Comparison of the Phenotype and Outcome of Granulomatosis with Polyangiitis Between UK and Japanese Cohorts

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ABSTRACT. ***Objective.*** There are differences in the frequencies of antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitis subgroups between different geographic regions, and we have reported differences in the phenotype of microscopic polyangiitis between Europe and Japan. In this retrospective observational study, we compared phenotypes and outcomes of granulomatosis with polyangiitis (GPA) between the United Kingdom and Japan.

Methods. We identified 128 UK and 82 Japanese patients with GPA diagnosed between 2000 and 2012. We evaluated baseline characteristics including ANCA status and organ involvement, treatment, patient and renal survival, and time to first relapse.

Results. Median age at onset was higher in Japan than in the UK (62.2 yrs vs 57.5 yrs, $p < 0.01$). The proportion of patients with proteinase 3 (PR3)-ANCA was lower in Japan than in the UK (61.0% vs 85.2%, $p < 0.01$), while the proportion of myeloperoxidase-ANCA was higher in Japan than the UK (34.1% vs 8.6%, $p < 0.01$). Serum creatinine at diagnosis was lower in Japan than the UK (68.1 μmol/l vs 101.0 μmol/l, $p < 0.01$). Respiratory involvement was more frequent in Japan than the UK (69.5% vs 40.6%, $p < 0.01$). In both countries, most patients received both glucocorticoids and cyclophosphamide. At 60 months the cumulative survival rates were 87.6% and 94.3% in Japan and the UK, respectively ($p = 0.03$). At 60 months the cumulative relapse rates were 37.1% and 68.1% in Japan and the UK, respectively ($p < 0.01$).

Conclusion. Japanese patients with GPA were older at disease onset, with less PR3-ANCA positivity, milder renal dysfunction, and more frequent respiratory involvement than UK patients. The relapse-free survival rate was higher in Japan than the United Kingdom. (J Rheumatol First Release November 1 2016; doi:10.3899/jrheum.160005)

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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, formerly Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). Proteinase 3 (PR3)-ANCA is the predominant serotype in GPA, while myeloperoxidase (MPO)-ANCA is usually found in MPA. Both genetic and environmental factors are associated with the onset of AAV. 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]. The European Vasculitis Genetics Consortium conducted a large genome-wide association study (GWAS) with 2687 European white patients with GPA and MPA, and they reported associations of HLA-DP, SERPINA1, and PRTN3 with GPA, and an association of HLA-DQ with MPA[3]. Also reported have been associations of the environmental pollutant silica with MPA, the bacterium *Staphylococcus aureus* with GPA, and the drugs

antithyroid agent with MPA and cocaine with both MPA and GPA[4,5,6].

Different frequencies of AAV among countries with different ethnicities and environments have been reported. In the previous population-based studies, the annual incidence of MPA was lower and the annual incidence of GPA was higher in European countries than in Japan[7,8,9,10]. For example, the annual incidences of MPA/GPA/EGPA in the United Kingdom were 6.5/14.3/0.9 per million, compared to 18.2/2.1/2.4 per million in Japan, respectively[10,11,12]. In Australia, located in the southern hemisphere with a majority white population, the incidences of MPA and GPA reflect those in Northern Europe[13]. Not only different frequencies of AAV but also different frequencies of ANCA subtypes have also been reported. The white AAV cohorts had more PR3-ANCA–positive patients (50%-60%), while MPO-ANCA–positive patients made up 84% of the Japanese cohorts. In China, there is no population-based study to our knowledge, but a large cohort of AAV (n = 426) from a single center showed a bias toward MPA (79%) and MPO-ANCA positivity (81%), similar to Japan[14]. Moreover, in addition to the different frequencies of the diseases and ANCA subtypes, we have previously reported regional differences in the phenotype of MPA[15]: higher onset age in Japan, more severe renal involvement in Europe, and more frequent pulmonary involvement in Japan. Such information is important when considering ongoing global trials with AAV, such as the PEXIVAS (ClinicalTrials.gov; NCT00987389) and RITA-ZAREM trials (ClinicalTrials.gov; NCT01697267), and future genetic studies of disease expression, treatment response, and disease course.

