Comparison of Phenotype and Outcome in Microscopic Polyangiitis Between Europe and Japan

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ABSTRACT. ***Objective.*** There are differences between Europe and Japan in the incidence and antineutrophil cytoplasmic antibody (ANCA) serotype of patients with microscopic polyangiitis (MPA). However, differences in phenotype or outcome have not been explored. We aimed to identify differences in phenotype and outcome of MPA between Europe and Japan.

Methods. Sequential cohorts of patients with MPA and renal limited vasculitis were collected from European and Japanese centers (n = 147 and n = 312, respectively). Trial databases from the European Vasculitis Society and the Japanese patients with Myeloperoxidase (MPO)-ANCA-Associated Vasculitis (JMAAV) trial were studied (n = 254 and n = 48, respectively). We evaluated baseline characteristics including ANCA status and organ involvement, treatment, survival, and renal survival. Differences in survival and renal survival were studied using multivariate analysis.

Results. The non-trial cohorts showed patients with MPA in Japan had a higher age at onset, more frequent MPO-ANCA positivity, lower serum creatinine, and more frequent interstitial pneumonitis than those in Europe (all $p < 0.01$). Comparisons between the trial databases demonstrated similar results. Cumulative patient survival and renal survival rates were not different between Europe and Japan ($p = 0.71$ and $p = 0.38$, respectively). Multivariate analysis identified age at onset, serum creatinine, gastrointestinal, and respiratory involvement as factors with higher risk of death. For endstage renal failure, serum creatinine and use of plasma exchange were identified as factors with higher risk, and immunosuppressant use as lower risk factors.

Conclusion. Phenotypes in patients with MPA were different between Europe and Japan. However, the outcomes of patient survival and renal survival were similar. (J Rheumatol First Release Jan 15 2014; doi:10.3899/jrheum.130602)

Key Indexing Terms:
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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by a small to medium-size vasculitis and the presence of ANCA. AAV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss). Myeloperoxidase (MPO)-ANCA is the predominant serotype in MPA, while proteinase 3 (PR3)-ANCA is usually found in GPA. Both

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genetic and environmental factors contribute to the onset of AAV and production of ANCA. In Europe an association of HLA-DPB1*0401 and GPA has been found[1], while in Japan, associations of HLA-DRB1*0901, HLA-DQB1*0303, and MPA were reported[2]. HLA-DRB1*0901 and HLA-DQB1*0303 are more common in Asian as compared to European populations. Outside the HLA region, associations of CTLA4 and GPA have been seen[3]. The European Vasculitis Genetics Consortium, in a genome-wide association study (GWAS) of 2687 white European patients with GPA and MPA, found associations of HLA-DP, SERPINA1, PRTN3, and GPA, and an association of HLA-DQ and MPA[4]. Associations of the environmental pollutant silica with MPA and the bacterium *Staphylococcus aureus* with GPA have been reported with vasculitis[5].

Europe and Japan are different geographic regions with different ethnicities and environments. Previous reports have revealed differences in the annual incidence of MPA/GPA/EGPA (6.5/14.3/0.9 per million in the UK and 18.2/2.1/2.4 per million in Japan) and proportions of MPO/PR3-ANCA positivity in patients with AAV (30% out of 58% vs 84% out of 7%) between the UK and Japan[6,7,8]. Differences in the frequency of different serotypes in patients with AAV imply that additional differences in phenotype and outcome within the main diagnostic groups are likely. This information is important when considering collaborative studies between different regions and future genetic studies of disease expression, treatment response, and disease course.

We aimed to identify differences in phenotype and outcome in patients with MPA between Europe and Japan. MPA was selected as the target subgroup for this study because it is the predominant form of AAV in Japan and comprises 50% of cases of AAV in Europe.

MATERIALS AND METHODS

Patients. Sequential patients with MPA and renal limited vasculitis (RLV) were collected from 1 European and 6 Japanese centers. Trial databases from the European Vasculitis Society (EUVAS) and Japanese patients from the MPO-ANCA-Associated Vasculitis (JMAAV) trial were studied. Data from the EUVAS database and the JMAAV trial was used to support the relationships seen in nontrial cohort data and for additional data fields absent from the cohort data.

One hundred thirty patients with MPA and 17 patients with RLV, diagnosed between 1999 and April 2012, were identified from a multidisciplinary clinic at Addenbrooke's Hospital, Cambridge, UK. Two hundred seventy-seven patients with MPA and 35 patients with RLV, diagnosed between 2002 and April 2012, were identified by the subgroup for international collaboration in the Research Group of Intractable Vasculitis, Ministry of Health, Labor, and Welfare (MHLW) of Japan from 6 Japanese centers: Asahi General Hospital, Chiba University Hospital, Jichi Medical University Hospital, Kitano Hospital, University of Miyazaki Hospital, and Tokyo Metropolitan Geriatric Hospital. Three were nephrology clinics and 3 included all clinics seeing vasculitis patients.

The EUVAS database contained data from 4 randomized controlled trials in AAV, the NORAM trial with early systemic disease[9], the CYCAZAREM[10] and cyclophosphamide daily oral versus pulsed (CYCLOPS)[11] trials with generalized disease, and the methylprednisolone versus plasma exchange (MEPEX) trial with severe renal disease[12]. Patients were recruited at time of diagnosis between 1995 and 2002 from 15 European countries and the database contained longterm followup data to 2006. Two hundred thirty-five patients with MPA and 19 patients with RLV were identified in this database.

The JMAAV trial was performed for evaluating severity-based treatment in newly diagnosed Japanese patients with MPA with mild to severe disease activity from 2008 to 2010[13]. The Research Group of Intractable Vasculitis in MHLW of Japan conducted this prospective multicenter trial. All 48 participants were limited to MPA with positive MPO-ANCA by inclusion criteria. The JMAAV trial had similar diagnostic eligibility criteria to the EUVAS trials.

