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ORIGINAL ARTICLE

The relationship between renal volume and renal function in autosomal dominant polycystic kidney disease

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Abstract
Background In patients with autosomal dominant polycystic kidney disease (ADPKD), renal cysts grow exponentially. Since remaining renal parenchyma has a capacity to compensate for the loss of glomerular filtration, the glomerular filtration rate (GFR) may be sustained until the disease progresses. The purpose of this study was to determine if renal volumetric indices and clinical parameters are associated with renal function in Japanese patients with ADPKD.
Methods In 73 ADPKD patients (28 men, 45 women), the associations of mean systolic blood pressure, mean diastolic blood pressure, estimated GFR (eGFR), the amount of proteinuria and albuminuria, body mass index (BMI), brachial-ankle pulse wave velocity (baPWV), ankle-brachial index, and total kidney volume (TKV) were retrospectively analyzed.
Results Multivariate linear regression analysis showed that eGFR was significantly and independently inversely correlated with patients' age and BMI. The median change in eGFR per year (ΔeGFR/y) was −2.8 ml/min/1.73 m^2/year. Multiple linear regression analysis showed that ΔeGFR/y was significantly and independently inversely correlated with the change in TKV per year (ΔTKV/y). Multiple linear regression analysis showed that ΔTKV/y was significantly related to initial TKV and the change in albuminuria per year.
Conclusions This study demonstrated a significant relationship between the change in renal function and the change in renal volume in Japanese ADPKD patients without renal insufficiency. It is possible that the volume measurements can be used as useful markers for disease progression in Japanese ADPKD patients.

Keywords Autosomal dominant polycystic kidney disease · Renal function · Renal volume · Marker

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common progressive hereditary kidney disease affecting all ethnic groups worldwide, with an incidence of 1:500–1:1000. Typically, only a few renal cysts are detected in most affected individuals before 30 years of age; however, by the fifth decade of life, hundreds to thousands of renal cysts are found in the majority of patients. Renal cysts grow exponentially in ADPKD [1]. This continuous growth and expansion of cysts leads to progressive, grotesque, renal enlargement and subsequent loss of renal function [2]. End-stage renal failure requiring renal replacement therapy occurs in approximately 50% of patients and typically develops in the sixth decade of life [3]. However, renal insufficiency is usually not detected until the fifth or sixth decade of life. Since the remaining kidneys have a capacity to compensate for the loss of glomerular filtration in ADPKD patients, the renal function remains stable for many years, but there is a sharp decline in the glomerular filtration rate (GFR) once a critical expansion of renal cysts is reached [4, 5]. GFR, the usual biomarker of renal disease progression, does not decrease substantially until extensive and irreversible damage to noncystic parenchyma occurs. Therefore, it is necessary to identify some reliable biomarkers to follow the progression of this disease [6]. Modeling experiments using prospective

clinical data from the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP) cohort have suggested that very high rates of kidney growth must occur during childhood to account for the kidney volumes observed in adults [7]. Recent data from the CRISP study indicate that kidney growth is a critical predictor of progression to renal failure in Caucasian ADPKD patients, playing a more important role than hypertension, proteinuria, age, or sex [1]. Consequently, kidney volume growth is considered the best surrogate marker predicting the decline of renal function in ADPKD [8].

The aim of our study was to investigate the associations among clinical parameters, renal volumetric indices, and renal function in Japanese ADPKD patients.

Materials and methods

The present study enrolled patients who had been diagnosed as having ADPKD, were older than 20 years, and who had magnetic resonance imaging (MRI) examinations with transverse and coronal section images. ADPKD was diagnosed based on the patient's family history and the results of several imaging studies, such as ultrasonography, computed tomography scanning, and MRI. Patients with end-stage renal disease were excluded. Age of enrollment, mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), estimated GFR (eGFR), 24-h proteinuria, 24-h albuminuria, body mass index (BMI), brachial-ankle pulse wave velocity (baPWV), ankle-brachial index (ABI), and total kidney volume (TKV) were retrospectively evaluated. Blood pressures were measured at every study visit in the sitting position after a rest of 5 min, using the conventional oscillometric method and mercury manometer in the outpatient clinic. The eGFR was used as a marker of renal function and was calculated using the simplified MDRD equation modified by the appropriate coefficient for Japanese populations by sex as follows [9]:

$$\mathrm{eGFR} = 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287} (\text{female: } \times 0.739)\ (\mathrm{mL/min/1.73\,m^2}).$$

Arterial stiffness was assessed by measuring baPWV and ABI using an automatic waveform analyzer (Form/ABI; Omron-Colin Co., Ltd., Komaki, Japan). Renal volumes were measured by performing standard abdominal MRI using a 1.5-T scanner. Length, width, and depth were measured in centimeters. TKV was obtained by summing the volumes of both kidneys and then calculating using a standard formula: renal volume $= \pi/6 \times$ length $\times$ width $\times$ depth [7]. Length and width were obtained from longitudinal images acquired in planes ranging from sagittal to coronal, whereas depth was obtained from transverse images of the mid-kidney acquired in the plane perpendicular to the longitudinal plane. In cases with at least two sequential examinations at least 3 months apart, the changes in variables per year were calculated by comparing values at baseline and the latest data.

Pearson's correlation coefficients were used to examine the associations among eGFR, the change in eGFR per year (ΔeGFR/y), the change in TKV per year (ΔTKV/y), and selected clinical variables. Multivariate linear regression was used to determine independent predictors of baseline eGFR, ΔeGFR/y, and ΔTKV/y. Two-tailed p values of <0.05 were considered to indicate a statistically significant difference.

Results

Patients' characteristics

The subjects for this study were 73 patients with ADPKD (28 men and 45 women, median age 48 years, age range 21–72 years). The diagnosis of ADPKD was made using the Japanese criteria of the Ministry of Health, Labor, and Welfare. Table 1 shows the baseline characteristics of the patients in this study. The baseline median eGFR, and TKV were 55.3 ml/min/1.73 m^2 (range 7.2–120.6 ml/min/1.73 m^2), and 1595.9 ml (range 404.7–9652.0 ml) respectively. Themedian baseline left TKV and right TKV were 755.3 ml (range 190.0–3629.0 ml) and 786.9 ml (range 176.7–7915.1 ml), respectively. There was no significant difference between the baseline left and right TKVs ($p = 0.49$).

Of 73 patients, 38 (52.1%) were treated with antihypertensive therapy. In these patients treated with antihypertensive therapy, 36 patients (94.7%) took some kinds of angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI). Compared with patients

Table 1 The baseline characteristics of the patients in this study

	Median	Range
Age (years)	48	21–72
s-Cr (mg/dl)	0.98	0.48–5.12
eGFR (ml/min/1.73 m^2)	55.3	7.2–120.6
TKV (ml)	1595.9	404.7–9652.0
SBP (mmHg)	135.0	100–201.3
DBP (mmHg)	82.5	56.5–105.0
Proteinuria (mg/day)	185.3	0–1665.0
Albuminuria (mg/day)	49.6	0–1413.0
BMI (kg/m^2)	22.2	17.1–36.0
baPWV (m/s)	1397.3	973.5–2119.5
ABI	1.155	0.955–1.310

treated without ARB or ACEI, eGFR was significantly reduced in patients treated with ARB or ACEI (with ARB or ACEI 48.388 ± 23.168 ml/min/1.73 m^2, without ARB or ACEI 62.166 ± 25200 ml/min/1.73 m^2, $p = 0.002$). This is partly because blood pressure is significantly low in these patients compared with patients treated without ARB or ACEI (SBP; with ARB or ACEI 138.6 ± 18.6 mmHg, without ARB or ACEI 128.6 ± 15.7 mmHg, $p = 0.002$: DBP; with ARB or ACEI 83.7 ± 8.7 mmHg, without ARB or ACEI 78.3 ± 11.4 mmHg, $p = 0.004$). There are no significant differences in albuminuria and TKV between patients with or without ARB or ACEI (albuminuria; with ARB or ACEI 134.9 ± 192.4 mg/day, without ARB or ACEI 162.6 ± 344.4 mg/day, $p = 0.735$: TKV; with ARB or ACEI 2012.3 ± 1144.6 ml, without ARB or ACEI 1724.4 ± 1338.4 ml, $p = 0.207$).

The relationship between eGFR and other clinical parameters

eGFR was significantly inversely correlated with age ($r = -0.570$, $p = 0.000$), TKV ($r = -0.318$, $p = 0.000$), proteinuria ($r = -0.246$, $p = 0.0497$), albuminuria ($r = -0.278$, $p = 0.038$), SAP ($r = -0.350$, $p = 0.000$), DAP ($r = -0.345$, $p = 0.000$), BMI ($r = -0.338$, $p = 0.000$), and PWV ($r = -0.461$, $p = 0.000$) (Table 2). The relationship between eGFR and TKV over the course of the study using all data points for each patient is shown in Fig. 1. eGFR was inversely related with the renal volumetric indices ($y = -0.0052x + 64.316$, $r = -0.313$, $p = 0.000$) (Fig. 1). Compared with the normal renal function group (eGFR ≥60 ml/min/1.73 m^2), TKV in deteriorated renal function group (eGFR <60 ml/min/1.73 m^2) was significantly large (2306.8 ± 1394.5 vs. 1640.9 ± 1334.5 ml, $p = 0.005$).