In this retrospective observational study, we aimed to compare phenotype and outcome in patients with GPA between the UK and Japan subsequently to the MPA comparison study[15].

MATERIALS AND METHODS

Patients. Sequential patients with GPA were collected from 1 UK and 14 Japanese centers. Patients with GPA, diagnosed between 2000 and 2012 (n = 261), were identified from a multidisciplinary clinic at Addenbrooke's Hospital, Cambridge, UK. Of the 261 patients with GPA, 133 who were referred by remote hospitals were excluded to minimize referral bias, and the remaining 128 patients residing in the East of England were analyzed. There were 82 patients with GPA diagnosed between 2000 and 2013 who were identified by the Research Group of Intractable Vasculitis, Ministry of Health, Labor, and Welfare of Japan from 14 Japanese centers, 6 rheumatology clinics, 3 nephrology clinics, 3 multidisciplinary clinics, 1 respiratory clinic, and 1 ear-nose-throat (ENT) clinic. There were no overlapping patients between this study and the prior MPA comparison study[15].

Diagnosis. All patients in this study were identified using the modified criteria for the classification of Wegener's granulomatosis by the American College of Rheumatology (ACR)[16,17]. Patients fulfilled at least 2 of the following 5 criteria: nasal or oral inflammation; nodules, fixed infiltrates, or cavities on a chest radiograph; microscopic hematuria or > 5 erythrocytes per high-power field; granulomatous inflammation on biopsy; and PR3-ANCA positivity.

Assessment. Phenotypic data included age, sex, ANCA, serum creatinine, and C-reactive protein (CRP), disease extent index (DEI)[18], and organ involvement. Organ involvement was derived from the DEI definitions, but we included arthralgia/myalgia/arthritis/myositis as a "general" symptom in our study. We also added hypertrophic pachymeningitis, which was not included in the DEI definitions, to "central nerve" involvement in this study. 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. All phenotypic descriptors except organ involvement were assessed at disease onset. Organ involvement occurring at or following diagnosis was assessed. These data were collated: the maximum oral glucocorticoid dose converted to the equivalent prednisolone dose, cumulative cyclophosphamide (CYC) exposure, the number of deaths, time to death, causes of death, the number of patients with endstage renal disease (ESRD), time to ESRD, the number of patients with relapse, and time to the first relapse. Relapse was defined as recurrence of vasculitis requiring treatment change, increasing dose of glucocorticoids and/or adding immunosuppressants, methylprednisolone pulse, intravenous immunoglobulins, plasma exchange, and biologics. Data were acquired from patients' medical charts and computer records.

Statistics. The distributions of age, DEI, serum creatinine, and CRP were described by median and interquartile range, and compared by 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 1 or more cells. The cumulative rates for survival and renal survival were assessed by the Kaplan-Meier survival curve, and compared by log-rank test. The cumulative rates for relapse were assessed by cumulative incidence function and compared by Gray's test. Risk factors for relapse were assessed by univariate and multivariate analysis with a competing risk model (Fine and Gray model) considering competing risks of death. Competing risk models jointly estimate the associations of each factor with the competing risk (death) and the event of interest (relapse). All analyses except analysis with a competing risk model used IBM SPSS Statistics version 22, and $p < 0.05$ was taken to indicate statistical significance. Analysis with competing risk model used SAS version 9.3.

RESULTS

Baseline characteristics. The median age at onset was higher in Japan than the UK (median 62.2 and 57.5 yrs, respectively, $p < 0.01$; Table 1). The proportion of PR3/c-ANCA–positive patients in Japan (61.0%) was lower than the UK (85.2%; $p < 0.01$), while the proportion of MPO/p-ANCA–positive patients in Japan (34.1%) was higher than the UK (8.6%; $p < 0.01$). Serum creatinine levels were lower in Japanese than UK cohorts (68.1 μmol/l and 101.0 μmol/l, respectively; $p < 0.01$). In the patients with renal involvement, a similar difference was observed between Japan and the UK (111.4 μmol/l and 252.5 μmol/l, respectively; $p < 0.01$).

