Current status of the treatment of microscopic polyangiitis and granulomatosis with polyangiitis in Japan

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Abstract

Background This study aimed to describe the epidemiologic characteristics of microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) in Japan. *Methods* We used the database of Ministry of Health, Labour and Welfare (MHLW) from 2006 to 2008, and analyzed data of 938 patients (MPA=697, GPA=241) who had registered within one year after their onsets and fulfilled the MHLW diagnostic criteria. *Results* The mean ages of MPA and GPA patients were 69.4±0.4 and 58.4±1.1 years, respectively. Renal (86.9%), chest (73.7%) and nervous system (45.2%) symptoms were common in MPA patients. Ear, nose and throat (86.7%), chest (78.0%) and renal (60.6%) symptoms frequently observed in GPA patients. The concomitant cyclophosphamide (CY) usages with corticosteroids were observed in 22.2% of MPA patients and 58.5% of GPA patients. In multivariate analysis, the concomitant use of CY was associated with younger age and pulmonary hemorrhage in MPA patients and the avoidance of CY was associated with nervous system symptoms and rapidly progressive glomerulonephritis in GPA patients. Plasma exchanges were inducted in 5.2% MPA patients and 4.1% GPA patients. The addition of plasma exchange was associated with the elevation of serum creatinine level in patients with both MPA and GPA.

Conclusion MPA dominancy and less frequency of renal involvement in GPA patients

may be significant feature in Japan. The clinical practice of MPA and GPA in Japan is characterized by less common use of CY and the employment of plasma exchange for the patients with deteriorated renal function.

Key words anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), cyclophosphamide, microscopic polyangiitis (MPA), plasma exchange, granulomatosis with polyangiitis (GPA)

Introduction

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) are the most common forms of anti-neutrophil cytoplasmic antibodies (ANCA) associated diseases characterized by necrotizing small-vessel vasculitis (AAV). Approximately 90% of patients with active, generalized MPA and GPA have circulating ANCA and such tight association raises the possibility of pathogenic roles of ANCA. The primary antigenic targets of ANCA are myeloperoxidase (MPO-ANCA) and proteinase-3 (PR3-ANCA) of granulocytes and monocytes (1). MPA is characterized by frequent association of MPO-ANCA and pauci-immune necrotizing vasculitis without the granulomatous lesions; while GPA is characterized by high positive rate of PR3-ANCA and granuloma formations in various affected organs (2).

Previous report showed that the prevalence of MPA is higher than that of GPA in Japanese patients with renal vasculitis while GPA is much more common in Europe (3). They also reported that the older Japanese patients were more likely to be affected compared with European patients and significant differences in the profile of ANCA positivity. Although this report demonstrated the features of Japanese patients with renal vasculitis, the characteristics and status of Japanese patients with systemic vasculitis have been not clarified. In EULAR recommendation, a combination therapy with cyclophosphamide (CY) and corticosteroids for remission induction of systemic vasculitis and necessity of dose reduction for renal function and age was proposed (4). It remains unknown how often CY was used and what is the major determinant for the usage of CY in clinical practice for Japanese AAV patients.

In Japan, MPA and GPA were recognized and officially certified as so called “the intractable diseases” by Ministry of Health, Labour and Welfare (MHLW). The patients recognized as MPA and GPA, who wish to receive public financial aid from MHLW covering medical costs, must sign agreements and submit applications. The patients certified according to MHLW diagnostic criteria of MPA or GPA (5)(6)(7) has been registered in MHLW database and their information, clinical characteristics, medical history, organ involvements, laboratory data, and modalities of treatments, were

digitally stored at the prefectural administrations and MHLW.

We performed this study to survey the characteristics of Japanese patients with MPA and GPA based on data set of MHLW. We also attempted to investigate frequency of the concomitant use of CY or plasma exchange with corticosteroids, and determine the factors which contributed the choice of therapies for their inductions in MPA and GPA.