Table 2 The relationship between eGFR and other clinical parameters

	Univariate analysis		Multivariate analysis	
	r	*p*	*p*	95% CI
Age (years)	−0.570	**0.000**	**0.001**	−1.361 to 0.357
TKV (ml)	−0.38	**0.000**	0.151	−0.001 to 0.006
Proteinuria (mg/day)	−0.246	**0.0497**	0.164	−0.011 to 0.063
Albuminemia (mg/day)	−0.278	**0.038**	0.928	−0.047 to 0.043
SAP (mmHg)	−0.350	**0.000**	0.964	−0.279 to 0.292
DAP (mmHg)	−0.345	**0.000**	0.413	−0.804 to 0.336
BMI (kg/m^2)	−0.338	**0.000**	**0.020**	−3.648 to 0.323
baPWV (m/s)	−0.461	**0.000**	0.093	−0.034 to 0.003
ABI	−0.177	0.113		

$p < 0.05$ is indicated by boldface

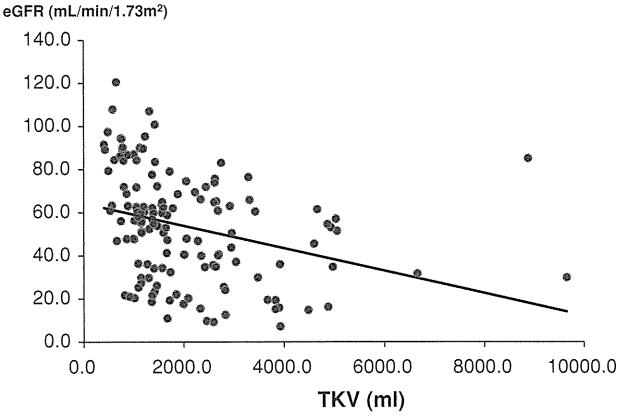

Fig. 1 Relationship between eGFR and TKV in 73 Japanese patients with ADPKD over the course of the study using all data points for each patient. eGFR is significantly inversely related with the renal volumetric indices ($y = -0.0052x + 64.316$, $r = -0.3126$, $p = 0.0002$)

Using the 8 significantly inversely correlated factors identified on univariate analysis, multivariate linear regression analysis was performed to determine the independent predictors of baseline eGFR. Multivariate linear regression showed that eGFR was significantly and independently inversely correlated only with age ($p = 0.001$) and BMI ($p = 0.020$) (Table 2).

The relationship between the change in eGFR per year (ΔeGFR/y) and other clinical parameters

Thirty-nine patients had at least two sequential examinations. The median follow-up period was 28.5 months (range 3–94 months). During the follow-up period, 111 evaluations were performed (median 2.8 times/patient). The median change in eGFR per year (ΔeGFR/y) was −2.8 ml/min/1.73 m^2/year. Figure 2 showed that eGFR decreased in most patients. ΔeGFR/y was significantly inversely correlated with ΔTKV/y ($r = -0.674$, $p = 0.000$, Fig. 3), Δu-pro/y ($r = -0.663$, $p = 0.014$), and ΔSAP/y ($r = -0.473$, $p = 0.004$) (Table 3). Multiple linear regression showed that ΔeGFR/y was significantly and independently inversely correlated with ΔTKV/y ($p = 0.039$) (Table 3). Consequently, the changes in TKV are a surrogate marker of renal function in ADPKD patients.

The relationship between the change in TKV per year (ΔTKV/y) and other clinical parameters

Assuming an exponential growth kinetic with a constant growth rate, the median change in TKV per year (ΔTKV/y) was 53.9 ml (Fig. 4). Figure 4 shows that TKV increased in most patients but decreased in some. In 8 of 39 patients

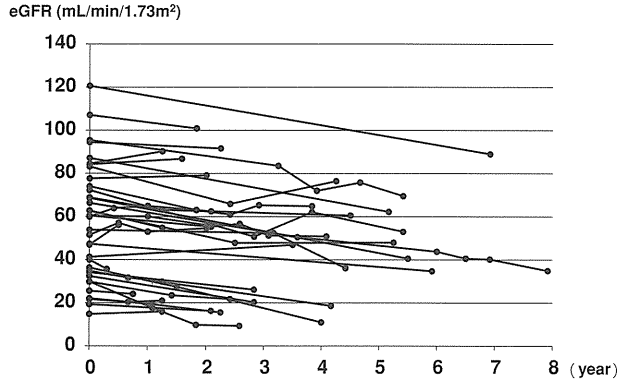

Fig. 2 eGFR decreased in most patients. The median change in eGFR per year (ΔeGFR/y) is −2.8 ml/min/1.73 m^2/year

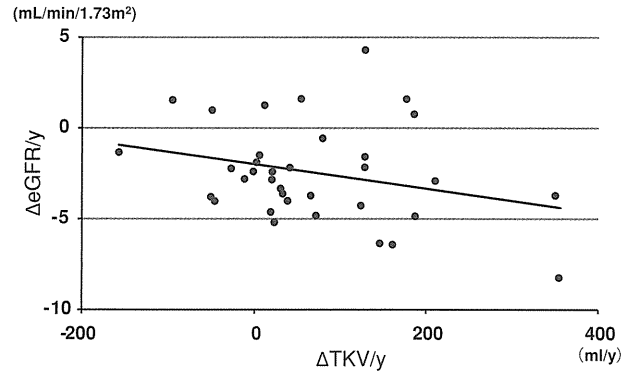

Fig. 3 Relationship between change in GFR per year (ΔeGFR/y) and rate of renal volume growth per year (ΔTKV/y) in 73 subjects with ADPKD ΔeGFR/y is significantly inversely correlated with ΔTKV/y ($y = -0.0067x - 1.9939$, $r^2 = 0.078$, $p = 0.0000$)

(20.5%), a substantial reduction of TKV was seen. The ΔTKV/y was significantly correlated with initial TKV ($r = 0.915$; $p = 0.000$), initial DAP ($r = 0.786$; $p = 0.007$), initial ABI ($r = 0.656$; $p = 0.040$), and change in albuminuria per year (Δu-alb/y) ($r = 0.902$; $p = 0.000$), and inversely correlated with ΔABI/y ($r = -0.770$; $p = 0.009$) (Table 4). Multiple linear regression showed that ΔTKV/y was significantly related to initial TKV ($p = 0.025$) and Δu-alb/y ($p = 0.017$) (Table 4). Accordingly, subjects with greater initial renal volume and greater changes in albuminuria had a significantly larger increase in renal volume.

Discussion

In most patients with ADPKD, renal function typically remains within the normal range for several decades, despite progressive renal enlargement. Compensatory hyperfiltration in surviving nephrons initially maintains serum creatinine levels at or near normal values; when levels start to rapidly rise appreciably above baseline, more than 50% of functioning parenchyma has been destroyed. It is only around the age of 40 years that renal function begins to decrease rather rapidly, leading to end-stage failure within about 10 years [5]. To monitor the progression of ADPKD, GFR has several limitations as a biomarker. GFR often does not decline until renal function damage is well established. Accordingly, GFR has no predictive value in the early stages of the disease, and it only becomes a useful indicator of renal function after major, irreversible damage to renal function has occurred [10]. In ADPKD, by the time that GFR has declined, renal volume has already substantially expanded, because renal cysts have already destroyed much of the renal parenchyma [1]. Consequently, measuring GFR alone has not been sufficient for the assessment of disease progression, especially in the early phase [11].

In Caucasian patients with ADPKD, at baseline, GFR decreased by 2.8 ± 2.8 ml/min/1.73 m^2/year [12] and 2.4 ± 2.8 ml/min/1.73 m^2/year [13] per year. The median ΔeGFR/y in this study was −2.8 ml/min/1.73 m^2/year. Accordingly, our data for the changes in GFR in Japanese ADPKD patients were in agreement with published Caucasian data. However, the rate of decline in the GFR of 2–3 ml/min per year in patients with ADPKD is so small that it is difficult to detect the benefit of any therapies. Thus, a tool that detects small changes in ADPKD early enough has been needed. An impressive body of evidence demonstrates that the kidneys of patients with ADPKD increase progressively in size from birth [1, 8, 10, 12–14]. The CRISP study [1] demonstrated that kidney growth occurs in an exponential fashion and that the growth of kidneys in patients with ADPKD is primarily the result of the growth of cysts.

