Table 2. Clinical features of 315 patients with eosinophilic granulomatosis with polyangiitis.

	N	%
Systemic	238	76
Skin	162	51
Mucous membranes/Eyes	31	10
ENT	72	23
Chest	190	60
Cardiovascular	50	16
Abdominal	50	16
Renal	122	39
Nervous system	293	93

ENT, ear, nose, and throat.
Eosinophilic granulomatosis with polyangiitis was defined by ACR and Lanham's criteria for all 315 patients.

Differences in clinical features between ANCA-positive and -negative patients

We analyzed the data of the clinical findings that had been collected from EGPA patients through the 2nd survey questionnaire, which applied the nine items subcategories on BVAS for determining the clinical findings. The clinical features of 139 MPO-/pANCA-positive EGPA patients were compared with those of 138 MPO-/pANCA-negative patients. In MPO-/p-ANCA-positive patients, renal involvement, mucous membranes or ophthalmological symptoms, and ENT symptoms were more frequent at diagnosis than in ANCA-negative patients (PR, 95% CI: renal 1.8, 1.3–2.5; mucous membranous or eye 2.5, 1.1–5.4; and ENT 1.7, 1.1–2.7; Table 3 and Figure 1). On the other hand, ANCA-positive patients had fewer skin lesions and cardiovascular involvement than ANCA-positive patients (PR, 95% CI: skin 0:8, 0.6–1.0; and cardiovascular 0.6, 0.3–1.0).

Discussion

Here, we report the results of a cross-sectional nationwide survey on EGPA in Japan. To our knowledge, this study was one of the largest epidemiological studies of EGPA that has been published worldwide, and the results demonstrated that the estimated prevalence of EGPA in Japan was 17.8 per 1,000,000 adults, which was similar to the prevalence reported for the USA and other countries in Europe (10.7–13 per 1,000,000 individuals) [3,4].

In this study, twice as many women had EGPA as men, with a male to female ratio of 1:2. In contrast, previous studies in the USA and Europe have reported a male to female ratio of around 1 [8,15–17]. Since the female predominance was also seen in several clinical studies for MPA in Japan [18–20], this difference in sex distribution may indicate potential environmental and/or genetic influences on the pathogenesis of ANCA-associated vasculitis.

Table 3. Differences in clinical features between MPO-/p-ANCA-positive and -negative patients with eosinophilic granulomatosis with polyangiitis.

	MPO-/p-ANCA (+)		MPO-/p-ANCA (−)		
	N	%	N	%	*P*-value
	139		138		
Systemic	112	81	104	75	0.2952
Skin	61	44	78	56	0.0354
Mucous membranes/Eyes	20	14	8	6	0.0177
ENT	44	32	25	18	0.0092
Chest	77	55	90	65	0.0948
Cardiovascular	15	11	27	20	0.0418
Abdominal	18	13	25	18	0.2351
Renal	72	52	39	28	<0.0001
Nervous system	129	93	129	94	0.8248

MPO, myeloperoxidase; ANCA, anti-neutrophil cytoplasmic antibody; ENT, ear, nose, and throat.

The clinical features frequently found in Japanese EGPA patients included neurological (93%), skin (51%), and respiratory system (58%) involvement. Consistent with this finding, previous reports have indicated that the frequencies of peripheral and central nervous system involvement, pulmonary abnormalities, and cutaneous lesions ranged from 65% to 76%, 51% to 96%, and 40% to 57%, respectively [8,15–17,21]. However, the greater prevalence of neurological manifestations in our study may suggest that mononeuritis multiplex is the most characteristic clinical feature of Japanese EGPA. On the other hand, ENT symptoms were less common than in previous studies, which ranged from 48% to 77% [8,15–17,21]. In the present study, we determined the presence or absence of ENT symptoms judged from the results of BVAS item lists. Therefore, asymptomatic or mild nasal and paranasal sinus diseases may be overlooked, and, furthermore, no surveys from the departments of otorhinolaryngology in our study may eventually resulted in the low frequency of ENT symptoms.

Several reports from Asian countries have shown MPO-/p-ANCA and MPA predominance in patients with ANCA-associated vasculitis, in contrast to the predominance of PR3-/c-ANCA and GPA in Europe and the USA [9,22]. Our study showed that the proportion of EGPA patients who had MPO-/p-ANCA at the onset of EGPA was almost 50%, and this frequency was some higher as compared with the previous reports, in which MPO-/p-ANCA had been detectable in less than 40% [8,16]. In present study, 277 of the 315 patients were tested for MPO-/p-ANCA. Since patients with vasculitic symptoms were highly more detectable for MPO-/p-ANCA than patients without such symptoms, the higher frequency of ANCA positivity may be simply due to more patients with vasculitic EGPA that had been preferentially recruited in our study than in previous reports. MPO-/p-ANCA-positive patients exhibited renal involvement, mucous membrane or eye involvement, and ENT symptoms more frequently than ANCA-negative patients. Furthermore, recent clinical studies have shown that ANCA-positive EGPA patients probably have organ manifestations associated with small-vessel vasculitis, such as focal segmental glomerulonephritis, peripheral neuropathy, purpura, and subcutaneous nodules [16]. Since involvement of the kidneys and mucous membranes or eyes is often seen in MPA and GPA, these results are consistent with those of previous studies. However, the higher prevalence of ENT symptoms in MPO-/p-ANCA-positive patients has not been found in previous studies. Chen et al. showed that MPO-ANCA-positive patients with GPA are common in Chinese populations [23], while PR3-ANCA-positive patients with GPA are common in European populations [24]. Bottero et al. suggested that both rhinitis and asthma in EGPA patients sometimes lack the allergic feature that is usually found in non-EGPA asthmatic patients [25]. Combined with the fact that a history of allergic ENT symptoms in Japanese EGPA patients was less common, this may indicate that ENT symptoms in Asian patients are caused by vasculitis rather than allergies.