Patients and Methods

Studied patients. We were permitted to use data of 1320 patients (MPA=988, GPA=332) who were newly registered from 2006 to 2008 in MHLW database and whose clinical data input was completed electronically. Of 1320 patients, we identified 1032 (MPA=787, GPA=246) patients, who had registered within one year after their onsets. Eventually we used the data of the 938 (MPA=697, GPA=241) patients fulfilled the above MHLW diagnostic criteria. The criteria of MPA indicate the following three symptoms; rapidly progressive glomerulonephritis (RPGN), pulmonary hemorrhage and other symptoms including purpura, subcutaneous hemorrhage, gastrointestinal bleeding, and mononeuritis multiplex. The patients were certified as definite MPA, who fulfill the following conditions; (1) positive for 2 or more of the symptoms, and positive histological findings, (2) Positive for 2 or more of the symptoms including the

symptoms RPGN and pulmonary hemorrhage, and positive MPO-ANCA. The conditions of probable MPA were (1) Positive for 3 of the symptoms, (2) Positive for 1 of the symptoms, and positive MPO-ANCA(6). Of 697 MPA patients, 294 were diagnosed definitely and 403 were possibly. As GPA symptoms, the criteria have nose and throat (E), lung (L), kidney (K) and others due to vasculitis. Definite GPA mean the following; (1) Positive for 3 or more of the symptoms, including E, L, and K symptoms, (2) Positive for 2 or more of the symptoms, and positive for either of the histological findings, (3) Positive for 1 or more of the symptoms, positive for either of the histological findings, and positive PR3-ANCA/C-ANCA(7). Of 241 GPA patients, 168 were diagnosed definitely and 73 were possibly.

Data collection and arrangement. The following information was extracted from database: sex, age, the presence of histological examination, the histological findings, organ symptoms, ANCA positivity, the level of serum creatinine (Cr) and C-reactive protein (CRP), corticosteroid dosage, and concomitant usage of steroid pulse therapy, cyclophosphamide (CY) and plasma exchange or hemodialysis. We categorized organ symptoms into nine groups according to BVAS scoring system(8), which are “systemic symptoms”, “cutaneous symptoms”, “mucous membranes and eyes symptoms”, “ear, nose and throat symptoms”, “chest symptoms”, “cardiovascular symptoms”,

“abdominal symptoms”, “renal symptoms” and “nervous system symptoms”. We sorted each items of the database into these categories. For example, we defined the existence of systemic symptoms as at least one “yes” of the following items; fever (38°C or higher, 2 weeks or longer), body weight loss (6 kg or more for 6 months), myalgia /myositis and arthralgia /arthritis.

Statistical analysis. After descriptive analysis of the characteristics and treatment status of the MPA and GPA patients, we compared the characteristics of patients with concomitant use of CY and corticosteroid alone. We calculated eGFR (estimated glomerular filtration rate) using the modification of diet in renal disease (MDRD) equation: $194.9 \times \text{serum Cr}^{-1.094.9} \times \text{age}^{-0.287}$ ($\times 0.739$ if women) (9). We categorized five groups according to eGFR and evaluated the correlation of these groups and CY usage in MPA and GPA by ANOVA. Similarly, in each disease category, we separated the subgroups with or without plasma exchange and compared their characteristics. In order to identify independent factors of concomitant usage of CY, the extracted variables in the univariate analysis were entered into multivariate analysis using the logistic regression model. All statistical analyses in this study were performed using the Statistical Package of JMP for Windows software, version 8.0 (SAS Institute Inc., Cary, NC, USA). Clinical variables with a possible relation to the outcomes were compared

by Mann-Whitney U and Chi-square tests (univariate model). All results were expressed as mean ± SE (standard error) and statistical significance was defined as a P-value of less than 0.05, two-tailed.