Organ involvement. The most frequent organ involvement was the ENT region in both groups: 87.8% (Japan) and 82.0% (UK; $p = 0.26$; Table 2). Constitutional disturbance was less frequent in Japan (70.1%) than the UK (82.8%; $p = 0.04$). Conversely, eye and mucosal involvement was more frequent in Japan (41.5%) than in the UK cohort (25.0%; $p = 0.01$).

Respiratory involvement was also more frequent in Japan than in the UK (69.5% and 40.6%, respectively; $p < 0.01$). The pattern of respiratory involvement was different between Japan and the UK. It was common that the most frequent respiratory involvement was nodule/cavity formation.

Table 1. Baseline characteristics. Data are n (%) unless otherwise indicated.

Characteristics	UK, n = 128	Japan, n = 82	p
Male:female (female rate)	65:63 (49.2)	34:48 (58.5)	0.19
Age at onset, yrs (IQR)	57.5 (42.5–66.8)	62.2 (56.9–70.3)	< 0.01
PR3-(c-) ANCA–positive	109 (85.2)	50 (61.0)	< 0.01
MPO-(p-) ANCA–positive	11 (8.6)	28 (34.1)	< 0.01
ANCA–double-positive	1 (0.8)	4 (4.9)	0.08
ANCA-negative	9 (7.0)	8 (9.8)	0.48
Granuloma on biopsy–positive	40 (31.2)	31 (37.8)	0.33
DEI (IQR)	7 (5–7)	7 (4–9)	0.43
Creatinine, μmol/l (IQR)	101.0 (74.5–257.3)	68.1 (48.6–122.9)	< 0.01
CRP, mg/l (IQR)	70 (15–187)	80 (15–153)	0.75
Followup, months (IQR)	59.6 (24.6–93.4)	36.4 (8.5–72.8)	

Age at onset, DEI scores, serum creatinine levels, and serum CRP levels are shown as median values. P value calculated by the chi-square test or Fisher's exact test for proportions. P value calculated by the Mann-Whitney U test for other distributions comparing the United Kingdom and Japan. DEI: disease extent index; CRP: C-reactive protein; IQR: interquartile range; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase.

Table 2. Organ involvement. Data are n (%).

	UK, n = 128	Japan, n = 82	p
General	106 (82.8)	58 (70.1)	0.04
Skin	19 (14.8)	10 (12.2)	0.59
Eye, mucosa	32 (25.0)	34 (41.5)	0.01
ENT	105 (82.0)	72 (87.8)	0.26
Heart	3 (2.3)	1 (1.2)	1.00
Nerve	29 (22.7)	13 (15.9)	0.23
Peripheral nerve	22 (17.2)	10 (12.2)	0.33
Central nerve	8 (6.3)	4 (4.9)	0.77
Intestine	2 (2.7)	3 (3.7)	0.38
Kidney	61 (47.7)	42 (51.2)	0.61
Respiratory	52 (40.6)	57 (69.5)	< 0.01
IP/fibrosis	6 (4.7)	17 (20.7)	< 0.01
Nodule/tumor/cavity	36 (28.1)	46 (56.1)	< 0.01
AH	15 (11.7)	5 (6.1)	0.23
Others*	4 (3.1)	3 (3.7)	

* In the United Kingdom, included temporal arteritis, splenic infarction, pancreatitis, and orchitis. In Japan, included aortitis, necrotizing lymphadenitis, and prostatitis. P value was calculated by the chi-square test comparing United Kingdom 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. IP/fibrosis: interstitial pneumonia/pulmonary fibrosis; AH: alveolar hemorrhage; ENT: ear, nose, and throat.

However, the second most-frequent involvement was interstitial pneumonia in Japan, while it was alveolar hemorrhage in the UK.