In contrast, ANCA-negative EGPA patients exhibited more cardiovascular involvement than ANCA-positive patients. Cardiac involvement is one of the most important predictors of adverse outcomes in EGPA and has been reported to be the primary cause of death in earlier studies, with frequencies up to 50% [6,26]. Of the patients with myocardial manifestations, 39% died during the early stages of the disease [26]. Moreover, although 49% of EGPA patients had cardiovascular involvement as defined by BVAS in a previous report [8], only 16% of EGPA

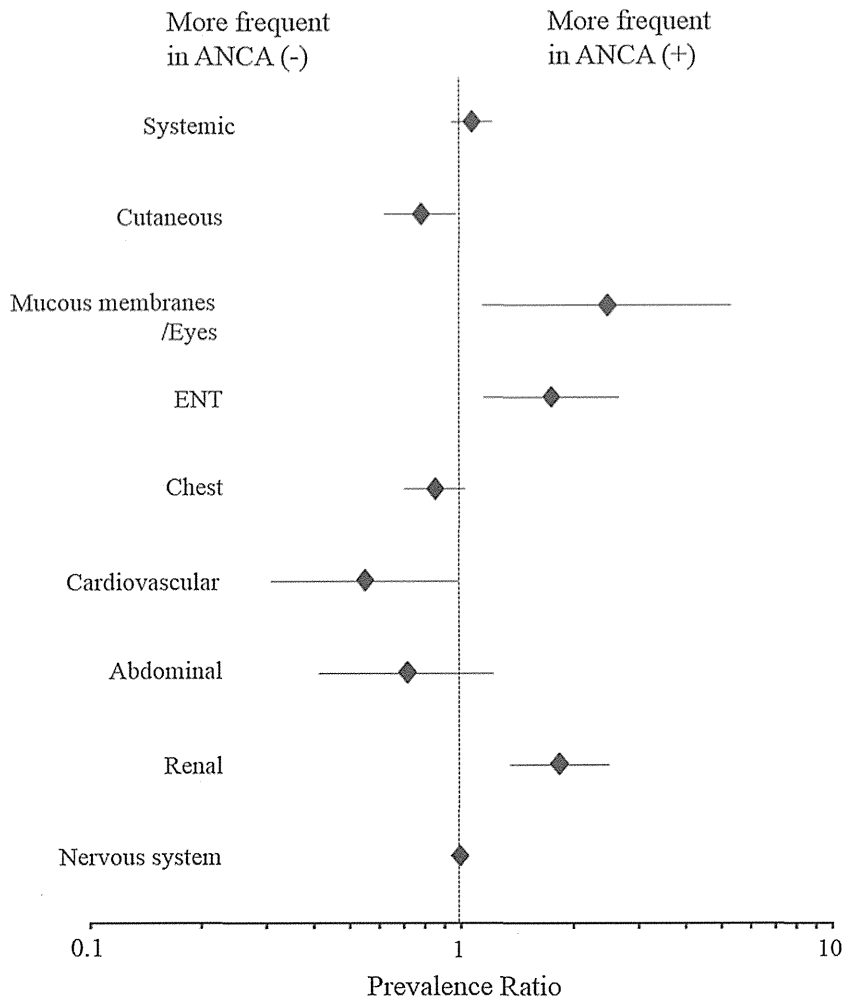

Figure 1. Prevalence ratio of organ involvement in ANCA-positive and -negative patients with eosinophilic granulomatosis with polyangiitis. The diamond reflects the prevalence ratio, and the horizontal bars reflect the 95% CI (logarithmic scale). ANCA, anti-neutrophil cytoplasmic antibody; ENT, ear, nose, and throat.

patients had cardiac involvement in our study. In addition, chronic cardiac disorders, as defined by persistent BVAS at the final visit, were rarely found. It was recently reported that 62% of EGPA patients showed cardiac abnormalities during remission using a combination of clinical evaluations, ECG, echocardiograms, and cardiac MRI [27]. However, the findings of another study support our results, reporting a similar prevalence of cardiac disorders as defined by BVAS [16]. Therefore, asymptomatic cardiac involvement may have been be detected more frequently during careful examinations in our patients. In addition, it is possible that a subset of EGPA patients with poor prognostic factors was excluded from our study because this survey was cross-sectional and required an observation period of 1 year.

A limitation of this study was that the prevalence of EGPA, as determined by the first survey, was measured based on the diagnosis of the physician involved, rather than a standard classification (e.g. ACR criteria or Lanham's criteria). Since only 67% of patients fulfilled the standard classifications, we may overestimate the prevalence of patients with EGPA. On the other hand, we may underestimate the EGPA prevalence, because failed to collect the patient data from the department of pulmonology and otorhinolaryngology in the selected hospitals, where a significant part of Japanese patients with EGPA had to be treated.

In conclusion, the prevalence of EGPA and ANCA in Japan were similar to those previously reported for the USA and Europe. However, recent studies showed MPO-/p-ANCA predominance and a high MPA to GPA incidence ratio in Japanese patients with ANCA-associated vasculitis. The female predominance and increased occurrence of neurological manifestations may be significant features unique to Japanese EGPA patients.

Acknowledgements

The authors would like to thank all the participants and physicians who supported this nationwide survey of EGPA in Japan.

Funding

This work was supported in part by grants from the Ministry of Health, Labour and Welfare of Japan (nannti-ippann-004).

Conflict of interest

None.