Results

Patient Characteristics of MPA and GPA (Table 1)

We identified 697 MPA patients and 241 GPA patients. Patient characteristics are shown in Table 1. The mean age of MPA patients was 69.4±0.4 years and that of GPA patients was 58.4±1.1 years. Renal involvement was most frequently observed in MPA patients (86.9%) while ear, nose and throat (ENT) symptoms were most common in GPA patients (86.7%). Other major symptoms were systemic (80.3%), chest (73.7%) and nervous system involvements (45.2%) in MPA patients while systemic (81.3%), chest (78.0%), and renal involvements (60.6%) are frequent in GPA patients. MPO-ANCA or p-ANCA was positive in 97.1% of MPA patients and PR3-ANCA or c-ANCA was positive in 73.0% of GPA patients. All but excluding 5 patients with MPA and 7 patients with GPA were treated with corticosteroids and the mean maximum daily dosage of prednisolone was 26.5±0.9 mg/day in MPA patients and 35.3±1.6mg/day in GPA patients. The concomitant use of cyclophosphamide (CY) was seen 22.2% in MPA

patients and 58.5% in GPA patients. Plasma exchanges with MPA and GPA were performed in 5.2% and 4.1%, respectively.

Characteristics of MPA and GPA patients treated with CY or corticosteroid alone (Tables 2 and 3)

The patients treated with CY were significantly younger than corticosteroid alone in MPA patients (66.1±0.9 *v.s.* 70.1±0.5 years, p=0.0002) and GPA patients (57.2±1.4 *v.s.*62.0±1.8 years, p=0.0395) . The concomitant CY usage was seen less frequently in GPA patients with lower eGFR significantly (Fig 1, p=0.014), although not significantly with MPA patients (Fig 1, p=0.370). The GPA patients who have RPGN or nervous system symptoms were treated with CY less frequently than corticosteroid alone. In contrast, MPA patients with cutaneous symptoms or pulmonary hemorrhage and GPA patients with ENT symptoms were treated with CY more frequently. In the multivariate analysis included these extracted variables in the univariate analysis, age and pulmonary hemorrhage in MPA and nervous system symptoms and RPGN in GPA were independent factors for concomitant usage of CY (Table 4). The mean maximum daily dose of prednisone of the patients with CY were significant higher than the patients with corticosteroid alone in both MPA (32.6±1.9 *v.s.* 25.2±1.0 mg/day,

p=0.0008) and GPA patients (39.4±2.1 *v.s.* 29.5±2.5 mg/day, p=0.0025).

Patient Characteristics of MPA and GPA treated with or without plasma exchange (Tables 5 and 6)

The mean ages were similar between patients with plasma exchange and without plasma exchange in both MPA (68.6±1.9 *v.s.* 69.4±0.5 years, p=0.7041) and GPA patients (57.9 ±5.3 *v.s.* 58.5 ±1.1 years, p=0.9162). The patients who had treated with plasma exchange had pulmonary hemorrhages more frequently than those who treated without it in MPA (18.1 *v.s.* 8.2%, p=0.0009). The serum levels of Cr in the groups with plasma exchange was higher than those without plasma exchange both in MPA (3.8± 0.5 *v.s.* 2.4±0.1 mg/dl, p=0.0132) and GPA patients (3.7 ±0.8 *v.s.* 1.5 ±0.2, p=0.0102). Furthermore, the patients treated with plasma exchange had RPGN more frequently than those without it in GPA, and all of GPA patients with plasma exchange had renal symptoms. Similarly, dialysis treatment was more frequent in the patients with plasma exchange than those without plasma exchange in MPA patients (50.0% *v.s.* 9.8%, p<0.0001) and GPA patients (60.0% *v.s.* 4.3%, P<0.0001).

Discussion

We determined the characteristics and the current status of treatments for MPA and GPA based on the data set of MHLW database in Japan. In present study, the ratio of the patients with MPA and the patients with GPA was 3: 1. Watts et al. reported that the ratio of the MPA patients and GPA patients was 3 : 4 in UK(10). The predominance of MPA compared with GPA in Japan was similar to previous report (3) (11). The MPO-ANCA or p-ANCA positive MPA patients and PR3-ANCA or c-ANCA positive GPA patients were more common in this study. These results are consistent with previous Japanese nationwide epidemiological survey showed 87.3% MPA patients have p-ANCA positive and 85.7% WG patients have c-ANCA positive (11). Otherwise, western report showed 30.4% MPO-ANCA or p-ANCA positivity in MPA and 57.4% PR3-ANCA or c-ANCA positivity in GPA (12). MHLW criteria of MPA and GPA is consist of three parts; clinical symptoms, histological findings, and ANCA positivity. Especially MPA criteria contain MPO-ANCA or p-ANCA positivity while GPA criteria contain PR3-ANCA or c-ANCA positivity. There was no reference of ANCA in classification criteria of American College of Rheumatology (ACR) or Chapel Hill Consensus Conference. Although Watts et al. applied ANCA positivity to their classification algorithm, the type of ANCA is not taken into account in the diagnosis of MPA and GPA. Therefore these differences between MHLW criteria and other criteria