Baseline characteristics and organ involvement in PR3-ANCA–positive patients. Findings in PR3-ANCA–positive patients were generally consistent with those in all of the patients with GPA (Supplementary Tables 1 and 2, available online from jrheum.org). Serum creatinine levels were lower in Japan than the UK ($p < 0.01$). Eye and mucosal involvement were more frequent in Japan than in the UK cohorts ($p = 0.03$). However, significant differences in age at onset and respiratory involvement that were observed in patients with GPA disappeared when focusing on PR3-ANCA–positive patients with GPA.

Treatments. Oral glucocorticoids were widely used in both Japan and the UK (97.6% and 97.7%, respectively; Table 3). Initial oral prednisolone doses were 40 mg/day in Japan and 45 mg/day in the UK. Glucocorticoid tapering was slower in Japan than in the UK, and oral prednisolone doses 6 months after treatment initiation were 14 mg/day and 10 mg/day in Japan and the UK, respectively.

Concomitant immunosuppressants were widely used in both Japan and the UK (87.8% and 95.3%, respectively). Although CYC was the most frequently used immunosup-

Table 3. Patients receiving various treatments during the observational period. Data are n (%) unless otherwise specified.

Type of Treatment	UK, n = 128	Japan, n = 82
Oral glucocorticoids	125 (97.7)	80 (97.6)
Initial dose, mg/day	45	40
Dose at 6 mos, mg/day	10	14
Immunosuppressants	122 (95.3)	72 (87.8)
Cyclophosphamide	105 (82.0)	63 (76.8)
Cumulative dose, g	6.7	3.0
Azathioprine	86 (67.2)	26 (31.7)
Mycophenolate	55 (43.0)	1 (1.2)
Methotrexate	28 (21.9)	7 (8.5)
Cyclosporine	0	6 (7.3)
Tacrolimus	1 (0.8)	5 (6.1)
Mizoribine	0	3 (3.7)
mPSL pulse	53 (41.4)	36 (43.9)
Plasma exchange	17 (13.3)	4 (4.9)
IVIG	10 (7.8)	4 (4.9)
Biologics	62 (45.3)	5 (6.1)
Rituximab	57 (44.5)	5 (6.1)
Infliximab	4 (3.1)	0
Adalimumab	6 (4.7)	0
Alemtuzumab	6 (4.7)	0

"Initial dose" and "dose at 6 mos" mean the median oral glucocorticoid dose converted to equivalent prednisolone dose at 0 and 6 months. "Cumulative dose" means the median cumulative cyclophosphamide dose during the observational period. mPSL: methylprednisolone; IVIG: intravenous immunoglobulins.

pressant in both regions, the median cumulative dose of CYC in Japan was 3.0 g, compared to 6.7 g in the UK. CYC was a component of initial therapy in 62/63 Japanese and 101/105 UK patients. Plasma exchange was less commonly used in Japan than in the UK (4.9% and 13.3%, respectively). Of patients in the UK, 45.3% were treated with biologic agents, whereas only 5 Japanese patients (6.1%) received rituximab (RTX). In the UK, biologics were mostly used for refractory or relapsing disease; only 2 patients were treated with RTX as initial therapy. All 5 Japanese patients had refractory disease and RTX was used off-label prior to its approval in Japan for AAV in 2013.

Patient survival, renal survival, and relapse. At 12 months, cumulative patient survival rates were 93.2% in Japan and 99.2% in the UK (Figure 1A). At 60 months, cumulative patient survival rates were 87.6% in Japan and 94.3% in the UK. The survival rate was lower in Japan than the UK ($p = 0.03$). We observed 11 deaths in Japan (4 infections including 1 *Pneumocystis jirovecii* and 1 coccidioidomycosis, 1 malignancy, 1 ESRD, 1 vasculitis of intestine, 1 gastric ulcer, 1 intestinal bleeding, and 2 unknown cause) and 9 deaths in the UK (3 malignancies, 1 infection, 1 ESRD, 1 respiratory failure, 1 ischemic heart disease, and 2 unknown cause). Median age at death was 78.9 years in Japan and 74.1 years in the UK. Most deaths occurred in older patients.