References

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol. 1951;27(2):277–301.
2. Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. Arthritis Rheum. 2000;43(2):414–9.
3. Martin RM, Wilton LV, Mann RD. Prevalence of Churg-Strauss syndrome, vasculitis, eosinophilia and associated conditions: retrospective analysis of 58 prescription-event monitoring cohort studies. Pharmacoepidemiol Drug Saf. 1999;8(3):179–89.
4. Mahr A, Guillevin L, Poissonnet M, Ayme S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and

Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis Rheum. 2004;51(1): 92–9.
5. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33(8):1094–100.
6. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore). 1984;63(2):65–81.
7. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37(2):187–92.
8. Sable-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med. 2005;143(9):632–8.
9. 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 UK. Rheumatology (Oxford). 2011;50(10):1916–20.
10. Tamakoshi A (editor). The Procedure in the Nationwide Epidemiological Survey of an Intractable Disease. Nagoya: Research Committee on Epidemiology of Intractable Diseases; 1994.
11. 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(2): 222–7.
12. Luqmani RA, Exley AR, Kitas GD, Bacon PA. Disease assessment and management of the vasculitides. Baillieres Clin Rheumatol. 1997;11(2):423–46.
13. Wakai K, Ohta A, Tamakoshi A, Ohno Y, Kawamura T, Aoki R, et al. Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. J Epidemiol. 1997;7(4):221–5.
14. Sakushima K, Tsuboi S, Yabe I, Hida K, Terae S, Uehara R, et al. Nationwide survey on the epidemiology of syringomyelia in Japan. J Neurol Sci. 2012;313(1–2):147–52.
15. Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. Am J Med. 2003;115(4):284–90.
16. Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum. 2005;52(9):2926–35.
17. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P; French Vasculitis Study Group (FVSG). The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore). 2011;90(1):19–27.
18. 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(3):394–404.
19. Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. Clin Exp Nephrol. 2009;13(6):633–50.
20. Itabashi M, Takei T, Morito T, Yabuki Y, Suzuki H, Ando M, et al. Estimation of BVAS in patients with microscopic polyangiitis in Japan. Clin Rheumatol. 2011;30(11):1499–505.
21. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum. 2013;65(1):270–81.
22. Chen M, Yu F, Zhang Y, Zhao MH. Clinical [corrected] 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(961): 723–7.
23. Chen M, Yu F, Zhang Y, Zou WZ, Zhao MH, Wang HY. Characteristics of Chinese patients with Wegener's granulomatosis with anti-myeloperoxidase autoantibodies. Kidney Int. 2005;68(5):2225–9.
24. Lane SE, Watts RA, Shepstone L, Scott DG. Primary systemic vasculitis: clinical features and mortality. QJM. 2005;98(2): 97–111.
25. Bottero P, Bonini M, Vecchio F, Grittini A, Patruno GM, Colombo B, Sinico RA. The common allergens in the Churg-Strauss syndrome. Allergy. 2007;62(11):1288–94.
26. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore). 1999;78(1):26–37.
27. Dennert RM, van Paassen P, Schalla S, Kuznetsova T, Alzand BS, Staessen JA, et al. Cardiac involvement in Churg-Strauss syndrome. Arthritis Rheum. 2010;62(2):627–34.

Supplementary material available online

Supplementary Appendix.

arthritis research&therapy

RESEARCH ARTICLE Open Access

Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study

Ken-ei Sada[1], Masahiro Yamamura[2], Masayoshi Harigai[3], Takao Fujii[4], Hiroaki Dobashi[5], Yoshinari Takasaki[6], Satoshi Ito[7], Hidehiro Yamada[8], Takashi Wada[9], Junichi Hirahashi[10], Yoshihiro Arimura[11], Hirofumi Makino[1*] and for the Research Committee on Intractable Vasculitides, the Ministry of Health, Labour and Welfare of Japan

Abstract

Introduction: We investigated the clinical and serological features of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in Japan using data from a nationwide, prospective, inception cohort study.

Methods: In total, 156 Japanese patients with newly diagnosed AAV were classified according to the European Medicines Agency (EMEA) algorithm with exploratory surrogate markers for AAV-related non-granulomatous pulmonary lesions, predefined as alveolar haemorrhage and interstitial lung disease (ILD), and their clinical and serological features were evaluated.

Results: Using the EMEA algorithm, we identified 14 patients (9.0%) with eosinophilic granulomatosis with polyangiitis (EGPA), 33 (21.2%) with granulomatosis with polyangiitis (GPA), 78 (50.0%) with microscopic polyangiitis and renal-limited vasculitis (MPA/RLV), and 31 (19.9%) with unclassifiable vasculitis. The average ages of patients with EGPA (male/female, 5/9), GPA (12/21), and MPA/RLV (35/43) and unclassifiable (9/22) were 58.0, 63.6, 71.1, and 70.6 years, respectively. Myeloperoxidase (MPO)-ANCA and proteinase-3 ANCA positivity was 50.0% and 0% for EGPA, 54.6% and 45.5% for GPA, 97.4% and 2.6% for MPA/RLV, and 93.5% and 3.2% for unclassifiable, respectively. According to the Birmingham Vasculitis Activity Score (BVAS), cutaneous (71.4%) and nervous system (92.9%) manifestations were prominent in EGPA and ear, nose, and throat manifestations (84.9%) and chest manifestations (66.7%) in GPA. Renal manifestations developed frequently in MPA/RLV (91.0%) and GPA (63.6%). The average serum creatinine levels were 0.71 mg/dL for EGPA, 1.51 mg/dL for GPA, 2.46 mg/dL for MPA/RLV, and 0.69 mg/dL for unclassifiable. The percentages of patients with ILD were 14.3% for EGPA, 9.0% for GPA, 47.4% for MPA/RLV, and 61.3% for unclassifiable. Patients with ILD ($n = 61$) had significantly lower BVAS ($P = 0.019$) with fewer ear, nose, and throat and cardiovascular manifestations than patients without ILD ($n = 95$).

Conclusions: MPO-ANCA-positive MPA/RLV is the most common form of AAV in Japanese patients, and one-half of patients with GPA were positive for MPO-ANCA. ILD is an important clinical manifestation in Japanese patients with AAV. Unclassifiable vasculitis with MPO-ANCA positivity and ILD may represent a novel variant of MPA.