The combined volume of polycystic kidneys in adults commonly exceeds 4000 ml, as compared with normal volumes of 308 ml in women and 404 ml in men [1, 15]. At baseline, TKV amounted to 1076 cm^3 [1] and increased at a mean rate of a range from 4.0% [12] to 9.4% [14], 24 ± 22 cm^3 [12], 46 ± 55 cm^3 [13], and 54 ± 10 cm^3 [14] per year in several studies. Assuming an exponential growth kinetic with a constant growth rate, the calculated median annual growth volume was 53.9 ml in our study and, hence, very similar to the CRISP results. Since ADPKD progresses in accordance with the increasing size of a very large number of renal cysts, which cause the whole kidney to enlarge, the sequential measurement of total kidney and cyst volume has been suggested as a surrogate marker of disease progression [1, 16]. According to the recent data, the most objective test to assess and monitor disease progression is MR-based estimation of total renal volume. Several studies revealed that the rates of increase in TKV were highly variable and that the patients with fast

Table 3 The relationship between ΔeGFR/y and other clinical parameters

	Univariate analysis		Multivariate analysis	
	r	*p*	*p*	95% CI
Age (years)	−0.074	0.668		
Initial eGFR (ml/min/1.73 m^2)	0.088	0.610		
Initial TKV (ml)	−0.011	0.950		
ΔTKV/y (ml/year)	−0.674	**0.000**	**0.039**	−0.019 to 0.001
Initial proteinuria (mg/day)	0.208	0.280		
Δu-pro/y (mg/day/year)	−0.663	**0.014**	0.971	−0.028 to 0.029
Initial albuminemia (mg/day)	0.190	0.362		
Δu-alb/y (mg/day/year)	0.224	0.507		
Initial SAP (mmHg)	0.014	0.936		
ΔSAP/y (mmHg/year)	−0.473	**0.004**	0.625	−0.020 to 0.146
Initial DAP (mmHg)	0.126	0.466		
ΔDAP/y (mmHg/year)	−0.204	0.233		
Initial BMI (kg/m^2)	−0.300	0.085		
ΔBMI/y (kg/m^2/year)	−0.340	0.057		
Initial baPWV (m/s)	−0.141	0.443		
ΔbaPWV/y (m/s/year)	0.361	0.118		
Initial ABI	−0.317	0.071		
ΔABI/y	−0.304	0.192		

$p < 0.05$ is indicated by boldface

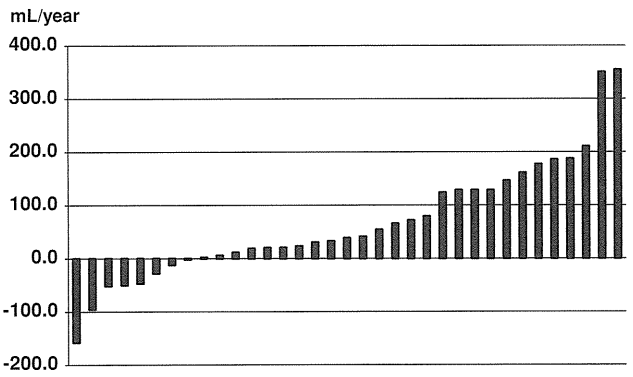

Fig. 4 Waterfall plot: the median change in TKV per year (ΔTKV/y) is 53.9 ml

rates of growth were likely to exhibit more serious declines in GFR than patients who exhibited slower growth rates [10, 17]. It was reported that inverse correlations existed between TKV and GFR [6, 13], and between the rate of increase in kidney volume and the rate of decrease in GFR [12, 13]. CRISP analyzed the results of serial assessment of the total volume of kidneys and cysts in 232 American patients with ADPKD who had preserved renal function at baseline [1] and demonstrated that renal volume exceeding 1500 ml is associated with a decrease in GFR and rapid progression of the disease [1, 2, 5, 11]. The initial TKV, the initial cyst volume, the initial percent cyst volume, and the changes in TKV were significantly greater in the renal failure group than in the normal renal function group ($p < 0.001$) [6, 13, 17]. MRI has been shown to be a more sensitive biomarker of disease progression than either serum creatinine or eGFR, and is already being used as a surrogate outcome for increases in creatinine in clinical trials. Multiple linear regressions showed that ΔeGFR/y was significantly inversely correlated with ΔTKV/y independently in this study (Table 3). Consequently, the changes in TKV are considered a surrogate marker of renal function in Japanese ADPKD patients.

To quantify the progression of ADPKD, sufficient sensitivity and reproducibility are required to enable the measurement of relatively small changes in renal and cyst volume [15]. The error in renal volume estimated using MRI is <5% [18]. Currently, the efficacy of various new drugs has been tested in clinical trials, including the mTOR inhibitors sirolimus (rapamycin) [19] and everolimus [20], the vasopressin V2 receptor antagonist tolvaptan [21], and the somatostatin analogue octreotide acetate [22]. In those trials, indices associated with TKV were standard measures in the assessment of ADPKD progression, although their utility in monitoring individual patients has not been established. Consequently, further studies are needed to verify the volumetric indices as an indicator of disease progression.

It is known that albuminuria increases with disease progression. A previous cross-sectional study showed that overt proteinuria (protein >300 mg/day) was associated with larger renal volumes, higher blood pressures, and lower creatinine clearances in patients with ADPKD [23]. The computed tomographic study of King et al. [12] involving nine patients with ADPKD showed that subjects

Table 4 The relationship between ΔTKV/y and other clinical parameters

	Univariate analysis		Multivariate analysis	
	r	*p*	*p*	95% CI
Age (years)	0.443	0.200		
Initial TKV (ml)	0.915	**0.000**	**0.025**	0.090 to 0.873
Initial proteinuria (mg/day)	0.044	0.905		
Δu-pro/y (mg/day/year)	−0.307	0.388		
Initial albuminemia (mg/day)	0.074	0.840		
Δu-alb/y (mg/day/year)	0.902	**0.000**	**0.017**	2.612 to 16.803
Initial SAP (mmHg)	0.455	0.187		
ΔSAP/y (mmHg/year)	−0.475	0.165		
Initial DAP (mmHg)	0.785	**0.007**	0.668	−31.277 to 44.745
ΔDAP/y (mmHg/year)	−0.330	0.352		
Initial BMI (kg/m^2)	0.631	0.050		
ΔBMI/y (kg/m^2/year)	−0.156	0.666		
Initial baPWV (m/s)	0.323	0.363		
ΔbaPWV/y (m/s/year)	−0.084	0.817		
Initial ABI	0.656	**0.040**	0.348	−3801.65 to 1619.409
ΔABI/y	−0.770	**0.009**	0.443	−10883.187 to 5555.587

$p < 0.05$ is indicated by boldface

with greater initial proteinuria had a significantly larger increase in renal volume and decline in GFR than those with less proteinuria. In this study, the subjects with greater initial renal volume and greater changes in albuminuria had a significantly larger increase in renal volume. Our results are in line with these previous studies, since TKV at baseline was positively correlated with hypertension, hematuria, and albuminuria, and albuminuria was associated with accelerated volume progression [8].

It has been previously reported that vascular endothelial dysfunction was present in small resistance vessels obtained from ADPKD patients. In this study, although eGFR was significantly inversely correlated with PWV on univariate analysis (Table 2), there are no significant correlations between eGFR and PWV on multivariate analysis. Consequently, we could not conclude the causal relationship between vascular endothelial dysfunction and ADPKD.

It is well established that the control of blood pressure is essential to prevent end-stage renal disease (ESRD) in ADPKD patients. We evaluated the efficacy of ARB or ACEI for ADPKD patients supplementarily. In this study, eGFR was significantly reduced in patients with ARB or ACEI compared with the patients without these drugs, mainly presumably because of significant high blood pressure. Consequently, we could not indicate the efficacy of antihypertensive therapy using ARB or ACEI in this study.

One limitation of this study is that it was a retrospective study, and selection bias may have been present. Another limitation is the technique to quantify TKV. We measured TKV on MRI manually, while other techniques are automatic [15]. Manual operation may have some skewedness and inconsistency. Meanwhile, fully automated segmentation is feasible for normal kidneys. However, this operation is exceedingly difficult when evaluating the kidneys of patients with ADPKD, since ADPKD has high variability in kidney morphology [15]. Moreover, markedly enlarged ADPKD kidneys often compress and distort surrounding healthy anatomical structures, which makes automatic discrimination of the anatomical boundaries of the kidneys challenging. Proper assessment of TKV warrants further studies.

To sum up, this study demonstrates a significant relationship between renal volume and renal function in Japanese ADPKD patients without renal insufficiency. Total renal volume possesses sufficient accuracy and reproducibility to be used to assess disease progression. The volume measurements can be used as useful markers for the progression of disease in Japanese ADPKD patients.

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Conflict of interest The authors have declared that no conflict of interest exists.

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ORIGINAL ARTICLE

Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study

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Abstract We (JMAAV [Japanese patients with MPO-ANCA-associated vasculitis] Study Group) performed a prospective, open-label, multi-center trial to evaluate the usefulness of severity-based treatment in Japanese patients with myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA)-associated vasculitis. Patients with MPO-ANCA-associated vasculitis received a severity-based regimen according to the appropriate protocol: low-dose corticosteroid and, if necessary, cyclophosphamide or azathioprine in patients with mild form; high-dose corticosteroid and cyclophosphamide in those with severe form; and the severe-form regimen plus plasmapheresis in those with the most severe form. We followed up the patients for 18 months. The primary end points were the induction of remission, death, and end-stage renal disease (ESRD). Fifty-two patients were registered, and 48 patients were enrolled in this study (mild form, $n = 23$; severe form, $n = 23$; most severe form, $n = 2$). Among the 47 patients

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who received the predefined therapies, 42 achieved remission within 6 months, 5 died, and 1 developed ESRD. Disease flared up in 8 of the 42 patients with remission during the 18-month follow-up period. The JMAAV trial is the first prospective trial for MPO-ANCA-associated vasculitis to be performed in Japan. The remission and death rates were comparable to those in several previous clinical trials performed in western counties. The regimen employed in this trial was tailor-made based on patients' disease severity and disease type, and it seems that standardization can be consistent with treatment choices made according to severity.