may affect the positivity of each ANCA in GPA and MPA in our study. In addition, the MHLW criteria emphasized specific clinical symptoms, such as RPGN and pulmonary hemorrhage, the study population may differ from previous reports. Considering the renal involvement represented only in 60% of patients with GPA in present study even if all items in renal symptom were included; while the glomerulonephritis represented in almost 80% of patients with GPA in their clinical course in USA(2). The patients within 1 year from their disease onset were included in this study. In addition, the MHLW criteria of possible GPA need fewer clinical symptoms than the ACR criteria to diagnosis of GPA. Therefore more organ-limited type may be contained in this study population.

The concomitant CY usage was less common option for treatment of AAV in the present study. Only 22% of patients with MPA and 59% of patients with GPA were treated with CY combined with corticosteroids, despite fact that several guidelines recommend the concomitant usage of CY for AAV (4, 13). Actually, 89 % of AAV patients were treated with CY combined with corticosteroids in previous European report(14). Even in Asian country, 94% of MPA patients were treated with a combination of CY and corticosteroids (15). Japanese previous nationwide survey showed CY usage of 62.3% MPA and 96.3% GPA patients (11) and recent Japanese

patients with MPO-ANCA-associated vasculitis (JMAAV) study also reported 58.3% of patients were treated with CY(16). Therefore less CY usage might be characteristic of present Japanese therapy for AAV. In multivariate analysis, the avoidance of concomitant CY usages was associated with older age and pulmonary hemorrhage in MPA, RPGN and nervous system symptoms in GPA. The several guidelines recommend the reduction of the dosage of CY for elderly patients or deteriorated renal function in order to avoid the adverse effects (4, 13). Additionally a Japanese nationwide survey of RPGN reported that no additional benefit of immunosuppressants in elderly patients for the renal prognosis based on data for 715 RPGN patients collected until 2001(17). Therefore the avoidance of concomitant usage rather than the proactive usage with dose reduction of CY for elderly patients and the patients with RPGN may be significant feature in current status of treatment for MPA in Japan.

The maximum daily dose of corticosteroids was higher in patient with concomitant usage of CY than without those of CY. The common practice of the treatment of AAV patients is that the initial dose of corticosteroids has been continued for one month whereas more rapid tapering regimen of corticosteroids is adopted in several recent clinical trials (patients initially received 1 mg/kg/day of oral prednisolone, which was reduced to 0.75 mg/kg/day after 1 week, 0.50 mg/kg/d after 2weeks) (18-20). Because

the body weight of patients with AAV was not registered in database and it was unable to assess in present study, the daily dose per body of corticosteroids could not be converted to dose per kilogram. But the patients of AAV are treated with about 0.8 mg/kg/day of oral prednisolone commonly in Japan. Although the tapering speed of corticosteroids could not be assessed in present study, the patients with concomitant usage of CY may treated with higher dose of corticosteroid and tapered more rapidly as the regimen of recent clinical trials.

In our study, about 5% patients were treated with plasma exchange. This result are similar to the JMAAV study that reported plasma exchange were procedure in only 2 of 48 patients (16). Recent western study for remission maintenance showed that almost 15% patients with AAV treated with plasma exchange and median levels of serum Cr was 2.9 or 2.7 mg/dl (18). The addition of plasma exchange was associated with the elevation of serum creatinine levels in patients with both MPA and GPA. The plasma exchange might be initiated based on renal dysfunction rather than disease classifications. The European randomized Methylprednisolone versus Plasma Exchange (MEPEX) trial showed that plasma exchange increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure (20). The EULAR recommendations propose the concomitant usage of plasma exchange for

patients with rapidly progressive severe renal disease based on this clinical trial (4). Because of less severe deterioration of renal functions in our population, the concomitant usage of plasma exchange might be less common. Among all chest symptoms, plasma exchange was performed for patients with pulmonary hemorrhage in our study. The British Society for Rheumatology and British Health Professionals in Rheumatology guidelines for vasculitis recommended that treatment with plasma exchange should be considered in patients with life-threatening manifestations of disease such as pulmonary hemorrhage as well as patients presenting with severe renal failure(13).