Trials were conducted according to the 1964 Declaration of Helsinki and subsequent amendments.

Diagnosis. In the UK and Japanese hospitals, the diagnosis of MPA was based on the definitions of the Chapel Hill Consensus Conference[14,15] with positive ANCA and/or biopsy-proven small vessel vasculitis. Diagnosis of RLV was made by presence of biopsy-proven necrotizing pauciimmune glomerulonephritis with positive ANCA without systemic vasculitis. RLV frequently coexists with positive MPO-ANCA and is considered a subgroup of MPA[16]. RLV and MPA data were combined for our study. In the EUVAS trials the diagnosis of MPA was based on the same criteria as that used for the UK and Japanese hospital cohorts, while the diagnosis was based on the diagnostic criteria for MPA of the Research Group of Intractable Vasculitis, MHLW of Japan[17] in the JMAAV trial. In the diagnostic criteria for the Japanese MHLW, more than 2 typical organ involvements with either biopsy-proven small vessel vasculitis or positive MPO-ANCA are mandatory for diagnosis.

Assessment. Phenotypic data included age, sex, ANCA, serum creatinine and C-reactive protein (CRP), disease extent index (DEI)[18], and organ involvement. MPO/PR3-ANCA results were available for almost all patients, but results of indirect immunofluorescence (p-/c-ANCA) were used when only these data were available. The maximum oral glucocorticoid dose converted to the equivalent prednisolone dose, cumulative cyclophosphamide exposure, the number of deaths, time to death, causes of death, the number with endstage renal disease (ESRD), and time to ESRD were collated. In addition, in the EUVAS and JMAAV data, the Birmingham Vasculitis Activity Score (BVAS)[19,20,21] were obtained. BVAS and DEI have slightly different purposes (disease activity and disease extent, respectively), but are highly correlated[22]. The EUVAS database used original BVAS and the JMAAV used BVAS version 3, but the 2 scores have comparable results[23]. Data were acquired from patients' medical charts and computer records.

Statistics. The distributions of age, BVAS, DEI, serum creatinine, and CRP were described by median and range, and compared by using the Mann-Whitney U test. Proportions of sex, ANCA serotype, and organ involvement were compared by chi-square test, or Fisher's exact test when the expected frequency was < 5 in one or more cells. The cumulative rates for survival and renal survival were assessed by Kaplan-Meier survival curve, and compared by log-rank test. Risk factors for death and ESRD were assessed by univariate and multivariate analysis with a proportional hazards model. All analyses used SPSS Statistics version 20 and $p < 0.05$ was taken to indicate statistical significance.

RESULTS

Baseline characteristics. There was a trend toward more women in the Japanese (54.5%) than UK cohorts (44.9%, $p = 0.06$; Table 1). A similar difference was seen between the EUVAS and JMAAV data (47.6% and 64.6%, respectively, $p = 0.03$). The median age at onset was higher in Japan than in the UK (median 71.0 and 64.8 yrs, respec-

Table 1. Baseline characteristics of the 4 groups. Age at the onset, BVAS scores, DEI scores, serum creatinine levels, and serum CRP levels are shown as median values.

	UK, n = 147	Japan, n = 312	p	EUVAS, n = 254	JMAAV, n = 48
Period	1999–2012	2002–2012		1995–2006	2008–2010
MPA:RLV	130:17	277:35		235:19	48:0
Male:Female, (female rate)	81:66 (44.9%)	142:170 (54.5%)	0.06	133:121 (47.6%)	17:31 (64.6%)
Age at onset, yrs (range)	64.8 (14.9–89.0)	71.0 (16.0–94.0)	< 0.01	64.5 (17.2–86.1)	70.0 (26.0–79.0)
MPO/p-ANCA-positive	102 (69.4%)	299 (95.8%)	< 0.01	173 (69.8%)	48 (100%)
PR3/c-ANCA-positive	33 (22.4%)	10 (3.2%)	< 0.01	69 (27.8%)	0
ANCA double-positive	3 (2.0%)	8 (2.6%)	1.00	4/248 (1.6%)	0
ANCA negative	15 (10.2%)	11 (3.5%)	< 0.01	10/248 (4.0%)	0
BVAS (range)	Not done	Not done		15 (4–45)	12.5 (0–34)
DEI (range)	5.0 (2–13)	5.0 (2–13)	0.37	Not done	Not done
Creatinine, μmol/l (range)	221.9 (58.3–1882.9)	159.1 (26.5–2130.4)	< 0.01	335.0 (54.8–1670.8)	108.7 (35.4–998.9)
CRP, mg/l (range)	72.0 (1.0–350.0)	62.7 (0.2–383.1)	0.12	41.0 (0.3–552.0)	65.3 (0.5–313.0)
Followup, mos (range)	49.0 (0–152)	34.0 (0–128)		62.7 (0.2–135.6)	15.6 (0–25.0)

In the EUVAS database, 6 patients had a missing ANCA status. P value was calculated by the chi-square test for proportions comparing the UK and Japan. In those analyses where the expected frequency was < 5 in 1 or more cells, the p value was calculated using the Fisher's exact test. P value was calculated using the Mann-Whitney U test for other distributions comparing the UK and Japan. EUVAS: European Vasculitis Society; JMAAV: Japanese patients from the MPO-ANCA-associated vasculitis trial; ANA: antineutrophil cytoplasmic antibody; MPA: microscopic polyangiitis; RLV: renal limited vasculitis; BVAS: Birmingham Vasculitis Activity Score; DEI: disease extent index; creatinine: serum creatinine levels; CRP: C-reactive protein; MPO: myeloperoxidase; PR3: proteinase 3.

tively, $p < 0.01$). A similar difference was seen between the EUVAS and JMAAV data (64.5 and 70.0 yrs, respectively, $p < 0.01$).