Trial Registration: The University Hospital Medical Information Network Clinical Trials Registry: UMIN000001648. Registered 28 February 2009.

* Correspondence: makino@md.okayama-u.ac.jp
[1]Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
Full list of author information is available at the end of the article

Introduction

Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's granulomatosis) (GPA), and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA) are the major categories of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), a multisystem autoimmune disease characterised by ANCA production and small-vessel inflammation [1,2]. Despite the overlapping clinicopathologic characteristics between the component diseases, the disease evolution, organ involvement, prognosis, and other clinical characteristics differ substantially among them. In addition, there are interesting geographic and ethnic differences in their relative incidence and myeloperoxidase (MPO)-ANCA or proteinase-3 (PR3)-ANCA positivity [3].

In 2007 Watts and colleagues proposed an AAV classification algorithm, the European Medicines Agency (EMEA) algorithm, with consensus of a group of European physicians interested in the epidemiology of vasculitis [4]. This stepwise algorithm incorporated both the American College of Rheumatology (ACR) criteria for EGPA and GPA and the Chapel Hill Consensus Conference (CHCC) definition of EGPA, GPA, and MPA [2]. In the EMEA algorithm, surrogate markers of granulomatous inflammation for GPA and those of renal vasculitis for renal-limited vasculitis (RLV), an organ-limited variant of MPA, were defined [4]. This algorithm is useful for classifying patients with AAV because no overlapping diagnoses occur and fewer patients are considered to have unclassifiable vasculitis [5], and has been used as the standard method for classification of AAV diseases in recent studies [6,7].

Only two reports have validated the algorithm in other ethnicities outside Europe using a good-quality database. Studies from China [5] and Japan [3] applied the EMEA algorithm to their patient populations and found that MPO-ANCA-positive MPA was the most common form of AAV. These studies, however, were retrospective and evaluated clinical data of patients from a small number of hospitals.

The lung is one of the organs frequently involved in AAV, and pulmonary granuloma, alveolar haemorrhage, and interstitial lung disease (ILD) are representative pulmonary lesions. Among these, only pulmonary granuloma is included in the EMEA algorithm. ILD in AAV is associated with MPO-ANCA and is more common in Asian countries [8-10] than in western countries [11,12], and some patients with MPO-ANCA and ILD subsequently develop typical MPA [13]. To understand the nature of AAV and classify the disease from a global perspective, it is essential to more precisely delineate the clinical implications of ILD in AAV in Asian countries.

To characterise the clinical and laboratory features, effectiveness, and safety of the remission-induction therapy used, as well as the prognosis of Japanese patients with AAV, the Research Committee on Intractable Vasculitides of the Ministry of Health, Labour and Welfare of Japan implemented a nationwide prospective cohort study of Remission Induction Therapy in Japanese Patients with ANCA-associated Vasculitides (RemIT-JAV). In this study, we classified Japanese patients with newly diagnosed AAV enrolled in the RemIT-JAV study according to the EMEA algorithm and compared their phenotypes across the AAVs. We also investigated the clinical relevance of ILD in the patient population.

Methods

Database

Twenty-two tertiary care institutions (university hospitals and referring hospitals) participated in this study (See Appendix) and enrolled consecutive patients with newly diagnosed AAV from April 2009 to December 2010. The criteria for enrolment in this study included receiving a diagnosis of AAV from the site investigators, fulfilling the criteria for primary systemic vasculitis proposed by the EMEA algorithm [4], and requiring immunosuppressive treatment based on the discretion of the site investigators. The exclusion criteria were age younger than 20 years, recurrent AAV, serological evidence for hepatitis B virus or hepatitis C virus infection, and a history of malignancies because this may influence treatment selection and prognosis of patients with AAV. We conducted this study according to the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research in Japan. Written informed consent was obtained from each participant, and the study protocol was approved by the ethics committee at each participating hospital (refer to Acknowledgements). This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000001648).

Data collection

Each patient's baseline data included demographic information, general performance categorised using scales of the World Health Organization performance status except category 5 (death) [14], comorbidities, laboratory data, disease activity scored using the Birmingham Vasculitis Activity Score (BVAS) 2003 [15], imaging data (for example, chest radiograph, thoracic computed tomography, and magnetic resonance imaging of the head), and respiratory function data. The World Health Organization performance status runs from 0 to 5, with 0 denoting perfect health and 5 denoting death (0, asymptomatic; 1, symptomatic but completely ambulatory; 2, symptomatic, <50% in bed during the day; 3, symptomatic, >50% in bed, but not bedbound; 4, bedbound; 5, death).

Patients were evaluated at months 3, 6, 12, 18, and 24 and at relapse, and the following data were collected: vital status, BVAS 2003, laboratory data, treatments, and

adverse events. The Vascular Damage Index score was recorded at months 6, 12, and 24. Chest radiography, thoracic computed tomography, arterial blood gas analysis, and respiratory function data were collected at months 12 and 24 in patients with pulmonary involvement. Observation was completed in March 2013. Only the baseline data are included in this study; the results from analyses of follow-up data will be reported separately.

The site investigators completed and sent the electronic case report form for each patient to the RemIT-JAV data centre at the Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

EMEA classification algorithm for AAV

The enrolled patients were classified using the stepwise EMEA algorithm as described previously [2,4]. Briefly, the ACR criteria and Lanham criteria for EGPA were applied first. Patients who did not fulfil the criteria for EGPA were classified as having GPA if they met the ACR criteria for GPA or the CHCC histological definition for GPA or if they showed histology compatible with the CHCC definition for MPA or ANCA positivity with either of the EMEA-defined GPA surrogate markers. The remaining patients were classified as having MPA if they had clinical features and histology compatible with small-vessel vasculitis without the GPA surrogate markers. In addition, ANCA-positive patients who had the EMEA-defined surrogate markers for renal vasculitis were classified as having RLV, a variant form of MPA. The rest of the patients without histology compatible with the CHCC definition of classic polyarteritis nodosa or typical angiographic features of classic polyarteritis nodosa were categorised as having unclassifiable vasculitis.