At 12 months, cumulative renal survival rates were 94.9% in Japan and 96.9% in the UK (Figure 1B). At 60 months, cumulative renal survival rates were 94.9% and 95.4%, respectively. The survival curves were not different between the 2 countries ($p = 0.79$).

At 12 months, cumulative relapse rates were 13.9% and 23.2% in Japan and the UK, respectively (Figure 1C). At 60 months, cumulative relapse rates were 37.1% and 68.1% in Japan and the UK, respectively. Relapse was less frequent in Japan than the UK ($p < 0.01$). The dose of prednisolone at relapse was 10 mg/day in Japan compared to 5 mg/day in the UK ($p < 0.01$).

Multivariate analysis for relapse. A total of 20 items were selected as potential explanatory variables: age, sex, MPO-/PR3-ANCA status, DEI, creatinine and CRP levels in Table 1; 9 systems of organ involvement in Table 2; initial dose of oral glucocorticoids, dose of oral glucocorticoids at 6 months, cumulative dose of CYC in Table 3; and geographical region (Japan/the UK). We confirmed in advance there was no collinearity between them. Explanatory variables with p values < 0.1 on univariate analysis (Table 4) were entered in the multivariate analysis model. Then a multivariate analysis with a competing risk model for the combined population of both the Japanese and the UK cohorts (n = 210) with 106 relapses was performed by a stepwise method (forward selection). Results for relapse are shown in Table 4. Significant factors for relapse associated with lower risks in the model were Japanese residence and higher serum creatinine level.

DISCUSSION

We have previously reported different incidences of MPA/GPA and different phenotypes in MPA between European and Japanese patients[10,15]. In the present report, we investigated whether there were also differences in phenotype and outcome between well-characterized patient cohorts with GPA. Patients in the UK were younger, and had higher PR3-ANCA positivity and serum creatinine levels at the onset of disease when compared to patients in Japan. These differences in patients with GPA in our study were in common with the differences in patients with MPA in our previous study[15]. The patterns of organ involvement also differed, with more frequent eye, mucosa, and respiratory involvement in Japan and more constitutional disturbance in the UK. The reasons for these phenotypic differences are not clear. The same diagnostic criteria were used between the cohorts. We suspect that underlying differences in genetic and environmental factors might explain the phenotypic differences.

Studies have reported the greater importance of ANCA subtypes[3,19,20]. Lyons, *et al* demonstrated in their GWAS that associations with particular genes were primarily aligned with ANCA subtypes rather than diagnostic subgroups[3]. Mahr, *et al*, using a cluster analysis approach, demonstrated that ANCA subtypes PR3-ANCA and MPO-ANCA divided AAV into more distinct subsets than diagnostic subgroups GPA and MPA[19]. Lionaki, *et al* demonstrated that ANCA