Keywords Anti-neutrophil cytoplasmic antibody · Microscopic polyangiitis · Prophylaxis · Pulmonary-limited vasculitis · Severity-based treatment

Introduction

Among small-vessel vasculitides, microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), and allergic granulomatous angiitis (AGA) are known collectively as anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) because of the involvement of ANCA as the common pathogenesis [1]. The major target antigens of ANCA associated with vasculitis are myeloperoxidase (MPO) and proteinase 3 (PR3). MPO-ANCA is related to MPA and AGA, and PR3-ANCA is the marker antibody in WG [2, 3]. MPO-ANCA-associated vasculitis is more common in Japan [4], whereas PR3-ANCA-associated vasculitis is more common in Europe and the United States. Granulomatosis with polyangiitis (GPA) (Wegener's) has been proposed as an alternative name for WG [5].

Untreated patients with severe AAV with multi-organ involvement have a poor prognosis, which can be improved by combination therapy with cyclophosphamide and high-dose corticosteroid [6]. Randomized controlled trials (RCTs) have indicated a rate of AAV remission induction of approximately 90% in 6 months with the standard regimen [7, 8]. As cyclophosphamide induces severe toxicity, there have been many attempts to develop less toxic regimens.

The European CYCAZAREM (cyclophosphamide vs. azathioprine as remission maintenance therapy for AAV) RCT compared the effectiveness of cyclophosphamide and azathioprine in the maintenance of remission [7]. The study population consisted of 155 patients (WG, $n = 95$; MPA, $n = 60$) who achieved remission after induction therapy with oral cyclophosphamide plus prednisolone. The patients were assigned randomly to one of two groups with continuation of either cyclophosphamide or azathioprine. The rates of relapse were not significantly different between the two groups at 18-month follow-up. Thus, this study clearly demonstrated that maintenance of remission could also be achieved with oral azathioprine.

Another European RCT, NORAM (non-renal vasculitis alternative treatment with methotrexate), compared methotrexate and cyclophosphamide with regard to remission induction and maintenance in patients with AAV without significant renal involvement [8]. In this trial, 95 patients with newly diagnosed AAV (89 with WG and 6 with MPA) were assigned to receive methotrexate or cyclophosphamide. At 6 months, 90 and 94% of patients in the methotrexate and cyclophosphamide groups, respectively, had achieved remission. Among the patients who achieved remission, the relapse rate at 18 months was significantly higher in the methotrexate group. Thus, methotrexate was as effective as cyclophosphamide for the induction of remission in patients with non-renal mild AAV, but was associated with a significantly higher relapse rate.

The two RCTs mentioned above included 250 patients with AAV, among whom 184 patients (74%) had WG, presumably related to the epidemiological background. This is a striking difference from the disease prevalence in Japan, where MPA and MPO-ANCA-associated vasculitis are more common [4]. Therefore, caution must be taken in applying the results of these RCTs to Japanese patients. In this regard, a prospective study was performed to clarify the effectiveness of the standard regimen in Japanese patients with MPO-ANCA-associated vasculitis.

Patients, materials, and methods

Study design

The protocol for a prospective, open-label, multi-center trial was developed by the investigators of the Research Group of Intractable Vasculitis, the Research Group of Progressive Glomerular Disease, and the Research Committee of Complications and Treatment of Immunological Disorders, Ministry of Health, Labor, and Welfare (MHLW) of Japan. The trial was registered as "Prospective study of the severity-based treatment protocol for Japanese patients with MPO-ANCA-associated vasculitis (JMAAV)" at the University Hospital Medical Information Network, Clinical Trials Registry (UMIN-CTR; http://www.umin.ac.jp/ctr/index-j.htm, registration number ID 000000867). The

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Patients positive for MPO-ANCA, who had newly diagnosed MPA according to the diagnostic criteria for MPA of the Research Group of Intractable Vasculitis, MHLW of Japan [9], were screened for eligibility. ANCA was tested by enzyme-linked immunosorbent assay (ELISA) for MPO or PR3. Eligible patients were included in the study after providing written informed consent, in accordance with the Declaration of Helsinki.

Exclusion criteria were as follows: (1) age >79 years, (2) peripheral leukocyte count <4000/mm^3, (3) peripheral platelet count <120,000/mm^3, (4) coexistence of active infection, (5) end-stage renal disease (ESRD) requiring hemodialysis, (6) respiratory failure with PaO_2 <60 Torr, (7) liver cirrhosis, (8) malignancy diagnosed within 5 years, (9) pregnancy, or (10) history of cyclophosphamide therapy with a cumulative dose of >10 g.

All patients were stratified into one of three categories based on their disease severity and distribution of organ involvement. (1) Severe form: this form included a generalized type (MPA with involvement of more than two organs), a pulmo-renal type (glomerulonephritis plus either limited pulmonary hemorrhage or extended interstitial pneumonia), and a rapidly progressive glomerulonephritis (RPGN) type. (2) Most severe form: this form was defined as patients with diffuse alveolar hemorrhage, intestinal perforation, acute pancreatitis, cerebral hemorrhage, or concurrent anti-glomerular basement membrane antibodies. This form also included patients with the severe form who were resistant to the severity-based treatment protocol described below. (3) Mild form: this form included a renal-limited type (except for RPGN), a pulmonary-limited type (except for pulmonary hemorrhage), and other mild forms. Patients were treated according to the predefined protocol described below.

Severity-based treatment protocol for induction of remission

To induce remission, patients with the severe form were treated with a regimen consisting of high-dose prednisolone (0.6–1.0 mg/kg/day) plus oral cyclophosphamide (0.5–2.0 mg/kg/day). Intravenous methylprednisolone (0.5–1.0 g/day for 3 days) was also considered in these patients. Instead of oral administration, the use of intravenous cyclophosphamide (0.5–0.75 g/m^2, monthly) was also allowed. In patients with impaired renal function (serum creatinine level >1.8 mg/dL) or those older than 60 years, the dose of cyclophosphamide was reduced to 75–50%. Patients with the RPGN type were further evaluated depending on their age, serum creatinine level, C-reactive protein (CRP), and presence of lung involvement. Details of this scoring system were described elsewhere [10]. Briefly, the scoring system employed was as follows. Score 1 included either serum creatinine ≥3 and <6 mg/dL, age 60–69 years, or CRP ≥2.6 and <10 mg/dL. Score 2 included either serum creatinine ≥6 mg/dL, age ≥70 years, or CRP ≥10 mg/dL, or the presence of lung involvement. Score 3 included the induction of hemodialysis. Patients were categorized into four clinical grades by the sum of the scores. Grades 1, 2, 3, and 4 are equivalent to the sums of the scores 0–2, 3–5, 6–7, and 8–9, respectively. The regimen for the patients classified as grade 1–2 and age ≥70 years or under hemodialysis consisted of prednisolone at 0.6–0.8 mg/kg/day. The regimen for patients classified as grade 3–4 and age ≥70 years or under hemodialysis consisted of intravenous methylprednisolone (0.5–1.0 g/day for 3 days) followed by prednisolone at 0.6–0.8 mg/kg/day. The use of oral cyclophosphamide (starting at 25 mg/day) was also allowed based on the disease activity. The regimen for the patients classified as any grade and age <70 years and without hemodialysis was the same as that for the generalized type and renal-pulmonary type of the severe form mentioned above. Cyclophosphamide, however, was not necessarily used, depending on the renal function.

Patients with the most severe form were treated with plasmapheresis (2.0–3.0 L/day for 3 days; several sessions) together with the regimen for the severe form described above.

Patients with the mild form were treated with oral prednisolone (0.3–0.6 mg/kg/day). Oral immunosuppressive agents (cyclophosphamide or azathioprine, 0.5–1.0 mg/kg/day or 25–75 mg/day, respectively) were also allowed.

Treatment protocol for maintenance of remission and prophylaxis against infection

Patients with any form who had attained remission received maintenance therapy for an additional year, consisting of prednisolone (5–10 mg/day), and in most cases oral cyclophosphamide or azathioprine (25–75 mg/day). Prophylaxis against infection, if necessary, was considered for each patient, and therefore no systematic regimen for prophylaxis was predetermined.