To identify a subset of unclassifiable vasculitis with AAV-related nongranulomatous pulmonary lesions, we defined exploratory surrogate markers for alveolar haemorrhage and ILD and then applied them to the EMEA-defined unclassifiable patient population. Surrogate markers for these conditions were as follows: haemoptysis or alveolar haemorrhage evaluated by bronchoscopic examination; or ILD diagnosed by chest X-ray or thoracic computed tomography.

Disease severity

The disease severity of the enrolled patients was classified as localised, early systemic, generalised, or severe according to the European League Against Rheumatism recommendation for conducting a clinical study in systemic vasculitis [16]. Organ failure, classified as severe disease, was defined by the presence of any of the following BVAS manifestations: massive haemoptysis/alveolar haemorrhage, respiratory failure, congestive cardiac failure, ischaemic abdominal pain, or stroke. Threatened vital organ function, classified as generalised disease, was defined by the presence of any of the following BVAS manifestations: sudden visual loss, blurred vision, retinal changes (vasculitis/thrombosis/exudates/haemorrhage), conductive deafness, sensorineural hearing loss, ischaemic cardiac pain, cardiomyopathy, peritonitis, bloody diarrhoea, meningitis, organic confusion, seizures, cord lesion, cranial nerve palsy, sensory peripheral neuropathy, or motor mononeuritis multiplex. Serum creatinine levels were also used to classify disease severity as localised and early systemic (<120 μmol/l (1.3 mg/dl)), generalised (<500 μmol/l (5.5 mg/dl)), and severe (≥500 μmol/l (5.5 mg/dl)) [16].

Statistical analysis

We used the baseline data of the patients enrolled in this study for statistical analysis. The primary purpose of this analysis was to determine the demographic and clinical characteristics of Japanese patients with AAV. Categorical variables were compared using Fisher's direct probability test, and continuous variables were compared using Student t test or the Mann–Whitney U test depending on data distribution. $P < 0.05$ was considered significant for statistical analyses between two categories. When comparing among three categories, statistical significance was determined by $P < 0.05/3$ using Bonferroni correction to avoid multiplicity. All statistical analyses were performed by a biostatistician using the Statistical Package of JMP for Windows software (version 8.0.2; SAS Institute Inc., Cary, NC, USA).

Results

Classification of 156 Japanese patients with AAV according to the EMEA algorithm

In total, 159 patients with AAV were initially enrolled in the RemIT-JAV study. Three patients were then excluded; two patients did not undergo treatment, and one patient had been diagnosed as having AAV and experienced a relapse at the time of enrolment. As a result, 156 patients with newly diagnosed AAV were enrolled in the study.

Using the EMEA algorithm, we identified 14 patients with EGPA, 33 patients with GPA, 78 patients with MPA/RLV, and 31 patients who were unclassifiable (Figure 1). The average ages of the patients with EGPA (male/female, 5/9), GPA (male/female, 12/21), and MPA/RLV (male/female, 35/43) were 58.0, 63.6, and 71.1 years, respectively (Table 1). Patients with MPA/RLV were significantly older at the time of presentation than those with EGPA and GPA ($P < 0.017$ for both), and there was a female predominance for all AAV diseases. MPO-ANCA was detectable in 50.0% of patients with EGPA, in 54.6% of those with GPA, and in 97.4% of those with MPA/RLV. In contrast, PR3-ANCA was detectable in none of the patients with EGPA, in 45.5% of those with GPA, and in 2.6% of those with MPA/RLV.

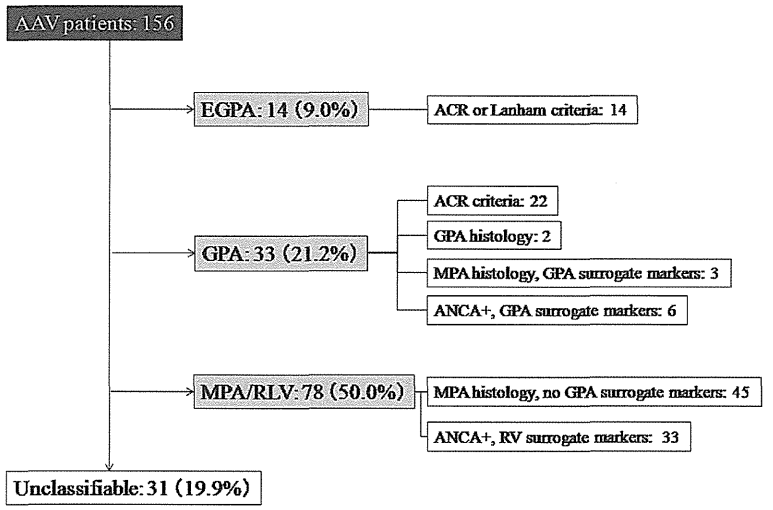

Figure 1 Classification of patients with antineutrophil cytoplasmic antibody-associated vasculitis according to the EMEA algorithm in this cohort study. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); EMEA, European Medicines Agency; GPA, granulomatosis with polyangiitis (Wegener's granulomatosis); MPA, microscopic polyangiitis; RLV, renal-limited vasculitis; RV, renal vasculitis.