The proportion of MPO/p-ANCA-positive patients in Japan (95.8%) was higher than in the UK (69.4%, $p < 0.01$), while the proportion of PR3/c-ANCA-positive patients in Japan (3.2%) was lower than in the UK (22.4%, $p < 0.01$). In the EUVAS database, the proportions of MPO/p-ANCA-positive and PR3/c-ANCA-positive patients were 69.8% and 27.8%, similar to the UK. In the JMAAV trial, the inclusion criteria required MPO-ANCA positivity.

The median DEI was 5 in both the Japanese and UK cohorts. In the EUVAS database and the JMAAV trial, DEI scores were not evaluated. BVAS in the EUVAS data was higher than in the JMAAV trial (15 and 12.5, respectively, $p < 0.01$), although their inclusion criteria differed.

Serum creatinine levels were lower in Japanese than in UK cohorts (159.1 μmol/l and 221.9 μmol/l, respectively, $p < 0.01$). In the patients with renal involvement, a similar difference was observed between Japan and the UK (197.1 μmol/l and 328.0 μmol/l, respectively, $p < 0.01$). Serum creatinine levels were also lower in the JMAAV (108.7 μmol/l) than in the EUVAS data (335.0 μmol/l).

Organ involvement. The most frequent organ involvement was the kidney in all groups: 82.3% and 86.9% (UK and Japan, respectively; $p = 0.19$; Table 2). The majority (98.3%) of patients in the EUVAS database had renal involvement, though the inclusion criteria required renal involvement in both the MEPEX and CYCLOPS trials.

Skin and eye involvement were more frequent in the UK than in Japan (both $p < 0.01$) and in the EUVAS (18.3%) compared to JMAAV data (6.3%) for skin involvement ($p = 0.04$).

Conversely, neurological involvement was more frequent in Japan than in the UK cohort (29.5% and 19.7%, respectively, $p = 0.02$), and in the JMAAV (50.0%) compared to the EUVAS data (14.9%; $p < 0.01$). In addition, peripheral nerve involvement was more frequent in Japan than in the UK (26.3% and 16.8%, $p = 0.02$), but involvement of the central nervous system was seen with similar frequency (5.1% and 4.8%, $p = 0.87$).

Respiratory involvement was more frequent in Japan than in the UK (52.5% and 34.7%, $p < 0.01$). The pattern of respiratory involvement differed, with Japanese patients having a predominance of interstitial pneumonitis/pulmonary fibrosis and the UK patients having more alveolar hemorrhage. Interstitial pneumonitis/pulmonary fibrosis was more frequent in Japan than in the UK (37.1% and 17.0%, $p < 0.01$). Conversely, alveolar hemorrhage was less common in Japan than in the UK (10.6% and 20.4%, $p < 0.01$). In the JMAAV trial, interstitial pneumonitis/pulmonary fibrosis (45.8%) was also more frequent than alveolar hemorrhage (4.2%).

Baseline characteristics and organ involvement in MPO-ANCA-positive patients. Findings in MPO-ANCA-positive patients were consistent with all the MPA patients (Table 3). Age at onset was higher in the Japanese than UK cohorts ($p < 0.01$) and serum creatinine levels were higher in the UK than Japanese cohorts ($p = 0.01$). Skin and eye involvement were more frequent in the UK than Japanese cohorts (both $p < 0.01$), while neurological and respiratory involvement were more frequent in Japanese than UK

Table 2. Organ involvement in the 4 groups.

	UK, n = 147	Japan, n = 312	p	EUVAS, n = 235	JMAAV, n = 48
General (%)	124 (84.4)	234 (75.0)	0.58	204 (86.8)	Not done
Skin (%)	36 (24.5)	35 (11.2)	< 0.01	43 (18.3)	3 (6.3)
Eye, mucosa (%)	22 (15.0)	21 (6.7)	< 0.01	36 (14.2)	3 (6.3)
Eye (%)	21 (14.3)	15 (4.8)	< 0.01	Not done	3 (6.3)
Mucosa (%)	3 (2.0)	9 (2.9)	0.76	Not done	0
ENT (%)	20 (13.6)	38 (12.2)	0.64	46 (19.6)	1 (2.1)
Heart (%)	6 (4.1)	9 (2.9)	0.57	14 (6.0)	1 (2.1)
Nerve (%)	29 (19.7)	92 (29.5)	0.02	35 (14.9)	24 (50.0)
Peripheral (%)	24 (16.3)	82 (26.3)	0.02	Not done	22 (45.8)
Central (%)	7 (4.8)	16 (5.1)	0.87	Not done	2 (4.2)
Intestine (%)	4 (2.7)	13 (4.2)	0.45	13 (5.5)	1 (2.1)
Kidney (%)	121 (82.3)	271 (86.9)	0.19	231 (98.3)	36 (75.0)
Respiratory (%)	51 (34.7)	157 (52.5)	< 0.01	102 (43.4)	25 (52.1)
IP/fibrosis (%)	25 (17.0)	116 (37.1)	< 0.01	Not done	22 (45.8)
AH (%)	30 (20.4)	33 (10.6)	< 0.01	Not done	2 (4.2)
Others	3 (2.0)	1 (0.3)		Not done	0

In the EUVAS database, 19 patients had only BVAS scores and without information about each organ involvement. "Others" in Cambridge included 2 aortitis and 1 vasculitis of testis. "Others" in Japan was aortitis. P value was calculated using the chi-square test comparing UK and Japan. In those analyses where the expected frequency was < 5 in 1 or more cells, the p value was calculated by Fisher's exact test. EUVAS: European Vasculitis Society; JMAAV: Japanese patients from the MPO-ANCA-associated vasculitis trial; ENT: ear, nose, and throat; IP/fibrosis: interstitial pneumonitis/pulmonary fibrosis; AH: alveolar hemorrhage; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score.

cohorts ($p < 0.01$ and $p = 0.01$, respectively). Similar differences were observed between the JMAAV and EUVAS data.

