in which renal involvement is more frequent than in GPA, as previously reported [6]. In this study, we evaluated the predictive potential of this newly proposed categorization in myeloperoxidase (MPO)-ANCA-dominant MPA patients in Japan.

Patients and methods

Eighty-seven patients with primary systemic vasculitis, in accordance with the Chapel Hill consensus criteria [7], diagnosed and treated from 2001 to 2010 in three centers (Kitano Hospital in Osaka, Tokyo Women Medical College

Table 2 Comparison among evaluations of GN histological categories with clinical background in Europe, China and Japan

	European [5]	Japan	China [8]
Patients (number)	100	87	121
Centers (number)	32	3	1
Median age (range)	62.6 (20–80)	63.0 (17–85)	57.2 (15–81)
Male to female (number)	54:46	37:50	64:57
Clinical diagnosis (%)			
GPA	39 (39)	0	49 (40.5)
MPA	61 (61)	87 (100)	68 (56.2)
Renal-limited vasculitis	0	0	4 (3.3)
ANCA test (indirect immunofluorescence or ELISA)			
PR3-ANCA	45	0	13
MPO-ANCA	47	76	108
ANCA(−)	2	0	0
Missing	3	11	0
Median number of glomeruli per biopsy (range)	14.8 (10–49)	26.5 (10–98)	25.7 (NS)
Pathological classification number (%)			
Focal	16 (16)	40 (46.0)	33 (27.3)
Crescentic	55 (55)	7 (8.0)	53 (43.8)
Mixed	16 (16)	26 (29.9)	24 (19.8)
Sclerotic	13 (13)	14 (16.1)	11 (9.1)
Serum creatinine (mg/dl)			
Focal	NS	1.51 ± 1.49	2.22 ± 1.90
Crescentic		2.42 ± 1.67	5.01 ± 2.73
Mixed		3.37 ± 3.17	3.86 ± 2.69
Sclerotic		7.52 ± 4.92	8.51 ± 3.42
Death at 1-year follow-up	25/100	11/84	NS
Renal survival at 1-year follow-up			
Focal, crescentic, mixed, sclerotic (%)	93, 84, 69, 50	100, 86, 96, 35	100, 73, 83, 29
Renal survival at 5-year follow-up			
Focal, crescentic, mixed, sclerotic (%)	93, 76, 61, 50	100, 86, 96, 29	NS

Data of three patients were lost due to transfer to different hospitals before 1-year follow-up

NS not shown in the report

in Tokyo and Shimoshizu National Hospital in Chiba) were analyzed. In all cases, renal biopsy was performed before treatment. Specimens including a minimum of 10 whole glomeruli were enrolled. Hematoxylin and eosin, methenamine silver, periodic acid-Schiff, and Masson trichrome staining were used for evaluation. The histological categorization based on glomerular lesion was performed following Berden's group [5]—focal ≥50 % normal glomeruli, crescent ≥50 % of glomeruli with cellular crescents, sclerotic ≥50 % of glomeruli with global sclerosis, and mixed <50 % normal, <50 % crescentic, <50 %

globally sclerotic glomeruli. A minimum of 6 months prognosis was observed for all patients. Renal and life survivals were analyzed at onset, 6 months, 1 year and 5 years after renal biopsy in available patients (87 at onset and 6 months, 84 at 1 year, 78 at 5 years).

Results

Patient profile and outcome in Japanese cohort

Median age was almost identical to the European study; however, males were dominant in Japan in contrast to a slight female dominance in Europe (Table 2).

All cases in Japan had MPA; MPO-ANCA was positive in 76/87 (87.3 %). The median glomerular number was 26.5 in Japanese samples. At 6 months follow-up, 11 patients reached ESRD and a further 8 patients had died. At 1-year follow-up, no more patients had reached ESRD and a total of 11 patients had died. At 5-year follow-up, 18 patients had died and another 12 patients had reached ESRD.

Classification of the renal biopsy in Japanese cohorts

In Japanese patients, almost half of the cases were categorized as focal (40/87; 46.0 %) with 14/87 (16.1 %) as sclerotic. Of the other 32 cases, only 7 (8.0 %) were categorized as crescentic, with the remaining 26 cases (29.9 %) being classed as mixed. As shown in Fig. 1, the Kaplan–Meier curve at the 5-year follow-up showed no increase of probability to ESRD in focal cases and a low increase in mixed cases; however, this increased with the ascending categories of crescentic and sclerotic GN.