Surrogate markers involved in the classification according to the EMEA algorithm

Of the patients classified with GPA, 22 patients fulfilled the ACR criteria, two patients showed CHCC-defined GPA histology, three patients showed CHCC-defined MPA histology in the presence of EMEA-defined GPA surrogate markers, and six patients were positive for ANCA in the presence of GPA surrogate markers. Consequently, nine patients were classified by the presence of GPA surrogate markers, mostly by the presence of

Table 1 Comparison of demographics and disease states among AAV diseases

	EGPA ($n = 14$)	GPA ($n = 33$)	MPA/RLV ($n = 78$)	Unclassifiable ($n = 31$)
Male/female	5/9	12/21	35/43	9/22
Mean (median) age (years)[a,c]	58.0 ± 16.9 (62)	63.6 ± 12.6 (61)	71.1 ± 10.0 (73)	70.6 ± 11.8 (73)
MPO-ANCA[a,c]	7 (50.0)	18 (54.6)	76 (97.4)	29 (93.5)
PR3-ANCA[b,c]	0 (0)	15 (45.5)	2 (2.6)	1 (3.2)
ANCA-negative[a,b]	7 (50.0)	3 (9.1)	1 (1.3)	2 (6.5)
Serum creatinine (mg/dl)[a]	0.71 ± 0.39	1.51 ± 1.32	2.46 ± 2.18	0.69 ± 0.23
Disease severity[c]				
Localised	0 (0)	4 (12.1)	0 (0)	0 (0)
Early systemic	1 (7.1)	5 (15.1)	15 (19.2)	15 (48.4)
Generalised	13 (92.9)	18 (54.6)	47 (60.3)	13 (41.9)
Severe	0 (0)	6 (18.2)	16 (20.5)	3 (9.7)
General performance[d]				
0/1/2/3/4	1/7/2/4/0	8/11/2/11/1	10/29/17/16/6	3/11/7/9/1
Nongranulomatous pulmonary involvement				
Interstitial lung disease[a]	2 (14.3)	3 (9.0)	37 (47.4)	19 (61.3)
Alveolar haemorrhage	0 (0)	2 (6.1)	9 (11.5)	2 (6.5)

Values expressed as mean ± standard deviation or number (percentage) unless otherwise noted. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); GPA, granulomatosis with polyangiitis (Wegener's granulomatosis); MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3; RLV, renal-limited vasculitis. Comparisons between the EGPA, GPA, and MPV/RLV groups were made by Student *t* test or Mann–Whitney *U* test. Statistical significance was determined by $P < 0.05/3$ using Bonferroni correction: [a]EGPA versus MPA/RLV, [b]EGPA versus GPA, [c]GPA versus MPA/RLV. Unclassifiable AAV was not compared with other forms of AAV. [d]General performance was categorised according to the World Health Organization performance status except category 5 (death).

chronic sinusitis or otitis media (Table 2). Of the patients classified with MPA/RLV, 45 patients showed histology compatible with small-vessel vasculitis without GPA surrogate markers and 33 patients were positive for ANCA with EMEA-defined surrogate markers for renal vasculitis. Three patients with allergic rhinitis, but not asthma, who had eosinophilia of peripheral blood and tissue were considered to have unclassifiable vasculitis. The eosinophilic vasculitis was confirmed histologically in all three patients, and two of these three patients were MPO-ANCA-positive. The exploratory surrogate markers for AAV-related nongranulomatous pulmonary lesions were positive in 16 of the 31 unclassifiable patients; three patients had both markers (alveolar haemorrhage and ILD), and 13 patients had only ILD. These 16 patients were all positive for MPO-ANCA.

Organ involvement of 156 Japanese patients with AAV

Patterns of organ involvement defined by the BVAS 2003 scoring system were described and compared among patients with EGPA, GPA, and MPA/RLV (Table 3). Most patients with AAV presented with constitutional symptoms. Cutaneous and nervous system manifestations were most common in patients with EGPA (71.4% and 92.9%, respectively). Ear, nose, and throat manifestations and chest manifestations were characteristic of patients with GPA (84.9% and 66.7%, respectively). It is noteworthy that ILD is not included in the BVAS 2003 scoring system. Renal manifestations developed frequently in patients with MPA/RLV (91.0%) but also in patients with GPA (63.6%). The mean serum creatinine level and prevalence of ILD in patients with MPA/RLV was higher than that in patients with EGPA and GPA, with a significant difference between MPA/RLV and EGPA for both (Table 1). Unclassifiable patients had cutaneous (32.3%), renal (48.4%), and nervous system (48.4%) manifestations (Table 3).

Differences in clinical features between MPO-ANCA-positive and PR3-ANCA-positive AAV

We compared the demographic and clinical features of Japanese patients with AAV who had MPO-ANCA and those who had PR3-ANCA (Table 4). Patients with MPO-ANCA were significantly older at the time of presentation ($P = 0.012$) and had a higher rate of ILD ($P = 0.0015$). The mean serum creatinine level was numerically higher in patients with MPO-ANCA. According to the BVAS 2003 scoring system, MPO-ANCA-positive patients had more cutaneous ($P = 0.046$) and renal ($P = 0.010$) manifestations and fewer ear, nose, and throat manifestations ($P < 0.0001$) with statistical significance.

Of the 33 patients with GPA, 15 patients, 12 patients, and three patients were positive for MPO-ANCA alone, for PR3-ANCA alone, or for both ANCAs, respectively, but three patients were negative for ANCA. Patients with GPA who had MPO-ANCA had a numerically higher rate of renal disease (86.7%) than those with PR3-ANCA (41.7%). The mean serum creatinine level of patients with MPO-ANCA-positive GPA (2.05 ± 0.35 mg/dl) was also numerically higher than that of patients with PR3-ANCA-positive GPA (1.03 ± 0.39 mg/dl).

Clinical features of patients with or without interstitial lung disease

We compared the demographic and clinical characteristics of the patients with and without ILD (Table 5). MPO-ANCA was found significantly more frequently ($P < 0.001$) and PR3-ANCA was found less frequently ($P = 0.038$) in patients with ILD. These patients also tended to have more early systemic diseases and less generalised or severe diseases ($P = 0.059$) and had significantly lower BVAS ($P = 0.019$). The mean serum creatinine level and rates of patients with constitutive symptoms were similar between the two subgroups. The patients with ILD also had statistically fewer ear, nose, and throat ($P = 0.006$) and cardiovascular ($P = 0.012$) manifestations.