Treatments. Oral glucocorticoids were widely used in both the UK and Japan (99.6% and 96.8%, respectively; Table 4). Maximum oral prednisolone dose, usually equal to initial dose, were 40 mg/day and 30 mg/day in the UK and Japan, respectively. Concomitant immunosuppressants were less common in Japan than in the UK (41.7% and 95.2%, respectively). Although cyclophosphamide was the most frequently used immunosuppressant in both regions, the median cumulative dose of cyclophosphamide in Japan was 1.5 g, compared to 6.3 g in the UK. Plasma exchange was less commonly used in Japan than in the UK (7.1% and 16.3%, respectively). Some patients (27.2%) in the UK were treated with biologics, whereas only 1 Japanese patient (0.3%) received infliximab. In the EUVAS and JMAAV trials, initial treatments were regulated by the trial protocols.

Patient survival and renal survival. At 12 months, cumulative patient survival rates were 91.5%, 89.5%, 81.5%, and 88.7% in the UK, Japan, and the EUVAS and JMAAV data (Figure 1A). At 60 months, cumulative patient survival rates were 81.4%, 80.7%, and 68.9% in the UK, Japan, and the EUVAS data. The JMAAV data lacked longterm followup. The survival curves were similar between the UK and Japan ($p = 0.89$). Both survival and renal survival rates in the EUVAS database were the lowest, and the majority of deaths (53/85, 62.3%) and ESRD cases (43/63, 68.3%) were observed in the MEPEX trial with severe renal disease.

Infection was the most frequent cause of death in all 4 datasets, although infection as a proportion of all deaths was higher in Japan than in the UK (25/52 vs 7/31, $p = 0.02$). Nine of 25 infection-related deaths in Japan were opportunistic infections (4 *Pneumocystis jirovecii*, 2 cytomegalovirus, 1 *Mycobacterium tuberculosis*, 1 *Candida*, 1 *Aspergillus*), while 1 of 7 in the UK were opportunistic infection (candida). All the patients in both the UK and Japan received prophylactic trimethoprim-sulfamethoxazole unless there was a contraindication or an intolerable side effect. The 4 patients who died from *P. jirovecii* infection were not receiving prophylaxis at the time of infection. In the UK and the EUVAS database, late deaths (after 1 yr from onset, n = 19 and 72, respectively) were seen more frequently than early deaths (within 1 yr, n = 12 and 13, respectively). Conversely, in Japan, early deaths (n = 30) were more frequent than late deaths (n = 22), with half of the early deaths being caused by infection.

At 12 months, cumulative renal survival rates were 83.5%, 85.8%, 79.6%, and 97.9% in the UK, Japan, and the EUVAS and JMAAV data (Figure 1B). At 60 months, cumulative renal survival rates were 76.6%, 78.3%, and 73.6% in the same datasets, excluding the JMAAV trial. The survival curves were not different between the UK and Japan ($p = 0.37$).

Multivariate analysis for survival and renal survival. Total 29 items, age, sex, MPO/PR3-ANCA status, DEI, creatinine, and CRP levels (Table 1), 9 systems of organ involvement (Table 2), and use of immunosuppressants, 7 individual immunosuppressants, methylprednisolone pulse, plasma exchange, intravenous immunoglobulins, and bio-

Table 3. Analysis with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-positive patients.

	UK, n = 102	Japan, n = 299	p	EUVAS, n = 173	JMAAV, n = 48
MPA:RLV	91:11	265:34		158:15	48:0
Male:Female (female rate)	55:47 (46.1%)	136:163 (54.5%)	0.14	87:85 (49.1%)	17:31 (64.6%)
Age at onset, yrs (range)	64.8 (14.9–88.2)	71.0 (16.0–94.0)	< 0.01	65.3 (22.3–86.1)	70.0 (26.0–79.0)
MPO/p-ANCA-positive	102 (100%)	299 (100%)		173 (100%)	48 (100%)
PR3/c-ANCA-negative	3 (2.9%)	8 (2.7%)	0.88	4 (2.3%)	0
BVAS (range)	Not done	Not done		16 (4–45)	12.5 (0–34)
DEI (range)	5.0 (2–13)	5.0 (2–13)	0.47	Not done	Not done
Creatinine, μmol/l (range)	225.4 (58.3–1882.9)	168.0 (26.5–2130.4)	0.01	299.7 (54.8–1650.4)	108.7 (35.4–998.9)
CRP, mg/l (range)	60.0 (1.0–250.0)	63.0 (0.2–383.1)	0.55	36.0 (0.3–552.0)	65.3 (0.5–313.0)
Followup, mos (range)	52.0 (0–152)	34.0 (0–124)		48.9 (0.2–117.3)	15.6 (0–25.0)
Organ involvement					
General (%)	80 (78.4)	224 (74.9)	0.38	138 (85.2)	NE
Skin (%)	25 (24.5)	30 (10.0)	< 0.01	22 (13.5)	3 (6.3)
Eye, mucosa (%)	15 (14.7)	20 (6.7)	0.01	17 (10.5)	3 (6.3)
Eye (%)	15 (14.7)	14 (4.7)	< 0.01	Not done	3 (6.3)
Mucosa (%)	1 (1.0)	9 (3.0)	0.46	Not done	Not done
ENT (%)	17 (16.7)	38 (12.7)	0.29	27 (16.7)	1 (2.1)
Heart (%)	5 (4.9)	8 (2.7)	0.33	8 (4.9)	1 (2.1)
Nerve (%)	14 (13.7)	87 (29.1)	< 0.01	29 (17.9)	24 (50.0)
Peripheral (%)	12 (11.8)	76 (25.4)	< 0.01	Not done	22 (45.8)
Central (%)	3 (2.9)	16 (5.4)	0.43	Not done	2 (4.2)
Intestine (%)	2 (2.0)	13 (4.3)	0.37	8 (4.9)	1 (2.1)
Kidney (%)	84 (82.3)	261 (87.2)	0.21	159 (98.1)	36 (75.0)
Respiratory (%)	36 (35.3)	151 (50.5)	0.01	71 (43.8)	25 (52.1)
IP/fibrosis (%)	20 (19.6)	111 (37.1)	< 0.01	Not done	22 (45.8)
AH (%)	19 (18.6)	32 (10.7)	0.03	Not done	2 (4.2)