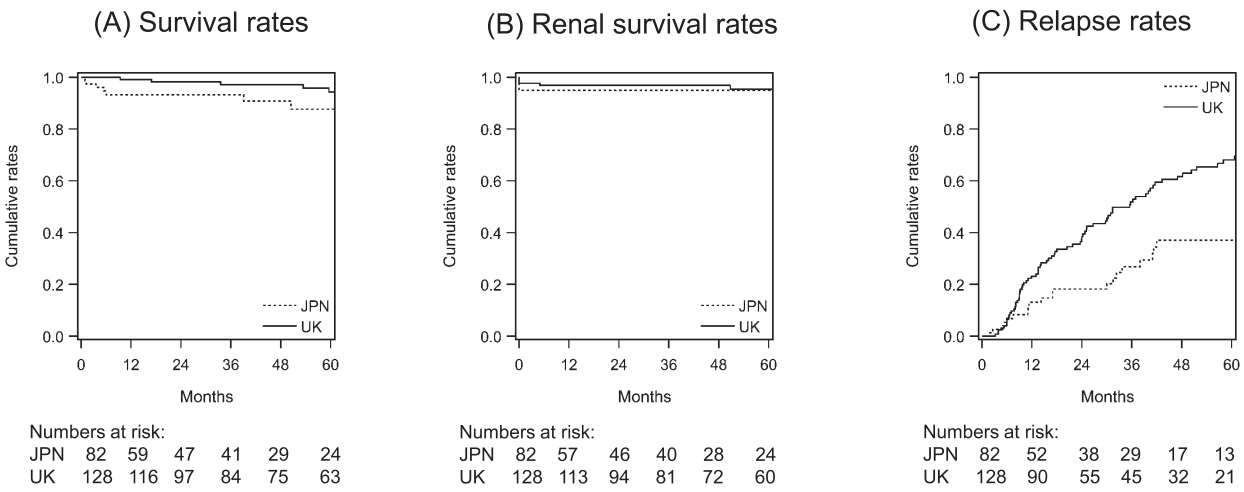

Figure 1. Cumulative survival, renal survival, and relapse rates. A. At 12 months, cumulative survival rates were 99.2% and 93.2% in the United Kingdom and Japan, respectively. At 60 months, cumulative survival rates were 94.3% in the United Kingdom and 87.6% in Japan. The survival rate was higher in the United Kingdom than in Japan (p = 0.03). B. At 12 months, cumulative renal survival rates were 96.9% in the United Kingdom and 94.9% in Japan. At 60 months, cumulative renal survival rates were 95.4% in the United Kingdom and 94.9% in Japan. The survival curves showed no significant difference between the United Kingdom and Japan (p = 0.79). C. At 12 months, cumulative relapse rates were 23.2% and 13.9% in the United Kingdom and Japan, respectively. At 60 months, cumulative relapse rates were 68.1% and 37.1% in the United Kingdom and Japan, respectively. The relapse rate was higher in the United Kingdom than in Japan (p < 0.01).

Table 4. Multivariate analysis for relapse.

	Univariate Analysis		Multivariate Analysis	
	sHR (95% CI)	p	sHR (95% CI)	p
Creatinine ≤ 100 µmol/l	1	NA	1	NA
100 < Creatinine ≤ 300	0.79 (0.50–1.25)	0.32	0.71 (0.44–1.14)	0.16
Creatinine > 300 µmol/l	0.42 (0.22–0.82)	0.01	0.33 (0.17–0.65)	< 0.01
Skin involvement	1.81 (1.04–3.15)	0.03		
Kidney involvement	0.65 (0.44–0.95)	0.03		
Country: Japan	0.49 (0.32–0.76)	< 0.01	0.39 (0.24–0.64)	< 0.01

Subdistribution hazard ratios (sHR), 95% CI, and p values were calculated by competing risk model for the combined population of Addenbrooke's Hospital and the 14 Japanese hospitals (n = 210). NA: not applicable; creatinine: serum creatinine levels.

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[20]. In addition, previous clinical trials conducted by the European Vasculitis Society (EUVAS) revealed that PR3-ANCA was associated with relapse risk and MPO-ANCA was associated with mortality, rather than GPA and MPA[21]. These results have suggested the classification of AAV into PR3-ANCA–positive angiitis and MPO-ANCA–positive angiitis. The modified ACR criteria for Wegener's granulomatosis used in our study was based on clinical and pathological findings as well as PR3-ANCA positivity. However, PR3-ANCA–positive angiitis and MPO-ANCA–positive angiitis often share these findings with each other. On the other hand, the previous population-based studies[10,11,12] revealed MPO-ANCA–positive angiitis was a dominant phenotype (83.7%) and PR3-ANCA–positive angiitis was a rare form (7.0%) in Japanese patients with AAV. The bias toward MPO-ANCA–positive angiitis in Japanese patients with AAV seemed to lead to more MPO-ANCA–positive GPA in Japan than in the UK (34.1% vs 8.6%, p < 0.01). The increased proportion of MPO-ANCA–positive GPA in Japan, which was consistent with the previous study in Japan[22], might explain some phenotypic differences observed in our study. Indeed, in the analysis focusing on PR3-ANCA–positive patients with GPA, the significance of differences of age and respiratory involvement was diminished. Older onset age and a higher frequency of respiratory involvement are also features of Japanese MPO-positive patients with AAV[15]. As a result, lower serum creatinine levels, lower frequency of constitutional symptoms, and higher frequency of eye involvement in Japan than in the UK are phenotypic differences in typical PR3-ANCA–positive GPA. When discussing only

PR3-ANCA–positive patients with GPA, the phenotypic differences between the countries were smaller than the differences previously observed in the MPA comparison study[15]. This was an unexpected result when considering previous studies suggesting a greater association of genetic factors with GPA than with MPA[3].