Several limitations of present study should be noted. At first, we are not able to reconfirm the clinical data by checking medical records. Sakauchi et al. who studied the etiology of primary biliary cirrhosis using MHLW database pointed the similar limitation(21). In addition, we cannot discuss the reliability of data of the present study since this is the first report about the characteristics of MPA and GPA patients in Japan. Secondly, we applied to the MHLW criteria for diagnosis of MPA and GPA in present study**;** however the specificity and sensitivity of MHLW criteria have not been validated yet. Third, the choice of therapeutic modalities may be influenced by the healthcare access bias. At last, our investigation failed to demonstrate the association between

these treatments and prognosis since it was cross-sectional study.

In conclusion, MPA dominancy and less frequency of renal involvement in GPA patients may be significant feature in Japan. The concomitant CY usage was less common for treatment of AAV in Japan. The plasma exchange was added to AAV patients with deteriorated renal function. Further investigations based on global definitions are required to further confirm these features in Japan.

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Figure legend

【Table 1】 Patient characteristics of MPA and GPA

CY: cyclophosphamide, SE: standard error, Cr: creatinine, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, p-ANCA: perinuclear anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, c-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody, PSL: prednisolone, m-PSL: methyl prednisolone

【 Table 2 】 Characteristics of MPA patients treated with concomitant cyclophosphamide usage and corticosteroids monotherapy.

CY: cyclophosphamide, CS: corticosteroids, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, p-ANCA: perinuclear anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, c-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody, PSL: prednisolone, m-PSL: methyl prednisolone, *$p<0.05$

【Table 3】Characteristics of GPA patients treated with concomitant cyclophosphamide usage and corticosteroids monotherapy.

CY: cyclophosphamide, CS: corticosteroids, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, PSL: prednisolone, m-PSL: methyl prednisolone, *p<0.05

【Table 4】 Logistic-regression analysis of independent factors of concomitant CY use
ENT: Ear, nose and throat, eGFR: estimated glomerular filtration rate, RPGN: Rapidly progressive glomerulonephritis, *p<0.05

【Table 5】 Patient characteristics of MPA treated with or without plasma exchange

CY: cyclophosphamide, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, PSL: prednisolone, m-PSL: methyl prednisolone, *p<0.05

【Table 6】 Patient characteristics of GPA treated with or without plasma exchange

PE: plasma exchange, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, PSL: prednisolone, m-PSL: methyl prednisolone, *p<0.05

【Fig 1】 The percentage of CY usages on each categories of eGFR
CY: cyclophosphamide, eGFR: estimated glomerular filtration rate, *p<0.05

Table 1 Patient characteristics of MPA and GPA

	MPA (n=697）	GPA (n=241）

Diagnosis		
Definite : possible	294 : 403	168 : 73
Men : Women	299 : 398	139 : 102
Age, mean ±SE years	69.4±0.4	58.4±1.1
Symptoms		
Systemic symptoms (%)	80.3	81.3
Cutaneous symptoms (%)	35.4	26.1
Mucous membrane and eyes (%)	13.1	46.1
Ear, nose and throat (%)	14.1	86.7
Chest (%)	73.7	78.0
Cardiovascular (%)	14.3	15.8
Abdominal (%)	10.2	7.1
Renal (%)	86.9	60.6
Nervous system (%)	45.2	32.3
Pulmonary hemorrhage (%)	11.3	ND
Rapidly progressive glomerulonephritis(%)	63.2	25.7
Examination		
Cr, mean ±SE (mg/dl)	2.5±0.1	1.6±0.2
eGFR（ml/min./1.73m^2）	43.2±1.3	75.3±3.2
CRP, mean ±SE (mg/dl)	9.0±0.3	10.2±0.5
MPO- or p-ANCA positive (%)	97.1	17.4
PR3- or c-ANCA positive (%)	7.0	73.0
Histological finding	30.6	52
Treatment		
Max. oral PSL dosage, mean ±SE mg/day	26.5±0.9	35.3±1.6
m-PSL pulse (%)	51.8	38.2
Immunosuppressants usage (%)	27.8	64.3
CY usage (%)	22.2	58.5
Plasma exchange (%)	5.2	4.1
Dialysis treatment (%)	11.9	6.6