Definitions

Remission was defined as the absence of clinical manifestations of active vasculitis and a Birmingham Vasculitis Activity Score 2003 (BVAS2003) of 0–1 point [11]. Relapses were defined as the recurrence or development of at least one manifestation of vasculitis. The involvement of each organ was diagnosed as follows: (a) localized pulmonary hemorrhage was defined as a hemorrhagic shadow

in <30% of the whole lung area on chest X-rays. Generalized interstitial lung fibrosis was defined as a fibrotic shadow in >30% of the whole lung area on chest X-rays, but lacking pulmonary failure, with PaO_2 <60 Torr. (b) Patients with RPGN were defined as those with hematuria, proteinuria, and/or urinary casts who developed renal failure within several weeks or months. Although not a necessary sign, increases in serum creatinine level more than twice in a month may aid in the diagnosis. (c) Cardiac involvement was defined as the occurrence of fresh myocardial infarction, pericarditis, or myocarditis. (d) Nervous system involvement was defined as fresh cerebral bleeding or infarction, mononeuritis multiplex, or organic consciousness disturbance. (e) Gastrointestinal involvement was defined as melena, pancreatic necrosis, or abnormal results on liver function tests. (f) Skin involvement was defined as multiple purpura or skin ulcers. (g) Involvement of the eyes and ear/nose/throat regions was defined as scleritis, uveitis, retinitis, optic neuritis, acute otitis media, acute internal otitis, or hemorrhagic rhinitis.

Evaluation

Study assessments were performed at entry, and at 6 weeks, 12 weeks, and 6 months, then every 3 months for 12 months, and at relapse. Assessments included complete blood count, measurement of the erythrocyte sedimentation rate (ESR), CRP, serum creatinine, liver enzymes, urinalysis, MPO-ANCA, and chest radiography. High-resolution computed tomography of the lung and pulmonary function tests such as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and carbon monoxide diffusion capacity (DLCO) were performed as required. BVAS was scored at every visit. The vasculitis damage index (VDI) [12] was scored at entry and then once every 6 months for 18 months. The Short-Form 36 functional questionnaire (SF-36) was also assessed at entry and then once every 6 months for 18 months. Adverse events were graded for severity according to predefined criteria, and their relationships to the trial medications were assessed.

Study end points

The primary end points were induction of remission at 6 months, and severe adverse events including death and ESRD. As secondary end points, the effectiveness and safety of the standard protocols, as well as health-related quality of life (HRQOL), were evaluated. With regard to the effectiveness, we evaluated time from initial treatment to remission; time from remission to relapse, if any; relapse rate; and VDI. With regard to safety and HRQOL, all adverse events and SF-36 were evaluated.

Statistical analysis

Quantitative variables were compared using Student's *t*-test or the Mann–Whitney nonparametric test. Categorical variables were compared using the χ^2 test or Fisher's exact test. In all analyses, $P < 0.05$ was taken to indicate statistical significance. Kaplan–Meier analysis was used to evaluate patient survival. SF-36 domain scores were calculated using the norm-based scoring algorithm, in which the scores were standardized to a mean of 50 and SD of 10 in the Japanese general population [13]. A one-sample *t*-test was used to determine whether the SF-36 domain scores of study subjects differed significantly from the Japanese general population norm. Repeated measures analysis of variance was used to test for changes with time in the SF-36 domain scores.

Results

Outcome of the study

Patients were enrolled in the study between July 2004 and September 2006. As illustrated in Fig. 1, 52 patients were screened, and 4 were excluded according to the criteria described above. The remaining 48 patients received the severity-based treatment: 2, 23, and 23 patients received treatment for the most severe, severe, and mild forms, respectively. One patient from the mild-form group was lost to follow-up within 6 weeks, and therefore the study population for further analysis consisted of the remaining 47 patients.

One patient in the severe-form group, with an RPGN type, started hemodialysis on day 4 and developed ESRD. Three patients died without remission, at 9 days, 2.5 months, and 3 months, respectively. At 6 months, 42 patients had achieved remission; 1, 20, and 21 of these patients were from the most severe form, severe form, and mild-form groups, respectively. One patient in the severe-form group died after achieving remission, without relapse, at 10 months. Eight patients showed relapse (3 and 5 from the severe-form group and the mild-form group, respectively). Among the relapsed patients, re-remission occurred in 7, while the remaining patient from the severe-form group died of sepsis due to opportunistic infection at 11 months. At the last observation, 32 patients had maintained remission without death or relapse; 1 in the most severe-form group, 15 in the severe-form group, and 16 in the mild-form group.

Baseline characteristics of patients

Patients were further stratified based on their organ involvement as described above. Table 1 shows the

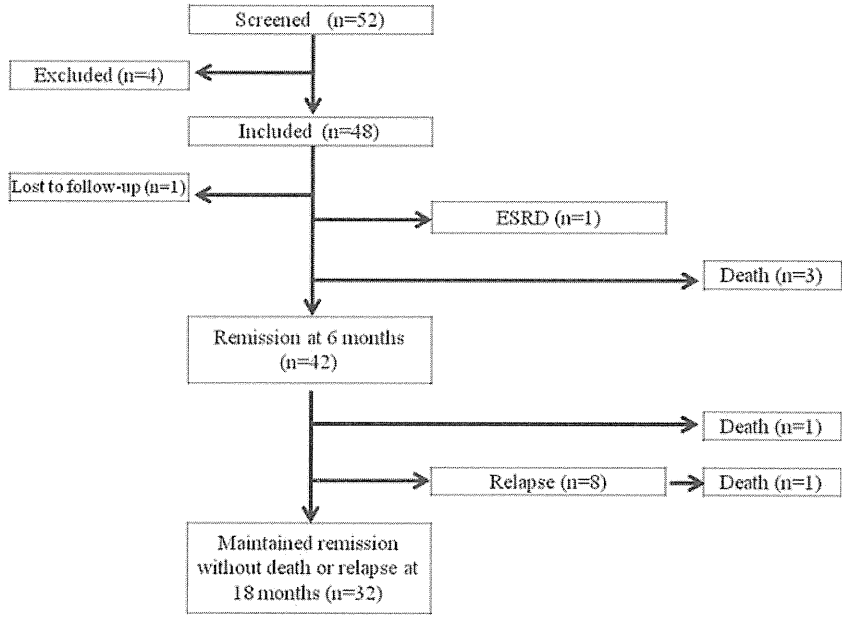

Fig. 1 Outcomes of the patients registered in the Japanese patients with MPO-ANCA-associated vasculitis (JMAAV) trial. *ESRD* End-stage renal disease

Table 1 Baseline characteristics of patients stratified by severity

Severity/Type	n	Age mean (range)	Gender M/F (%Male)	Renal involvement n (%)	Pulmonary involvement n (%)	BVAS mean (SD)	MPO-ANCA (EU/mL) mean (SD)	Serum creatinine (mg/dL) mean (SD)
Most severe	2	66.5 (62-71)	0/2 (0)	2 (100)	2 (100)	11.5 (12.0)	406.5 (19.1)	3.70 (1.90)
Severe	23	67.6 (56-76)	12/11 (52.2)	23 (100)	9 (30.1)	15.3 (9.0)	648.7 (1112.9)	3.33 (2.71)
Generalized	3	64.3 (57-74)	3/0 (100)	3 (100)	2 (66.7)	25.7 (7.2)	522.7 (78.2)	1.40 (0.53)
Pulmo-renal	4	68.8 (56-75)	1/3 (25)	4 (100)	4 (100)	15.8 (5.7)	448.5 (353.0)	2.36 (2.15)
RPGN	16	67.9 (56-76)	8/8 (50)	16 (100)	3 (18.8)	13.2 (13.2)	722.4 (1330.8)	3.93 (2.91)
Mild	23	65.7 (26-79)	5/18 (21.7)	11 (47.8)	11 (47.8)	9.2 (8.2)	199.6 (169.4)	0.96 (0.67)
Renal-limited	4	59.3 (45-69)	1/3 (25)	4 (100)	0	14.3 (7.9)	164.2 (172.3)	1.78 (1.14)
Pulmonary-limited	6	66.3 (57-75)	1/5 (16.7)	0	6 (100)	3.3 (3.1)	135.3 (94.0)	0.61 (0.18)
Miscellaneous	13	67.4 (26-79)	3/10 (23.1)	7 (53.9)	5 (38.5)	10.3 (9.0)	240.2 (193.0)	0.87 (0.43)
Total	48	66.6 (26-79)	17/31 (35.4)	36 (75)	22 (45.8)	12.2 (9.1)	423.4 (801.6)	2.20 (2.28)

BVAS Birmingham vasculitis activity score, *MPO-ANCA* myeloperoxidase-anti-neutrophil cytoplasmic antibodies, *RPGN* rapidly progressive glomerulonephritis, *SD* standard deviation

numbers of patients with each type and their baseline characteristics. One of the 2 patients in the most severe-form group had a cerebral bleeding type, and the other had resistant severe disease. No other types defined above were included in the most severe form group. RPGN type was most frequent among the severe-form group. The mean age of the patients was 66.6 years, and the majority of the patients (all except for two patients) ranged in age between 56 and 79 years. The patients were predominantly female. Males were more common in the severe-form group (52.2%) and much less common in the mild-form group (21.7%). In total, 75% of the patients showed renal involvement, and 45.8% showed pulmonary involvement.

The mean BVAS new/worse of the 48 patients enrolled in this study was 12.2 at baseline. The BVAS in the severe-form group was significantly higher than that in the mild-form group ($P < 0.05$). In the severe-form group, the generalized type showed the highest BVAS, followed by the pulmo-renal type, and the RPGN type.

The mean titer of MPO-ANCA at baseline was 423 EU/mL. The highest average titer was detected in the severe-form group; in the patients in this group, the RPGN

type showed the highest average titer, followed by the generalized type, and the pulmo-renal type. PR3-ANCA was tested in 25 patients, all of whom showed negative results.