Comparison among evaluations of GN histological categories in Europe, China and Japan

The predictive value and reproducibility of this new classification from Japan, Europe and China were compared in a recent report [8]. As shown in Table 2, among the 100 respective patients (32 centers; Europe), 121 (1; China) and 87 (3; Japan), the GPA:MPA ratio was similar between Europe and China (39:61 and 49:64) in contrast to all MPA (0:87) in Japan. On the other hand, for serum ANCA positivity, MPO-ANCA positivity was dominant in China (89.1 %) and Japan (87.4 %) compared to Europe (45 %), where there was relatively high PR3-ANCA positivity (47 %) compared with China and Japan (10.7 and 0 %, respectively). The average numbers of glomeruli per case were significantly higher both in Japan (26.5) and China (25.7) than in Europe (14.8). The distribution of the four histological categories of GN were similar in Europe and
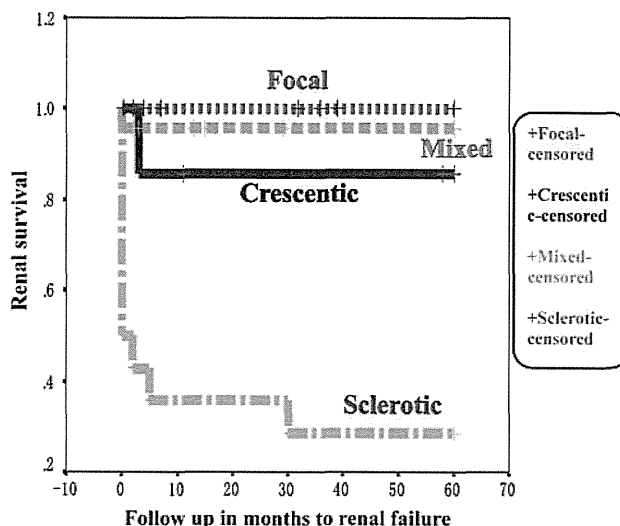

Fig. 1 Renal survival (no development of end-stage renal failure) according to the four histologic categories in Japanese cohorts

China with crescentic cases being dominant (55 and 47 %, respectively), whereas in Japan, the number in this category was significantly lower (8.0 %). The probability of developing ESRD increased with the ascending categories of focal, crescentic, mixed, and sclerotic in Europe, and focal, mixed, crescentic and sclerotic in China. In Japan, as mentioned above, there was no increase of probability to ESRD in focal and mixed, but there was a high increased in sclerotic, as in Europe and China.

Discussion

The histopathological findings of AAV in the kidney are considered to show a variety of lesions, of which crescentic and/or focal necrotizing GN as well as small-vessel arteritis are the most prominent [7]. In addition to the baseline laboratory data concerning renal lesions such as hematuria, proteinuria and decreased estimated glomerular filtration rate with systemic inflammatory signs such as C-reactive protein and organ involvement symptoms such as hemoptysis, renal histological findings have been expected to give highly reliable information not only to select the treatment protocol but to predict the outcome at baseline. Trials for the global standardization of active and chronic pathological parameters specifically in AAV have been performed not only in EUVAS but also in Japan, where a higher prevalence of MPA than EUVAS has been recognized, although the AAV prevalence itself is almost the same [9]. As shown in Table 1, these parameters are common findings in AAV. Almost all parameters are common in EUVAS selection, so our Japanese standardization of clinicopathologically critical parameters in AAV seems to be globally fulfilled.

The new classification of GN into four categories (focal, crescentic, mixed, sclerotic) by selecting some of the parameters of Berden et al. [5] was highly predictive in AAV patients from multicenters in Europe. In Japan, the significantly lower frequency of crescentic and relatively higher frequency of focal cases were noted; this might be partly attributed to the earlier intervention of renal biopsy after discovering a urinary or renal function abnormality in Japan. The relatively low creatinine level of the focal group in Japan compared with that of the same group in China might support this tendency. As the progression of renal injury tends to be different between MPA and GPA, comparisons should be performed only between MPA in Europe and in Japan. This was not possible in this classification study because there were no data on the ratio of MPA in the crescentic group in Europe. In this study, the Kaplan–Meier curve revealed the highly favorable prognosis of the mixed group. This indicates that the prognosis of this group is attributed to additional pathological parameter such as tubulointerstitial or vascular lesions nominated previously in Europe and Japan. At present, at least for MPA-oriented cohorts in Japan, this classification only by glomerular parameters might be insufficient to predict the probability of progressing to ESRD.

The comparison of European, Japanese and Chinese cohorts would be highly informative. The similarity of the GPA/MPA ratio between Europe and China in contrast to that of MPO-ANCA dominancy between Japan and China indicates that many GPA are MPO-ANCA-positive in China, as Chinese authors have stated. The GPA dominancy might be attributed partly to the localization of the center at a high latitude, which has been reported to be related to the high prevalence of GPA [10]. Although the numbers in the four categories were similar between Europe and China, there was a difference in the order of the increase of probability of progressing to ESRD between mixed and crescentic. The significantly more favorable prognosis of mixed than crescentic in China is similar to Japan, where both focal and mixed rarely showed progress to ESRD.

In conclusion, the mixed group in the new classification has high heterogenicity of histological activity and chronicity, which shows the insufficiency of this classification for prediction of the probability of progressing to ESRD. Re-evaluation of the predictive value by adding other parameters such as interstitial or vascular lesions for MPA-oriented cohorts is expected.

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