CY: cyclophosphamide, SE: standard error, Cr: creatinine, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, p-ANCA: perinuclear anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, c-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody, PSL: prednisolone, m-PSL: methyl prednisolone

Table 2 Characteristics of MPA patients treated with concomitant cyclophosphamide usage and corticosteroids monotherapy.

	Concomitant CY usage (n=155)	CS monotherapy (n=503)	p
Age, mean ±SE years	66.1±0.9	70.1±0.5	0.0002*
Symptoms			
Systemic (%)	81.9	80.0	0.6440
Cutaneous (%)	43.2	32.0	0.0120*
Mucous membrane and eyes (%)	11.6	13.0	0.7823
Ear, nose and throat (%)	15.5	13.4	0.5083
Chest (%)	74.8	73.0	0.6785
Cardiovascular (%)	11.0	14.8	0.2873
Abdominal (%)	12.9	9.4	0.2252
Renal (%)	85.8	87.2	0.6833
Nervous system (%)	45.8	44.2	0.7815
Pulmonary hemorrhage (%)	18.1	8.2	0.0009*
Rapidly progressive glomerulonephritis(%)	59.4	64.8	0.2518
Cr, mean ±SE mg/dl	2.1±0.3	2.7±0.2	0.0635
eGFR（ml/min./1.73m^2）	48.0±2.7	41.8±1.5	0.0452*
CRP, mean ±SE mg/dl	9.6±0.6	8.9±0.3	0.2763
Max. oral PSL dosage, mean ±SE mg/day	32.6±1.9	25.2±1.0	0.0008*
m-PSL pulse (%)	58.1	50.0	0.0813
Plasma exchange (%)	9.7	3.8	0.0066*
Dialysis treatment (%)	9.0	12.2	0.3146

CY: cyclophosphamide, CS: corticosteroids, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, p-ANCA: perinuclear anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, c-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody, PSL: prednisolone, m-PSL: methyl prednisolone, *$p<0.05$

Table 3 Characteristics of GPA patients treated with concomitant cyclophosphamide usage and corticosteroids monotherapy.

	Concomitant CY usage (n=141)	CS monotherapy (n=86)	p
Age, mean ±SE years	57.2±1.4	62.0±1.8	0.0395*
Symptoms			
Systemic (%)	83.7	75.0	0.1566
Cutaneous (%)	26.2	26.3	1.000
Mucous membrane and eyes (%)	46.8	43.8	0.6760
Ear, nose and throat (%)	90.1	80.0	0.0421*
Chest (%)	80.9	75.0	0.3106
Cardiovascular (%)	13.5	23.8	0.0637
Abdominal (%)	6.4	7.5	0.7846
Renal (%)	59.6	61.3	0.8865
Nervous system (%)	27.0	45.0	0.0077*
Rapidly progressive glomerulonephritis (%)	19.9	37.5	0.0065*
Cr, mean ±SE mg/dl	1.5±0.2	1.8±0.3	0.4520
eGFR（ml/min./1.73m^2）	80.2±3.9	63.3±5.3	0.0106*
CRP, mean ±SE mg/dl	10.6±0.7	9.3±0.9	0.2039
Max. PSL dosage, mean ±SE mg/day	39.3±2.0	28.7±2.7	0.0018*
m-PSL pulse (%)	39.0	41.3	0.7760
Plasma exchange (%)	5.0	2.5	0.4933
Dialysis treatment (%)	5.0	10.0	0.1711