Age at the onset, BVAS scores, DEI scores, serum creatinine levels, and serum CRP levels are shown as median values. In the EUVAS database, 6 patients had a missing ANCA status. In the EUVAS database, 11 patients had only BVAS scores and without information about each organ involvement. P value was calculated using the chi-square test for proportions comparing the UK and Japan. In those analyses where the expected frequency was < 5 in 1 or more cells, the p value was calculated using the Fisher's exact test. P value was calculated using the Mann-Whitney U test for other distributions comparing the UK and Japan. EUVAS: European Vasculitis Society; JMAAV: Japanese patients from the MPO-ANCA-associated vasculitis trial; MPA: microscopic polyangiitis; RLV: renal limited vasculitis; BVAS: Birmingham Vasculitis Activity Score; DEI: disease extent index; creatinine: serum creatinine levels; CRP: C-reactive protein; NE: not examined; ENT: ear, nose, and throat; IP/fibrosis: interstitial pneumonitis/pulmonary fibrosis; AH: alveolar hemorrhage; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase 3.

logics (Table 4), and geographical region (the UK/Japan), were selected as potential explanatory variables. We confirmed in advance there was no collinearity between them. Explanatory variables with $p < 0.10$ on univariate analysis were entered in the multivariate analysis model. Then multivariate analysis with a proportional hazard model for the combined population of the UK and Japanese cohorts (n = 459) with 83 deaths and 87 ESRD cases was performed by a stepwise method (forward selection). Results for death and ESRD are shown in Table 5. P-value was < 0.01 for the model chi-square test for both death and ESRD. For death, significant factors with higher risks in the model were age at onset, serum creatinine, gastrointestinal involvement, and respiratory involvement. For ESRD, significant factors with higher risks in the model were serum creatinine and use of plasma exchange, and the factor with a lower risk was use of any immunosuppressants.

DISCUSSION

In the light of differences in the epidemiology of AAV between Europe and Japan we investigated whether there were also differences in phenotype and outcome between well-characterized patient cohorts with MPA. There were clear phenotypic differences, with patients in the UK being younger with a lower proportion of MPO-ANCA positivity and higher serum creatinine when compared to patients in Japan at the onset of the disease. The patterns of organ involvement also differed, with more frequent interstitial pneumonitis/pulmonary fibrosis in Japan and more alveolar hemorrhage in the UK, as well as differences in the frequencies of skin, eye, and neurological disease.

The reasons for these phenotypic differences are not known. Similar diagnostic criteria were used between cohorts following a longterm collaboration between Europe and Japan established in 2001. According to the national population statistics in 2010, the proportion of older people (> 65 yrs) in Japan was higher than in Europe (23.0% and 16.2%, respectively)[24]. Higher age in Japan might influence the higher female rate in Japan, because females form a greater proportion of the older population. However, we

Table 4. Treatments during the observational period. Values in parentheses are percentages.

	UK, n = 147	Japan, n = 312	EUVAS, n = 254	JMAAV, n = 48
Oral glucocorticoids	145 (99.6)	302 (96.8)	254 (100)	48 (100)
Maximum dose	40 mg/day	30 mg/day	Not done	35 mg/day
Immunosuppressants	140 (95.2)	130 (41.7)	254 (100)	31 (64.6)
Cyclophosphamide	112 (76.2)	100 (32.1)	252 (99.2)	28 (58.3)
Cumulative dose	6.3 g	1.5 g	Not done	2.7 g
Azathioprine	98 (66.7)	47 (15.1)	230 (90.6)	6 (12.5)
Mycophenolate	51 (34.7)	1 (0.3)	18 (7.1)	0
Methotrexate	11 (7.5)	4 (1.3)	3 (1.2)	1 (2.1)
Cyclosporine	2 (1.4)	3 (1.0)	4 (1.6)	0
Tacrolimus	2 (1.4)	4 (1.3)	5 (2.0)	1 (2.1)
Mizoribine	0	13 (4.2)	0	1 (2.1)
mPSL pulse	39 (26.5)	106 (34.0)	44 (17.3)	19 (39.6)
Plasma exchange	24 (16.3)	22 (7.1)	51 (20.1)	2 (4.2)
IV-IG	13 (8.8)	30 (9.6)	1 (0.4)	0
Biologics	40 (27.2)	1 (0.3)	1 (0.4)	1 (2.1)
Rituximab	32 (21.8)	0	0	1 (2.1)
Infliximab	2 (1.4)	1 (0.3)	1 (0.4)	0
Adalimumab	7 (4.8)	0	0	0

"Maximum dose" means the median maximum oral glucocorticoid dose converted to equivalent prednisolone dose during the observational period. "Cumulative dose" means the median cumulative cyclophosphamide dose during the observational period. EUVAS: European Vasculitis Society; JMAAV: Japanese patients from the MPO-ANCA-associated vasculitis trial; mPSL: methylprednisolone; IV-IG: intravenous immunoglobulins; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibody.