The mean serum creatinine level at baseline was 2.2 mg/dL. The highest average level was detected in the severe-form group; in these patients, the RPGN type showed the highest average level, followed by the pulmo-renal type, and the generalized type.

Time courses of changes in BVAS, MPO-ANCA, and serum creatinine

Figure 2a shows the time courses of changes in BVAS in the severe- and mild-form groups in the present study population. The scores declined rapidly during the first 6 weeks. However, even at 6 weeks, the mean BVAS in the severe-form group was significantly higher than that in the mild-form group ($P < 0.05$). The scores in the severe- and mild-form groups were increased at 6 months and thereafter, reflecting the 8 patients showing relapse described above. On the other hand, there were no significant differences in BVAS scores for persistent disease between the baseline and any other examination time points (data not shown). Among the forms, however, the BVAS persistent scores in the severe-form group were significantly higher than those in the mild-form group at all examination time points (data not shown).

Figure 2b shows the time courses of changes in the MPO-ANCA titers in the severe- and mild-form groups. In both forms, the titer declined quickly during the first 6 weeks, and became negative at 9 months.

Figure 2c shows the time courses of changes in serum creatinine levels in the severe- and mild-form groups. In the severe-form group, the level decreased rapidly to 1.8 mg/dL during the first 6 weeks, and remained relatively constant thereafter. In contrast, the creatinine level in the mild-form group remained within the normal range throughout the observation period.

VDI

The mean ± SD VDI values at the baseline and at 18 months were 2.2 ± 2.1 (median 2, range 0–12) and 3.2 ± 2.9 (median 2, range 0–12), respectively. Compared with VDI values in the CYCAZAREM trial [7], where the mean VDI (95% confidence interval) values at baseline and at 18 months were 1.3 (1.0–1.6) and 2.5 (2.1–3.0), respectively, those in the present trial were higher by 0.9 and 0.7, respectively.

Both the baseline VDI and the VDI at 18 months were significantly higher in the severe-form group than in the mild-form group ($P = 0.004$ for baseline and $P = 0.001$ for 18 months). The baseline VDI in patients with remission ($n = 42$) was 1.71 ± 1.55, which was significantly lower than that in patients without remission ($n = 5$), 2.61 ± 1.52 ($P < 0.001$).

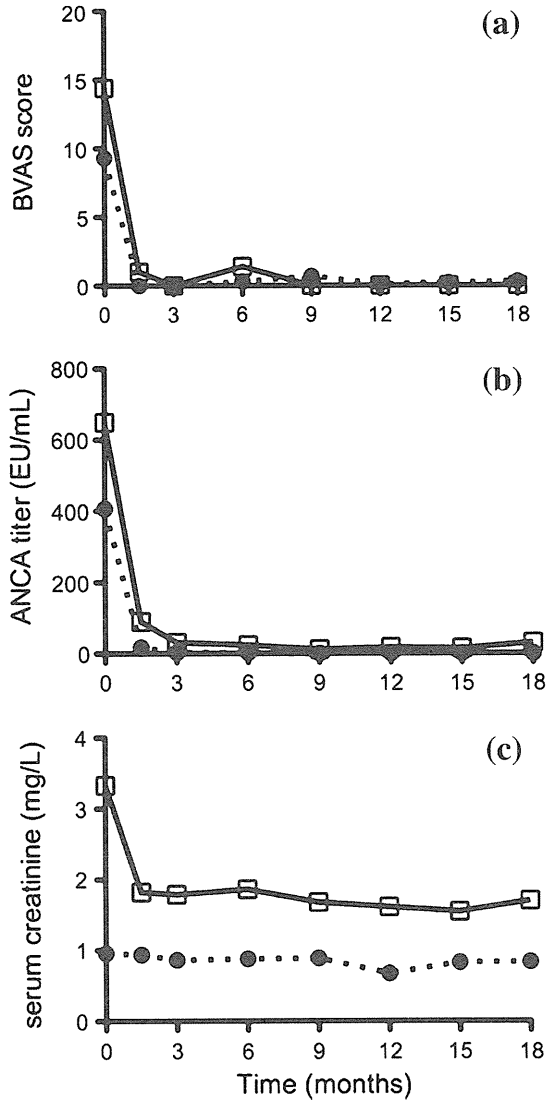

Fig. 2 Time courses of changes in the Birmingham vasculitis activity score (BVAS), myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-*ANCA*) titer, and serum creatinine. The mean values of **a** BVAS, **b** ANCA titers, and **c** serum creatinine in each group stratified according to severity are plotted at 6 weeks, 3 months, 6 months, 9 months, 12 months, 15 months, and 18 months. *Open squares/solid lines* and *closed circles/dotted lines* indicate severe- and mild-form groups, respectively. The data for the most severe-form group were omitted from the figure as this group included only a single patient

The correlation between VDI and BVAS was studied. Patients with baseline BVAS persistent of ≥4 ($n = 22$) showed a significantly higher VDI (4.32 ± 3.70) at 18 months than those with BVAS persistent of <4 ($n = 25$), in whom VDI was 2.29 ± 1.61 at 18 months ($P = 0.024$). However, there was no significant correlation

between VDI and BVAS new/worse (data not shown). Therefore, the baseline value of BVAS persistent seemed to be important for indicating organ damage during the course of treatment of AVV.

SF-36

Of the 48 patients enrolled in the study, 32 had completed the SF-36 questionnaire at baseline. The mean norm-based scores for SF-36 domains at baseline were significantly lower than the Japanese general population norm. The lowest value (mean ± SD) was found in physical functioning (27.3 ± 18.9), followed by role physical (31.5 ± 15.3), role emotional (37.4 ± 15.3), social functioning (39.0 ± 13.8), general health (41.5 ± 10.5), and mental health (43.9 ± 11.2). Patients with remission showed significant improvements in all SF-36 domains, except for general health and role emotional. The physical components had improved significantly but remained considerably impaired at the 18-month follow-up, whereas the mental components approximated to the Japanese general population norm by 6 months.

Remission

As described above, 42 patients achieved remission. As illustrated in Fig. 3a, the majority of patients ($n = 36$) had achieved remission by the first 6 weeks, followed by 6 patients within 3 months, and the last patient by 6 months. The overall remission induction rate was 89.4% (42/47).

Table 2 presents a summary of the remission induction therapy employed in each form/type of patient. All patients received oral prednisolone, with a mean initial dose of 37.5 mg/day. The highest and lowest mean initial doses were observed in the generalized type of the severe form and the pulmonary-limited type of the mild form, respectively. Sixteen patients received only glucocorticoid without any immunosuppressive agents (7 of 23 patients in the severe-form group and 9 of 23 patients in the mild-form group). Six of 16 patients with the RPGN type and 3 of 6 patients with the pulmonary-limited type received no additional immunosuppressive agents.

Death and ESRD

A total of 5 patients died in this prospective study. As shown in Fig. 3b, death occurred at 9 days, 2.5 months, 3 months, 10 months, and 11 months after the start of the treatment in these 5 patients. Of the 5 deaths, only one was considered to be disease-associated; this death occurred on day 9 in a patient with the most severe form, cerebral bleeding type, despite intensive treatment including high-dose glucocorticoid and intravenous cyclophosphamide,

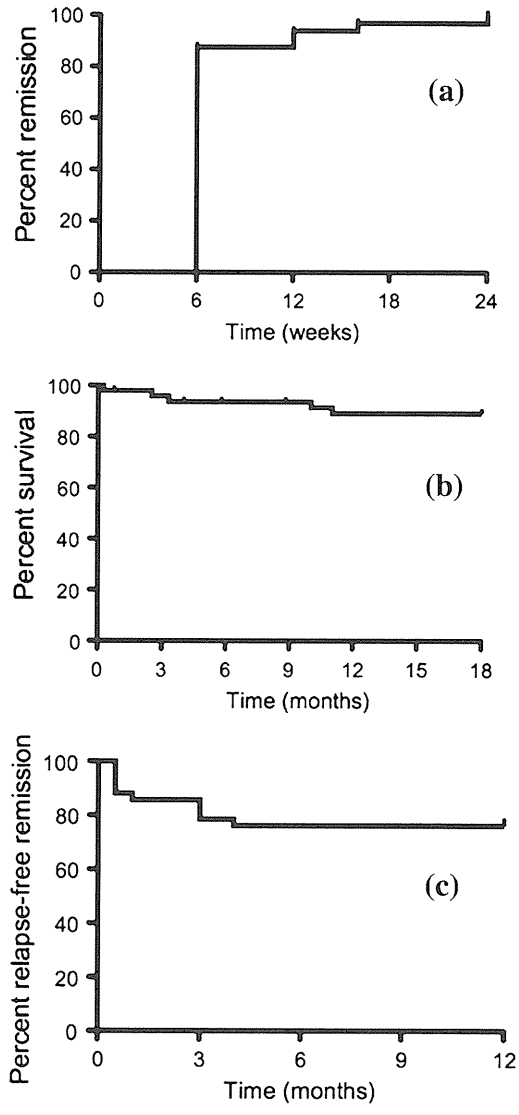

Fig. 3 Kaplan-Meier estimates of time to remission induction, survival, and relapse. **a** Time to remission induction within 6 months after the start of treatment. The *vertical axis* indicates the percentage of patients with remission among 47 patients receiving predefined treatment protocols. **b** Survival during the 18-month observation period. The *vertical axis* indicates the percentage of patients who survived among 47 patients receiving predefined treatment protocols. **c** Time from remission to relapse. The *vertical axis* indicates the percentage of relapse-free patients among 42 patients who achieved remission. The *horizontal axes* indicate time from the start of treatment in **a** and **b**, and time from remission in **c**

but no plasmapheresis. In the 4 remaining patients who died the disease was the severe form in 3 and mild form in 1. Two patients died after remission: one due to opportunistic infection, and the other due to pulmonary failure, presumably associated with *Pneumocystis jirovecii* pneumonia (PCP). The remaining two patients died without remission, at 2.5 and 3 months: one due to cerebral hemorrhage as an atherosclerotic event and the other due to interstitial lung disease of undetermined origin. In this trial,