Treatment strategies differed between the UK and Japan. Although the initial dose of glucocorticoids was lower in Japan, doses of glucocorticoids at 6 months were higher there. This suggested slower glucocorticoid tapering in Japan. The frequency of concomitant CYC, a standard immunosuppressant for remission induction, was similar, but the frequency of concomitant azathioprine (AZA), a standard immunosuppressant for remission maintenance, was lower in Japan. As remission maintenance therapy, no or minimal dose of glucocorticoids with AZA was popular in the UK, compared to the higher dose of glucocorticoids without immunosuppressant that was common in Japan. Less RTX use in Japan reflected the fact that RTX was approved for AAV in Japan in 2013.

Survival rates were higher in the UK than Japan but relapse-free survival rates were lower there than in Japan. Multivariate analysis identified lower serum creatinine levels at onset, consistent with previous EUVAS studies[21], but also identified UK residency as a predictor for relapse. Reasons for the effect of geographical region (the UK/Japan) on relapse were not clear. Simple genetic and environmental differences between the regions might be the explanation. In general, PR3-ANCA positivity is associated with relapse risk[20,21], thus lower PR3-ANCA positivity in Japanese patients with GPA could be one of the reasons. Multivariate analysis did not identify the ANCA subtypes, but this study statistically did not include enough MPO-ANCA–positive patients with GPA. Treatment strategy could also have influenced the outcome; in particular, the higher doses of glucocorticoids during the remission maintenance phase in Japan may have influenced the relapse rate there. Unfortunately, in our study we were unable to determine sequential doses of glucocorticoids during the remission maintenance period, and the multivariate analysis did not identify the treatment factors in Table 3 as significant predictors for relapse. Even if higher doses of glucocorticoids in Japan were associated with lower relapse risk, we were unable to evaluate the side effects of glucocorticoids, such as infection, osteoporosis, metabolic disorders, and atherosclerosis. The optimal dose and duration of glucocorticoids in the remission maintenance phase is still unknown.

We compared the Cambridge data to that from other European cohorts[23,24,25,26]. Phenotypes, such as onset age, renal function, and frequencies of organ involvement, were mostly compatible. Bligny, *et al*[26] reported serum creatinine level at baseline was 124 μmol/l and Hilhorst, *et al*[25] reported estimated glomerular filtration rate was 70-71 ml/min/1.73m^2. However, the frequency of respiratory involvement in the Cambridge data (40.6%) was lower than most of the other cohorts (38%-84%). GPA was a rare form of AAV in Japan. There were few studies with Japanese patients with GPA, and numbers of patients with GPA in those studies were small. Ikeda, *et al*[27] reported a serum creatinine level at baseline similar to our study (58 μmol/l). Conversely, Sada, *et al*[28] reported 141 μmol/l, which was much higher than our study. They used the European Medicines Agency algorithm[29] for classifying GPA. As a result, PR3-ANCA was positive in only 35.9% and MPO-ANCA was positive in 62.3% of patients with GPA in their cohort. Patients with GPA identified in their study were quite a different population from those in our study.