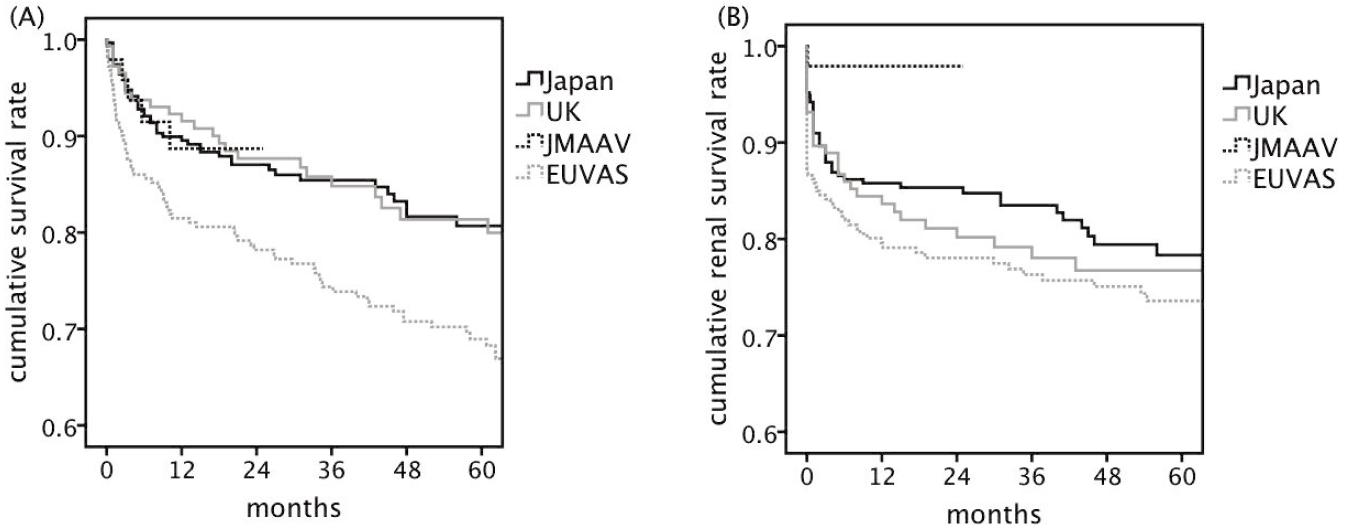

Figure 1. Cumulative patient and renal survival rates of the 4 groups. (A) At 12 months, cumulative survival rates were 91.5%, 89.5%, 81.5%, and 88.7% in UK, Japan, the EUVAS database, and the JMAAV trial, respectively. At 60 months, cumulative survival rates were 81.4%, 80.7%, and 68.9% in UK, Japan, and the EUVAS database, respectively. The JMAAV trial lacked longterm followup data. The survival curves showed no significant difference between UK and Japan (p = 0.89). (B) At 12 months, cumulative renal survival rates were 83.5%, 85.8%, 79.6%, and 97.9% in UK, Japan, the EUVAS database, and the JMAAV trial, respectively. At 60 months, cumulative renal survival rates were 76.6%, 78.3%, and 73.6% in UK, Japan, and the EUVAS database, respectively. The JMAAV trial lacked longterm followup data. The survival curves showed no significant difference between UK and Japan (p = 0.37). EUVAS: European Vasculitis Society; JMAAV: Japanese patients from the Myeloperoxidase Antineutrophil cytoplasmic Antibody Vasculitis trial.

suspect that underlying differences in genetic and environmental factors explain the phenotypic differences.

The previous population-based studies revealed higher rates of MPO-ANCA and MPA in Japanese patients with AAV[6,7,8]. In view of insufficient preliminary data on GPA in Japan, this study focused on MPA but accepts that occasional patients, especially if PR3-ANCA positive, may be diagnosed with MPA before GPA-defining features of

Table 5. Multivariate analysis for death and endstage renal disease (ESRD).

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
Death				
Age ≤ 60 yrs	1	NA	1	NA
60 yrs < age ≤ 70 yrs	1.74 (0.81–3.74)	0.16	1.84 (0.80–4.23)	0.15
> 70 yrs	4.09 (2.05–8.17)	< 0.01	4.15 (1.93–8.95)	< 0.01
Creatinine ≤ 100 μmol/l	1	NA	1	NA
100 < creatinine ≤ 290	1.67 (0.87–3.22)	0.12	1.62 (0.83–3.14)	0.16
Creatinine > 290 μmo/l	2.93 (1.60–5.39)	< 0.01	3.12 (1.68–5.79)	< 0.01
ENT inv	0.42 (0.17–1.03)	0.06		
Heart inv	2.34 (0.95–5.80)	0.07		
Intestine inv	2.39 (1.04–5.49)	0.04	3.22 (1.38–7.52)	< 0.01
Respiratory inv	1.63 (1.06–2.51)	0.03	1.61 (1.02–2.54)	0.04
Azathioprine use	0.58 (0.35–0.95)	0.03		
ESRD				
Creatinine ≤ 100 μmol/l	1	NA	1	NA
100 < Creatinine ≤ 290	5.72 (1.28–25.55)	0.02	5.18 (1.16–23.20)	0.03
Creatinine > 290 μmol/l	43.48 (10.64–177.63)	< 0.01	35.97 (8.75–147.91)	< 0.01
Skin inv	0.53 (0.26–1.10)	0.09		
Nerve inv	0.52 (0.30–0.93)	0.03		
Immunosuppressant use	0.49 (0.32–0.75)	< 0.01	0.42 (0.27–0.66)	< 0.01
PE use	4.15 (2.55–6.74)	< 0.01	2.20 (1.31–3.71)	< 0.01
IV–mPSL use	1.58 (1.03–2.43)	0.04		
CPA use	0.67 (0.44–1.04)	0.07		
Azathioprine use	0.58 (0.35–0.95)	0.03		

Hazard ratios, 95% CI, and p values were calculated by proportional hazard model for the combined population of Addenbrooke's Hospital and the 6 Japanese hospitals (n = 459) with 83 deaths and 87 ESRD. Twenty-nine items were tested as potential explanatory variables by univariate analysis and explanatory variables with p < 0.10 on univariate analysis were entered in the multivariate analysis model. NA: not applicable; HR: hazard ratio; creatinine: serum creatinine levels; ENT: ear, nose, and throat; inv: involvement; mPSL: methylprednisolone; PE: plasma exchange; CPA: cyclophosphamide.

disease appear, or may be difficult to categorize into MPA or GPA.