Table 2 Remission induction therapy

Severity/Type	n	mPSL Pulse	Oral PSL plus (-)	IVCY	POCY	AZA	MTX	PE	Mean PSL (mg/day)
Most severe	2	2	0	2	0	0	0	1	50
Severe	23	13	7	15	1	0	0	1	41
Generalized	3	2	0	3	0	0	0	0	55
Pulmo-renal	4	2	1	3	0	0	0	0	39
RPGN	16	9	6	9	1	0	0	1	38
Mild	23	4	10	7	3	2	1	0	33
Renal-limited	4	3	2	2	0	0	0	0	46
Pulmonary-limited	6	0	3	1	1	0	1	0	27
Miscellaneous	13	1	5	4	2	2	0	0	37
Total	48	19	17	24	4	2	1	2	37.5

mPSL Methylprednisolone, *IVCY* intravenous cyclophosphamide, *POCY* oral cyclophosphamide, *AZA* azathioprine, *MTX* methotrexate, *PE* plasma exchange, *PSL* prednisolone

Table 3 Remission maintenance therapy

Severity/Type	Total(*)	Oral prednisolone plus(*) None	IVCY	AZA	MZB	TAC
Most severe	1(0)	0	1(0)	0	0	0
Severe	20(3)	14(2)	1(0)	4(1)	1(0)	0
Generalized	3(1)	0	0	3(1)	0	0
Pulmo-renal	3(0)	3(0)	0	0	0	0
RPGN	14(2)	11(2)	1(0)	1(0)	1(0)	0
Mild	21(5)	16(3)	3(1)	1(0)	0	1(1)
Renal-limited	3(1)	3(1)	0	0	0	0
Pulmonary-limited	6(3)	4(1)	1(1)	0	0	1(1)
Miscellaneous	12(1)	9(1)	2(0)	1(0)	0	0
Total	42(8)	30(5)	5(1)	5(1)	1(0)	1(1)

Numbers in parentheses indicate numbers of relapsed patients

IVCY Intravenous cyclophosphamide, *AZA* azathioprine, *MZB* mizoribin, *TAC* tacrolimus

one patient with severe form, RPGN type, underwent hemodialysis on day 4 and developed ESRD despite high-dose glucocorticoid therapy.

Relapse

Table 3 shows the remission-maintenance therapy administered in the 42 patients after achieving remission. Thirty patients (71.4%) received only glucocorticoid, and the remaining 12 patients also received immunosuppressive agents: 5 patients received intravenous cyclophosphamide and 5 received azathioprine. Relapse occurred in 8 of the 42 patients (relapse rate = 19.0%); relapse occurred in 3 of 20 patients with the severe form (relapse rate = 15.0%), but 5 cases of relapse occurred among the 21 patients with the mild form (relapse rate = 23.8%). Of the latter 5 relapses, 4 occurred in 17 patients who received no immunosuppressant. As shown in Fig. 3c, all relapses occurred between 12 and 30 weeks after the induction of remission. The relapse group had significantly higher BVAS new/worse values at 6 months than the non-relapse group (3.75 ± 5.78 vs. 0.125 ± 0.554, respectively; $P = 0.0001$). However, there was no significant difference in BVAS persistent values between the relapse and non-relapse groups (3.75 ± 3.73 vs. 3.34 ± 2.72, respectively). There were no significant differences in several serological markers, such as CRP and ANCA titers, between the relapse and non-relapse groups (data not shown).

Adverse events

During the 18-month observation period, 29 events of infection of grade 3 or higher were observed. Among these, bacterial infection was noted in 11 events (10 patients): 8 events were grade 3, 2 were grade 4, and the remaining 1 was grade 5. Fungal infection was observed in 6 events (5 patients): 3 cases of aspergillosis and 3 cases of candidiasis (1 patient developed both aspergillosis and

candidiasis). Of these 6 events, 3 were associated with aspergillus pneumonia without prophylactic antifungal agents. In total, however, fungal infection was observed in 1 of 13 patients with prophylaxis and 4 of 35 without prophylaxis (no significant difference, $P > 0.05$).

There were 7 viral infection events (in 7 patients): 4 with varicella-zoster virus (VZV), 2 with cytomegalovirus (CMV) (1 encephalitis and 1 positive antigenemia), and 1 with hepatitis C virus (HCV) (the hepatitis occurred in an HCV carrier). All patients with VZV developed herpes zoster and one patient with CMV developed encephalitis while receiving cyclophosphamide.

There were 3 PCP events (in 3 patients). Of the 48 patients enrolled in this study, 31 received prophylactic trimethoprim-sulfamethoxazole (TMP-SMX), while the remaining 17 did not. Two patients with PCP did not receive prophylaxis, and the other patient developed PCP 2 months after prophylaxis was stopped due to liver damage. Thus, no patients who received prophylaxis developed PCP.

Other adverse events included diabetes mellitus (9 events), bone fracture (3 events), cerebral vascular events (3 events), and cardiac vascular event (1 event). Two of the cerebral vascular events were of grade 5.

Discussion

We performed a prospective, open-label, multicenter trial (JMAAV) to evaluate the usefulness of a severity-based regimen for Japanese patients with MPO-ANCA-associated vasculitis. In this trial, patients were stratified into 3 severity groups and 12 disease types, and then received predetermined severity- and type-based protocols. These protocols were designed to choose an appropriate treatment regimen and to promote prediction of the outcome for each patient. The rates of remission, death, ESRD, and relapse obtained in the trial were comparable to those reported previously in European RCTs [7, 8] with minor differences. Thus, tailor-made treatment based on patients' disease severity and disease type seemed to be useful in determining treatment regimens. The validity of the stratification we used, however, is also a matter of investigation in that it is related to other severity-based classifications, such as the five-factor score used by the French study group [14, 15].

Another finding of this trial was the concept of pulmonary-limited vasculitis. To date, the only organ-limited ANCA-associated vasculitis has been renal-limited vasculitis [16]. Six patients with only pulmonary involvement were included in the JMAAV trial. These patients were positive for MPO-ANCA, and showed interstitial lung disease without other major organ involvement. It may be possible to designate this type as pulmonary-limited vasculitis, another type of organ-limited vasculitis. As renal-limited vasculitis includes a wide spectrum of renal damage, from mild glomerulonephritis to RPGN, pulmonary-limited vasculitis may also include pulmonary lesions of varying severity. Further prospective studies are required to clarify these points.

Recently, the British Society of Rheumatology (BSR)/British Health Professionals in Rheumatology (BHPR) and the European League Against Rheumatism (EULAR) issued guidelines and recommendations, respectively, dividing patients with ANCA-associated vasculitis into 3 (localized/early systemic, generalized, and severe) [17] and 5 categories (localized, early systemic, generalized, severe, and refractory) [18], respectively, and recommended category-based treatment. These recommendations were based on several RCTs dealing with large numbers of patients with WG, and therefore caution is required in applying them to Japanese patients with MPO-ANCA-associated vasculitis. However, these recommendations also referred to precise dose reduction of cyclophosphamide and adjunctive therapy including prophylaxis against opportunistic infections, which must also be considered in the treatment of Japanese patients.

In our trial, two cases of grade 4 and 1 case of grade 5 infection (death) were observed as treatment-related severe infections. All of these patients showed urinary tract infection by *Escherichia coli*, which occurred during remission-maintenance treatment with glucocorticoid and cyclophosphamide. Oral cyclophosphamide or azathioprine was indicated as an immunosuppressive agent during remission maintenance in the JMAAV protocol, but the agents were employed at the discretion of the attending physician. As the CYCAZAREM, WEGENT (Wegener's granulomatosis-entretien trial) [19], and IMPROVE (international mycophenolate protocol to reduce outbreaks of vasculitides randomized trial) trials [20] have indicated that azathioprine is the best adjunctive immunosuppressant during maintenance treatment, the use of this agent for MPA patients should be analyzed in future trials. In addition, a tapering protocol was not determined in the JMAAV trial, and therefore the total amounts of glucocorticoid administered were greater than those outlined in the European recommendations (data not shown). This greater amount seemed to be associated with several glucocorticoid-associated adverse events, including infection.