There were several classification systems for GPA, such as the modified ACR criteria[16], the 1990 ACR criteria[17], the European Medicines Agency algorithm[29], and the definitions of the Chapel Hill consensus conference[30]. Using different inclusion criteria might lead to different results. We selected the modified ACR criteria for our study. It has been widely used in recent clinical trials and contains ANCA subtype information consistent with the trend of valuing ANCA subtypes[3,19,20]. The original 1990 ACR criteria[17] were the same as the modified ACR criteria with the exception of not incorporating ANCA data. That allowed us to reanalyze the patients with GPA using the original 1990 ACR criteria[17] (Supplementary Tables 3 and 4, available online from jrheum.org). The results were mostly similar, but frequencies of renal and respiratory involvements were higher in the cohorts using the original 1990 ACR criteria[17] than in the cohorts using the modified ACR criteria[16].

There were limitations in our study. Relapse rates were different between the UK and Japan; however, treatment strategies seemed different too. Treatments obviously influenced outcomes and could be confounding factors in a nontrial setting such as our study. Next, our study was not population-based and may have been influenced by referral bias. Regarding the Cambridge data, we excluded 128 of 261 patients with GPA referred from outside the local practice area, to minimize referral bias. Those patients were generally severe or refractory cases. As for the Japanese data, we chose a multicenter design because of the rarity of GPA in Japan. This study assembled the largest number of Japanese patients with GPA and referral bias was reduced by the multicenter design. Finally, we did not assess the exact number of patients who received a chest computed tomography (CT) scan. It might influence detection of respiratory involvement, although in general, frequencies of chest CT scans seemed similar between Japan and the UK.

The disease phenotypes were different between European and Japanese patients with GPA. Focusing on PR3-ANCA–positive patients, phenotypic differences were diminished. Relapses were less frequent in Japan than in the United Kingdom. This study will facilitate interpreting the results of international AAV trials and studies covering different geographic areas.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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 Japanese. Genes Immun 2006;7:81-4.
3. 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.
4. Furuta S, Jayne DR. Antineutrophil cytoplasm antibody-associated vasculitis: recent developments. Kidney Int 2013;84:244-9.
5. Balavoine AS, Glinoer D, Dubucquoi S, Wémeau JL. Antineutrophil cytoplasmic antibody-positive small-vessel vasculitis associated with antithyroid drug therapy: how significant is the clinical problem? Thyroid 2015;25:1273-81.
6. Graf J. Rheumatic manifestations of cocaine use. Curr Opin Rheumatol 2013;25:50-5.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. Furuta S, Chaudhry AN, Hamano Y, Fujimoto S, Nagafuchi H, Makino H, et al. Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. J Rheumatol 2014;41:325-33.
16. The WGET Research Group. Design of the Wegener's Granulomatosis Etanercept Trial (WGET). Control Clin Trials 2002;23:450-68.
17. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
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. 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.
20. 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.
21. Walsh M, Flossmann O, Berden A, Westman K, Höglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheum 2012;64:542-8.
22. Sada KE, Yamamura M, Harigai M, Fujii T, Dobashi H, Takasaki Y, et al. Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study. Arthritis Res Ther 2014;16:R101.
23. Holle JU, Gross WL, Latza U, Nölle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011;63:257-66.
24. Lane SE, Watts RA, Shepstone L, Scott DG. Primary systemic vasculitis: clinical features and mortality. QJM 2005;98:97-111.
25. Hilhorst M, Arndt F, Kemna MJ, Wieczorek S, Donner Y, Wilde B, et al. HLA-DPB1 as a risk factor for relapse in antineutrophil cytoplasmic antibody–associated vasculitis: a cohort study. Arthritis Rheumatol 2016;68:1721-30.
26. Bligny D, Mahr A, Toumelin PL, Mouthon L, Guillevin L. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. Arthritis Rheum 2004; 51:83-91.
27. Ikeda S, Arita M, Misaki K, Kashiwagi Y, Ito Y, Yamada H, et al. Comparative investigation of respiratory tract involvement in granulomatosis with polyangiitis between PR3-ANCA positive and MPO-ANCA positive cases: a retrospective cohort study. BMC Pulm Med 2015;15:78.
28. Sada KE, Harigai M, Amano K, Atsumi K, Atsumi T, Fujimoto S, et al. Comparison of severity classification in Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study. Mod Rheumatol 2016;26:730-7.
29. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007;66:222-7.
30. 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.