Older patients with AAV in Europe have more severe renal disease at diagnosis, so it was a surprise that, despite Japanese patients being older at diagnosis, their creatinine levels were lower. Although differences in primary care and referral pathways may have influenced the speed of diagnosis, this appears unlikely to explain the difference in renal function in view of similar DEI scores and CRP levels.

Respiratory involvement was more common in Japan than in the UK. However, details of respiratory involvement differed: in Japan, interstitial pneumonitis was the dominant pattern. Such differences might be influenced by genetic backgrounds. Smoking is a risk factor for interstitial lung disease, but smoking rates are similar between the UK and Japan (21.5% and 19.5%, respectively)[25]. Interestingly, more frequent acute exacerbations of interstitial pneumonitis in Japan have been reported, and drug-induced interstitial pneumonitis and collagen disease-associated interstitial pneumonitis, such as dermatomyositis, are more common in Japan[26,27,28].

Differing treatment strategies between the UK and Japan might have been influenced by differences in phenotype. The frequency of concomitant immunosuppressants, such as cyclophosphamide, was lower in Japan. However, outcomes, including death and ESRD, were similar. Multivariate analysis identified age and serum creatinine at onset as predictors, consistent with previous EUVAS studies, but it also identified gastrointestinal and respiratory involvement as significant factors for death, and use of any immunosuppressants or plasma exchange as significant factors for ESRD. We also investigated the effect of geographical region (the UK/Japan), and found no significance by univariate analysis (p = 0.72 for death and p = 0.39 for ESRD), suggesting the absence of important genetic and environmental effects on outcomes apart from the phenotypic difference. We speculate that the similar survival rates represented a balance of adverse predictors with older age and frequent respiratory involvement in Japan as compared to worse renal function in the UK. In our study, we did not have the opportunity to explore renal histology as a predictor of ESRD; EUVAS has developed an outcome-based histological classification of glomerulonephritis in AAV[29]. Four classes in this classification, "Focal", "Crescentic", "Mixed", and "Sclerotic", were independent predictors for renal survival, as well as serum creatinine levels at the onset. Recently, a Japanese group also showed the difference in renal survival between these 4 classes[30].

The nature of our retrospective analysis prevents conclu-

sions about the various types of treatment. Treatments could be confounding factors in the non-trial setting, while treatments obviously influenced outcomes. For example, plasma exchange might have been used for more severe cases. Indeed, the significance of these factors was not seen in the combined population of the EUVAS database and the JMAAV (data not shown), where treatment was defined by a clinical trial protocol.

Our study highlights an unmet need in the management of MPA that affects patient survival and infection-related deaths, especially in Japan. Concomitant use of immunosuppressants was less common in Japan, whereas differences in speed of reduction of glucocorticoids and cumulative glucocorticoid exposure between the EU and Japan may have been a relevant factor, as well as older age.

In previous geoepidemiological reports in Europe, the annual incidence of MPA was lower and the annual incidence of GPA was higher than in Japan[6,31,32,33]. In Australia, the incidences of MPA and GPA reflect those of Northern Europe[34]. The white AAV cohorts had more PR3-ANCA-positive patients (50% to 60%), while MPO-ANCA-positive patients comprised 84% of the Japan cohorts. Interestingly, in China, there is no population-based study, but a large cohort of AAV (n = 426) from a single center showed a bias to MPA (79%) and MPO-ANCA positivity (81%), similar to Japan[35].

A systematic review focusing on survival in MPA (18 studies with 940 patients, mainly white) showed cumulative survival rates of 77% to 100% at 1 year and 46% to 80% at 5 years; age with renal involvement was a risk factor for survival[36]. The previous Japanese cohort studies with MPO-ANCA-positive patients with glomerulonephritis showed cumulative survival rates of 75% to 85% and cumulative renal survival rates of 68% to 83% at 1 year[37,38]. These data are consistent with our results.

Recently, Mahr, *et al,* using a cluster analysis approach, demonstrated the importance of ANCA serotype in deriving novel subgroups of AAV[39]. Lionaki, *et al* demonstrated that ANCA subtypes (MPO/PR3-ANCA) were better predictors of relapse than diagnostic subgroups (MPA/GPA), with PR3-ANCA-positive patients twice as likely to relapse as those with MPO-ANCA[40]. Lyons, *et al* demonstrated by a GWAS in patients with AAV that genetic associations were primarily aligned with ANCA subtypes (MPO/PR3-ANCA) rather than diagnostic subgroups (MPA/GPA)[4]. Their results have suggested the classification of AAV into MPO-ANCA-positive angiitis and PR3-ANCA-positive angiitis. In our study, MPO-ANCA positivity was different between the UK and Japan. However, findings in MPO-ANCA-positive patients were consistent with all the patients with MPA. The proportions of PR3-ANCA and ANCA-negative patients in this study might be too small to permit meaningful comparisons.

Our results may have been influenced by referral bias. It was not population-based and tertiary referrals may have led to more severe phenotypes in the Cambridge data. However, MPA is typically managed by specialized centers, and we could not identify clear referral bias in this cohort. This study assembled the largest number of Japanese patients with MPA studied to date and referral bias was reduced by the multicenter design. In addition, most of the features were common between the non-trial data and trial data, and this suggested legitimacy of the results in our study.

The disease phenotypes in patients with MPA were different between Europe and Japan. However, survival outcomes were similar. Our study provides essential information to interpret the results of future international trials and will facilitate studies of the genetic and environmental factors underpinning the causes and presentation of MPA.