Table 2 Surrogate markers in nine patients who were classified with granulomatosis with polyangiitis using these markers

	Number of patients (MPO-ANCA/PR3-ANCA[a])
X-ray evidence of fixed pulmonary infiltrates, nodules, or cavitations present for >1 month	1 (1/0)
Bronchial stenosis	0 (0/0)
Bloody nasal discharge and crusting for 1 month or nasal ulceration	1[b] (0/1)
Chronic sinusitis, otitis media, or mastoiditis for >3 months	7[c] (4/5)
Retro-orbital mass or inflammation (pseudotumor)	0 (0/0)
Subglottic stenosis	1 (0/1)
Saddle nose deformity/destructive sinonasal disease	1 (0/1)

ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase-3. [a]MPO-ANCA/PR3-ANCA, anti-myeloperoxidase antibody-positive versus anti-proteinase-3 antibody-positive patients. [b]One patient had bloody nasal discharge and crusting and chronic sinusitis, and another patient had subglottic stenosis and saddle nose deformity. [c]Five patients with chronic sinusitis, three patients with otitis media, and no patients with mastoiditis.

Table 3 Comparison of disease activity and organ involvement among AAV diseases

	EGPA (*n* = 14)	GPA (*n* = 33)	MPA/RLV (*n* = 78)	Unclassifiable (*n* = 31)
BVAS	16.1 ± 7.7	19.9 ± 7.4	18.4 ± 7.3	12.1 ± 7.6
General	10 (71.4)	23 (69.7)	56 (71.8)	29 (93.6)
Cutaneous[a,b]	10 (71.4)	3 (9.1)	16 (20.5)	10 (32.3)
Mucous membranes/eyes	1 (7.1)	8 (24.2)	9 (11.5)	2 (6.5)
Ear, nose, and throat[a,b,c]	6 (42.9)	28 (84.9)	7 (9.0)	1 (3.2)
Chest[c]	5 (35.7)	22 (66.7)	30 (38.5)	6 (19.4)
Cardiovascular	2 (14.3)	4 (12.1)	6 (7.7)	0 (0)
Abdominal	0 (0)	1 (3.0)	0 (0)	1(3.2)
Renal[a,b]	2 (14.3)	21 (63.6)	71 (91.0)	15 (48.4)
Nervous system[a,b]	13 (92.9)	14 (42.4)	33 (42.3)	15 (48.4)

Values expressed as mean ± standard error or number (percentage). Disease activity and patterns of organ involvement were defined by the BVAS 2003 scoring system. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis (Wegener's granulomatosis); MPA, microscopic polyangiitis; RLV, renal-limited vasculitis. Comparisons between the EGPA, GPA, and MPV/RLV groups were made by Student *t* test or Mann–Whitney *U* test. Statistical significance was determined by $P < 0.05/3$ using Bonferroni correction: [a]EGPA versus GPA, [b]EGPA versus MPA/RLV, [c]GPA versus MPA/RLV. Unclassifiable AAV was not compared with other forms of AAV.

Discussion

This is the first study to apply the EMEA algorithm to prospectively collected and high-quality data of AAV patients outside Europe and to elucidate the clinical phenotypes of the disease. In this study, 156 Japanese patients with newly diagnosed AAV were enrolled from major universities and referring hospitals across Japan and classified according to the EMEA algorithm. The results clearly indicated that MPO-ANCA-positive MPA/RLV was the most common form of AAV in the Japanese population, and more than one-half of the patients with EMEA algorithm-classified GPA showed MPO-ANCA positivity. In addition, we showed that ILD was a common manifestation in Japanese patients with AAV, especially in those with MPA.

The predominance of MPA/RLV and MPO-ANCA positivity in the Japanese population is in marked contrast to the results of studies previously reported from European countries and the United States [3,17-19]. Watts and colleagues validated the EMEA algorithm using 80 paper cases that were originally written for evaluation of the BVAS system for systemic vasculitis with some modifications, representing the relative frequency of AAV in their communities as follows: GPA > MPA > EGPA [4]. It is therefore indispensable and important to evaluate the utility of the EMEA algorithm in ethnicities outside Europe, as we did in this study. We found some difficulties in the classification between GPA and MPA with the EMEA algorithm; for example, of the nine patients classified as having GPA owing to the presence of GPA surrogate markers, five had chronic sinusitis in which granulomatous inflammation was not proven by histology. Because chronic sinusitis is a common disease and because fixed pulmonary infiltrates and otitis media are sometimes observed in AAV diseases other than GPA, classification of AAV using GPA surrogate markers should be cautiously applied in the countries or regions where MPA is more prevalent than GPA.

Within the spectrum of AAV, there are interesting geographic differences in the relative incidence of GPA versus MPA as well as of MPO-ANCA versus PR3-ANCA positivity [20]. In European countries, the incidence of GPA is approximately 4.9 to 10 per million, depending on the geographic location, with higher incidences reported in more northern countries and lower incidences in more southern countries [21,22]. A similar inverse relationship between GPA and MPA has been observed in the Southern Hemisphere [22]. A higher incidence of MPA/RLV than GPA and the predominance of MPO-ANCA found in the Japanese and Chinese AAV populations [3,5] could be related to the lower latitude of these countries.