Prophylaxis is another countermeasure to cope with opportunistic infection. In the JMAAV trial, prophylactic protocols such as the use of TMP-SMX for PCP and the use of antifungal agents for fungal infection were not precisely determined. Three patients without prophylaxis suffered from PCP, whereas there were no cases of PCP among patients with prophylactic TMP-SMX. This result indicated that TMP-SMX should be recommended to prevent PCP in

future trials in Japan. Although there were no significant differences in the incidences of fungal infection between those who received and those who did not receive prophylactic antifungal agents, patients at high risk of severe pulmonary fungal infection should receive prophylactic antifungal agents.

The relapse rate in the JMAAV trial was 19%, which was higher than that in the MPA subgroup (8%) and as high as that in the WG subgroup (18%) in the CYCAZAREM trial [7]. In our trial, the relapse rate was highest in patients with the mild form, especially in those with the pulmonary-limited type (3 cases of relapse in 6 patients), followed by those with the renal-limited type (1 relapse in 3 patients). Although all patients in the CYCAZAREM trial were treated with oral cyclophosphamide as well as glucocorticoid to induce remission, the use of cyclophosphamide was not obligatory in our trial, especially in our regimen for patients in the mild-form group. This may explain the differences in relapse rates between the trials. Further prospective studies are required to evaluate whether cyclophosphamide and azathioprine may be essential for the induction and maintenance of remission, respectively, for a certain population of patients in the mild-form group.

Health-related quality of life (HRQOL) in our trial showed considerable deterioration in patients with MPO-ANCA-associated vasculitis before treatment. During 18 months of follow-up, there were significant improvements in all SF-36 domains, except for general health and role emotional, in patients who achieved and sustained remission during the follow-up period. Therefore, the development of more effective treatment strategies for MPO-ANCA-associated vasculitis may be required to achieve better HRQOL.

In conclusion, the first prospective trial for Japanese patients with MPO-ANCA-associated vasculitis, the JMAAV trial, revealed the usefulness of severity-based treatment, and indicated the possible disease entity of "pulmonary-limited vasculitis" as a type of organ-limited ANCA-associated vasculitis. To achieve better outcomes, we propose several points to improve the treatment protocol: i.e., a glucocorticoid-tapering protocol, the use of less toxic immunosuppressants such as azathioprine in remission-maintenance therapy, and intensive prophylaxis for PCP or profound fungal infection.

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Conflict of interest None.

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ORIGINAL ARTICLE

Estimation of BVAS in patients with microscopic polyangiitis in Japan

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Abstract The validity of the Birmingham Vasculitis Activity Score (BVAS) as an index of disease activity and a predictor of the prognosis and outcome in patients with MPA has not yet been established in Japan. We conducted a retrospective study of the data of 73 patients with MPA who were followed up for at least 2 years. We divided the patients into two groups according to the BVAS, namely, the high-BVAS group (≥16) and the low-BVAS group (<16), and compared the clinical characteristics. In addition, the distribution of the BVAS items in the patients and the items contributing to the total score in MPA patients were analyzed. Remission was achieved in 85% of patients at 1 month. There were no significant differences in the serum CRP, creatinine (Cre), or MPO-ANCA between the high- and low-BVAS group; however, the survival time was significantly shorter (p=0.048) and the mortality rate significantly higher in the high-BVAS group (p=0.04). The items of the BVAS contributing to the total score were motor neuropathy, sensory neuropathy, pulmonary infiltrate, hematuria, proteinuria, Cre ≥5.6 mg/dL, hypertension, scleritis, rise in Cre by ≥30%, and myalgia. BVAS was found to be a useful tool for determining the disease activity and outcome in patients with MPA in Japan. The initial BVAS was also predictive of the mortality and survival time and can also be used as a prognostic tool; therefore, use of the tool may facilitate the selection of appropriate treatment.

Keywords BVAS · Disease activity · MPA

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Introduction

Microscopic polyangiitis (MPA) is a systemic vasculitis characterized histologically by pauci-immune necrotizing small-vessel vasculitis, without granulomatous inflammation. The American College of Rheumatology published classification criteria for Wegener's granulomatosis (WG), Churg–Strauss syndrome (CSS), and polyarteritisnodosa (PAN), but not MPA, while the Chapel Hill Consensus Conference (CHCC) recommended definitions for WG, CSS, and MPA. The CHCC definitions were not intended for classification, but for providing a method for describing MPA [1–4]. Watts et al. recently reported an algorithm, derived by consensus, for systemic vasculitis, for reevaluating existing definitions and developing new criteria [5]. However, the classification of vasculitis including MPA has been controversial for many years.

The typical clinical manifestations of MPA are rapidly progressive glomerulonephritis and alveolar hemorrhage. The disease is characterized by complex multisystem processes that usually threaten vital organs and are associated with substantial morbidity and increased mortal-

ity. MPA also belongs to the group of ANCA-associated vasculitides, and 75–80% of patients have myeloperoxidase (MPO)-ANCA [6].

The clinico-epidemiological characteristics of MPA show geographic variations. According to a nationwide, hospital-based survey, the number of patients with MPA is higher than that with WG in Japan [7].Therefore, it is important to establish evidence for Japanese patients with MPA.

The current standard assessment tool for scoring disease activity in patients with systemic vasculitis is the Birmingham Vasculitis Activity Score (BVAS). The BVAS is a clinical index of disease activity that is based on symptoms and signs pertaining to nine separate organ systems. Disease features are only considered when they are attributable to active vasculitis [8–11]. We examined the association between the BVAS and the activity of MPA, which has not previously been analyzed in detail in Japan.

Patients and methods

Patients

Among the patients who were diagnosed as having MPA between 1995 and 2006 at the Department of Medicine of the Kidney Center at Tokyo Women's Medical University, Department of Nephrology at Kameda Medical Center, Department of Nephrology at Saiseikai Kurihashi Hospital, and Department of Nephrology at Tokyo Metropolitan Komagome General Hospital, the data of 73 patients were reviewed. The diagnosis of MPA was established by the presence of the characteristic clinical features and histological findings, and all the patients satisfied the criteria proposed by the CHCC for MPA. Inclusion criteria for MPA were the following signs and symptoms, in variable combinations: (1) presence of RPGN and/or alveolar hemorrhage, which could be associated with other systemic manifestations of vasculitis; (2) histologic demonstration of small-sized vessel vasculitis or segmental pauci-immune necrotizing glomerulonephritis (GN); or (3) symptoms suggesting small-vessel involvement, e.g., purpura, without GN and/or alveolar hemorrhage [6].

Only patients with MPA were included, and patients with other small-vessel vasculitides, such as renal-limited vasculitis (RLV), WG, and CSS, were excluded from this study. For each patient, the following data were recorded: gender, age, clinical features (including symptoms, signs and organ involvement at presentation, and duration of follow-up), laboratory data, treatment, outcome, and cause of death. Laboratory data included 24-h urinary protein excretion (in grams/day), urinary red blood cell counts (per HPF), serum creatinine (in milligrams per deciliter), serum albumin (in grams per deciliter), estimated glomerular filtration rate (in milliliters per minute/1.73 m^2) [12], serum immunoglobulin G (in milligrams per deciliter), and serum C-reactive protein (CRP, in milligrams per deciliter). Serum titers of MPO-ANCA and PR3-ANCA were measured by enzyme-linked immunosorbent assay (SRL Inc., Tokyo, Japan). Patients were observed for a follow-up period of at least 2 years, and the laboratory data were measured at the time of diagnosis, at 3 months, 6 months, and 2 years after the diagnosis. Same researcher scored BVAS each time.

Evaluation criteria

We applied the BVAS to evaluate the disease activity. The BVAS form is divided into symptoms/signs pertaining to nine organ-based systems, with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis. The clinician only scored features that were believed to be due to active vasculitis. Upon completion of the form, a numerical score was obtained. The BVAS form was first published in 1994. Over the past years, there have been a number of changes to further improve the assessment form. We used BVAS 2003 for this study [10], although subsequently a newer version has been developed called BVAS V3.0 [11].

Disease outcome was defined by BVAS. Remission was defined as the absence of new or worse signs of disease activity on the BVAS. We defined relapse as the recurrence or first appearance of at least one BVAS item indicating organ function attributable to active vasculitis.

Treatment

All patients received induction therapy with a corticosteroid at various doses. Thirty-one MPA patients with multiorgan involvement received intravenous pulse methylprednisolone (dose, 0.5–1.0 g) for 3 consecutive days. Twenty-seven patients who had rapidly progressive glomerulonephritis or were less than 60 years old received more than 0.8 mg/kg/day of prednisolone orally for 4 weeks or more as the subsequent maintenance therapy. Cyclophosphamide was administered to 17 patients. Among these 17 patients, 12 were given intravenous cyclophosphamide (250–500 mg/day × one to four courses) and the others, oral cyclophosphamide (0.5–1.5 mg/kg body weight). One patient received mizoribine for maintenance therapy. Four patients underwent plasma exchange. No strict protocol was followed in regard to prophylaxis against opportunistic infections.

Statistical analysis

Data are expressed as means±standard deviation (SD). The significance of differences between groups was examined