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REFERENCES

1. Heckmann M, Holle JU, Arning L, Knaup S, Hellmich B, Nothnagel M, et al. The Wegener's granulomatosis quantitative trait locus on chromosome 6p21.3 as characterised by tagSNP genotyping. Ann Rheum Dis 2008;67:972-9.
2. Tsuchiya N, Kobayashi S, Hashimoto H, Ozaki S, Tokunaga K. Association of HLA-DRB1*0901-DQB1*0303 haplotype with microscopic polyangiitis in Japan. Genes Immun 2006;7:81-4.
3. Carr EJ, Niederer HA, Williams J, Harper L, Watts RA, Lyons PA, et al. Confirmation of the genetic association of CTLA4 and PTPN22 with ANCA-associated vasculitis. BMC Med Genet 2009;10:121.
4. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367:214-23.
5. Furuta S, Jayne DR. Antineutrophil cytoplasm antibody-associated vasculitis: recent developments. Kidney Int 2013;84:244-9.
6. Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. Rheumatology 2011;50:1916-20.
7. Watts RA, Scott DG, Jayne DR, Ito-Ihara T, Muso E, Fujimoto S, et al. Renal vasculitis in Japan and the UK — are there differences in epidemiology and clinical phenotype? Nephrol Dial Transplant 2008;23:3928-31.
8. Fujimoto S, Uezono S, Hisanaga S, Fukudome K, Kobayashi S, Suzuki K, et al. Incidence of ANCA-associated primary renal vasculitis in the Miyazaki Prefecture: the first population-based, retrospective, epidemiologic survey in Japan. Clin J Am Soc Nephrol 2006;1:1016-22.
9. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461–9.
10. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniené J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.

11. De Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.
12. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180–8.
13. Ozaki S, Atsumi T, Hayashi T, Ishizu A, Kobayashi S, Kumagai S, et al. Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study. Mod Rheumatol 2012;22:394-404.
14. Jennette J, Falk R, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994; 37:187-92.
15. Jennette J, Falk R, Bacon P, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1-11.
16. Hauer HA, Bajema IM, van Houwelingen HC, Ferrario F, Noël LH, Waldherr R, et al. Renal histology in ANCA-associated vasculitis: differences between diagnostic and serologic subgroups. Kidney Int 2002;61:80-9.
17. What is an intractable disease? Japan Intractable Diseases Information Center. [Internet: Accessed Nov. 12, 2013.] Available from: www.nanbyou.or.jp/entry/245
18. De Groot K, Gross WL, Herlyn K, Reinhold-Keller E. Development and validation of a disease extent index for Wegener's granulomatosis. Clin Nephrol 2001;55:31-8.
19. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87:671–8.
20. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827-32.
21. Luqmani RA, Exley AR, Kitas GD, Bacon PA. Disease assessment and management of the vasculitides. Baillieres Clin Rheumatol 1997;11:423-46.
22. Merkel PA, Cuthbertson DD, Hellmich B, Hoffman GS, Jayne DR, Kallenberg CG, et al. Comparison of disease activity measures for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Ann Rheum Dis 2009;68:103-6.
23. Merkel PA, Seo P, Aries P, Neogi T, Villa-Forte A, Boers M, et al. Current status of outcome measures in vasculitis: focus on Wegener's granulomatosis and microscopic polyangiitis. Report from OMERACT 7. J Rheumatol 2005;32:2488-95.
24. National Institute of Population and Social Security Research (Japan). 2010. [Internet. Accessed Nov. 12, 2013.] Available from: www.ipss.go.jp/syoushika/tohkei/Popular/Popular2012.asp?chap=0
25. Organisation for Economic Co-operation and Development [Internet. Accessed Dec. 11, 2013.] Available from: www.oecd.org/els/health-systems/oecdhealthdata 2013-frequentlyrequesteddata.htm
26. Sato T, Inokuma S, Sagawa A, Matsuda T, Takemura T, Otsuka T, et al. Factors associated with fatal outcome of leflunomide-induced lung injury in Japanese patients with rheumatoid arthritis. Rheumatology 2009;48:1265-8.
27. Azuma A, Hagiwara K, Kudoh S. Basis of acute exacerbation of idiopathic pulmonary fibrosis in Japanese patients. Am J Respir Crit Care Med 2008;177:1397-8.
28. Sato S, Kuwana M. Clinically amyopathic dermatomyositis. Curr Opin Rheumatol 2010;22:639-43.
29. Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010;21:1628-36.
30. Muso E, Endo T, Itabashi M, Kakita H, Iwasaki Y, Tateishi Y, et al. Evaluation of the newly proposed simplified histological classification in Japanese cohorts of myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in comparison with other Asian and European cohorts. Cli Exp Nephrol 2013;17:659-62.
31. Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. Arthritis Rheum 2003;49:388–93.
32. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gross WL. Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. Arthritis Rheum 2005;53:93–9.
33. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology 2009;48:1560-5.
34. Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Intern Med J 2008;38:816-23.
35. Chen M, Yu F, Zhang Y, Zhao MH. Clinical and pathological characteristics of Chinese patients with antineutrophil cytoplasmic autoantibody associated systemic vasculitides: a study of 426 patients from a single centre. Postgrad Med J 2005;81:723-7.
36. Corral-Gudino L, Borao-Cengotita-Bengoa M, Del Pino-Montes J, Lerma-Márquez JL. Overall survival, renal survival and relapse in patients with microscopic polyangiitis: a systematic review of current evidence. Rheumatology 2011;50:1414-23.
37. Watanabe K, Tani Y, Kimura H, Tanaka K, Hayashi Y, Asahi K, et al. Clinical outcomes of Japanese MPO-ANCA-related nephritis: significance of initial renal death for survival. Intern Med 2012;51:1969-76.
38. Yamagata K, Usui J, Saito C, Yamaguchi N, Hirayama K, Mase K, et al. ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes. Clin Exp Nephrol 2012;16:580-8.
39. Mahr A, Katsahian S, Varet H, Guillevin L, Hagen EC, Höglund P, et al. Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. Ann Rheum Dis 2013;72:1003-10.
40. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: The role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum 2012;64:3452-62.