CY: cyclophosphamide, CS: corticosteroids, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, PSL: prednisolone, m-PSL: methyl prednisolone, *p<0.05

Table 4 Logistic-regression analysis of independent factors of concomitant CY use

Variable	Odds Ratio (95%CI)	P value
MPA		
Age (per yr)	0.97(0.96-0.99)	0.0025*
Pulmonary hemorrhage	2.76(1.61-4.71)	0.0003*
eGFR（ml/min./1.73m^2）	1.00(1.00-1.01)	0.1660
Cutanous	1.40(0.94-2.09)	0.0986
GPA		
Age (per yr)	0.99(0.97-1.00)	0.1889
ENT symptoms	1.96(0.85-4.60)	0.1151
Nervous system symptoms	0.48(0.26-0.88)	0.0174*
RPGN	0.45(0.24-0.87)	0.0165*

ENT: Ear, nose and throat, eGFR: estimated glomerular filtration rate, RPGN: Rapidly progressive glomerulonephritis, *p<0.05

Table 5 Patient characteristics of MPA treated with or without plasma exchange

	PE (n=36)	non-PE (n=661)	p
Age, mean±SE years	68.6±1.9	69.4±0.5	0.7041
Symptoms			
Systemic (%)	69.4	80.9	0.1280
Cutaneous (%)	44.4	35.0	0.2835
Mucous membrane and eyes (%)	27.8	12.3	0.0178*
Ear, nose and throat (%)	16.7	13.9	0.6229
Chest (%)	83.3	73.2	0.2426
Cardiovascular (%)	25.0	13.8	0.0827
Abdominal (%)	8.3	10.3	1.0000
Renal (%)	97.2	86.4	0.0722
Nervous system (%)	33.3	45.8	0.1697
Pulmonary hemorrhage (%)	36.1	10.0	<.0001*
Rapidly progressive glomerulonephritis (%)	72.2	62.8	0.2902
Cr, mean ±SE mg/dl	3.8±0.5	2.4±0.1	0.0132*
eGFR（ml/min./1.73m^2）	26.7±5.7	44.1±1.3	0.0031*
CRP, mean ±SE mg/dl	12.2±1.1	8.8±0.3	0.0037*
Max. oral PSL dosage, mean ±SE mg/day	23.5±4.2	26.7.±0.9	0.4580
m-PSL pulse (%)	86.1	49.9	<.0001*
CY usage (%)	41.7	21.2	0.0068*
Dialysis treatment (%)	50.0	9.8	<.0001*

CY: cyclophosphamide, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, PSL: prednisolone, m-PSL: methyl prednisolone, *p<0.05

Table 6 Patient characteristics of GPA treated with or without plasma exchange

	PE (n=10)	non-PE (n=231)	p
Age, mean ±SE years	57.9±5.3	58.5±1.1	0.9162
Symptoms			
Systemic (%)	80.0	81.4	1.000
Cutaneous (%)	40.0	25.5	0.2931
Mucous membrane and eyes (%)	40.0	46.3	0.7566
Ear, nose and throat (%)	80.0	87.0	0.6262
Chest (%)	90.0	77.5	0.6958
Cardiovascular (%)	40.0	14.7	0.0547
Abdominal (%)	10.0	6.9	0.5258
Renal (%)	100.0	58.9	0.0071*
Nervous system (%)	50.0	31.6	0.3000
Rapidly progressive glomerulonephritis (%)	60.0	24.2	0.0203*
Cr, mean ±SE mg/dl	3.7±0.8	1.5±0.2	0.0102*
eGFR（ml/min./1.73m^2）	33.1±15.5	77.1±3.2	0.0058*
CRP, mean±SE mg/dl	11.2±2.6	10.2±0.5	0.7008
Max. oral PSL dosage, mean ±SD mg/day	20.0±8.4	35.9±1.6	0.0663
m-PSL pulse (%)	90.0	35.9	0.0009*
CY usage (%)	70.0	57.6	0.5268
Dialysis treatment (%)	60.0	4.3	<.0001*

PE: plasma exchange, SE: standard error, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, PSL: prednisolone, m-PSL: methyl prednisolone, *p<0.05