GPA and MPA are heterogeneous entities with overlapping phenotypes. Recent studies have indicated that the classification system based on ANCA specificity (that is, MPO-ANCA versus PR3-ANCA) may better reflect the phenotypic spectrum of AAV. Cluster analysis of patients with newly diagnosed GPA and MPA from five clinical trials showed that the ANCA specificity classification may be more strongly associated with outcomes such as death and relapse rate than the traditional GPA-MPA separation [23]. Moreover, compared with the CHCC definition and the EMEA algorithm, ANCA specificity was more predictive of relapse in patients with biopsy-proven AAV; patients with PR3-ANCA were almost twice as likely to experience a relapse as those with MPO-ANCA [24]. In this regard, it is intriguing that a genome-wide association study of a European population revealed the presence of genetic distinctions between GPA and MPA that are associated with

Table 4 Comparison of demographics and disease manifestations in MPO-ANCA-positive and PR3-ANCA-positive patients

	MPO-ANCA ($n = 125$)	PR3-ANCA ($n = 13$)	*P* value
Male/female	47/78	6/7	0.56
Mean (median) age (years)	70.0 ± 1.04 (73)	61.3 ± 3.2 (61)	0.012
Serum creatinine (mg/dl)	1.94 ± 0.17	1.22 ± 0.53	0.19
Interstitial lung disease	57 (45.6)	0 (0)	0.0015
Alveolar haemorrhage	11 (8.8)	1 (7.7)	0.89
Disease severity			0.26
Localised	2 (1.6)	1 (7.7)	
Early systemic	33 (26.4)	2 (15.4)	
Generalised	68 (54.4)	8 (61.5)	
Severe	22 (17.6)	2 (15.4)	
General performance[a]			0.26
0/1/2/3/4	16/44/26/31/8	4/6/1/2/0	
BVAS[b]			
BVAS	17.5 ± 0.71	17.5 ± 2.2	0.99
General	95 (76.0)	10 (76.9)	0.94
Cutaneous	30 (24.0)	0 (0)	0.046
Mucous membranes/eyes	16 (12.8)	4 (30.8)	0.08
Ear, nose, and throat	22 (17.6)	12 (92.3)	<0.0001
Chest	49 (39.2)	7 (53.9)	0.31
Cardiovascular	8 (6.4)	2 (15.4)	0.23
Abdominal	2 (1.6)	0 (0)	0.65
Renal	98 (78.4)	6 (46.2)	0.010
Nervous system	55 (44.0)	4 (30.8)	0.36

Values expressed as mean ± standard error or number (percentage) unless otherwise noted. Five patients who were double-positive for both ANCAs were excluded from this analysis. ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; PR3, proteinase-3. [a]General performance was categorised according to the World Health Organization performance status except category 5 (death). [b]Disease activity and patterns of organ involvement were defined by the BVAS 2003 scoring system.

Table 5 Comparing patients with or without interstitial lung disease

	Patients with ILD ($n = 61$)	Patients without ILD ($n = 95$)	*P* value
Male/female	28/33	33/62	0.16
Mean (median) age (years)	69.3 ± 1.6 (71)	67.3 ± 1.3 (71)	0.26
MPO-ANCA	60 (98.3)	70 (73.7)	<0.001
PR3-ANCA	3 (4.9)	15 (15.8)	0.038
Serum creatinine (mg/dl)	1.61 ± 0.23	1.83 ± 0.19	0.45
Disease severity			0.059
Localised	1 (1.7)	3 (3.1)	
Early systemic	21 (34.4)	15 (15.8)	
Generalised	31 (50.8)	60 (63.2)	
Severe	8 (13.1)	17 (17.9)	
General performance[a]			
0/1/2/3/4	11/25/11/12/2	11/33/17/28/6	0.47
BVAS[b]			
BVAS	15.4 ± 1.0	18.4 ± 0.8	0.019
General	49 (80.3)	69 (72.6)	0.27
Cutaneous	13 (21.3)	26 (27.4)	0.39
Mucous membranes/eyes	5 (8.2)	15 (15.8)	0.17
Ear, nose, and throat	9 (14.8)	33 (34.7)	0.006
Chest	22 (36.1)	41 (43.2)	0.38
Cardiovascular	1 (1.7)	11 (11.6)	0.012
Abdominal	0 (0)	2 (2.1)	0.25
Renal	44 (72.1)	65 (68.4)	0.62
Nervous system	28 (45.9)	47 (49.5)	0.66

Values expressed as mean ± standard error or number (percentage) unless otherwise noted. ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; ILD, interstitial lung disease; MPO, myeloperoxidase; MPA, microscopic polyangiitis; PR3, proteinase-3. [a]General performance was categorised according to the World Health Organization Performance Status except category 5 (death). [b]Disease activity and patterns of organ involvement were defined by the BVAS 2003 scoring system.

ANCA specificity [25]. Because of the limited number of patients with PR3-ANCA in our RemIT-JAV cohort, we were not able to perform cluster analysis within this database. We are currently implementing another large-scale cohort study of Japanese patients with AAV, and the combined database will enable us to clarify an association between ANCA positivity and clinical characteristics of AAV in the Japanese population.

MPO-ANCA may contribute to the severity of chronic renal injury and the prevalence of ILD in patients with AAV. Studies of renal biopsy specimens from patients with AAV have demonstrated a higher prevalence and/or severity of renal lesions in MPO-ANCA-positive patients compared with PR3-ANCA-positive patients [26]. These reports are in line with our findings that the mean serum creatinine level of MPO-ANCA-positive patients was numerically higher than that of PR3-ANCA-positive patients (1.94 versus 1.22 mg/dl).

A number of case reports and small case series have indicated that ILD developed more frequently in patients with MPO-ANCA-positive AAV, mainly in those with a diagnosis of MPA, compared with patients with PR3-ANCA-positive AAV [27,28]. A high ratio of MPO-ANCA positivity to PR3-ANCA positivity and a high prevalence of ILD have been reported in Asian countries [8-10], and *vice versa* in northern European countries; ILD was reported in 7.2% of all patients with MPA in the United Kingdom and in less than 10% in other European

countries [11,12]. In this study, we confirmed a high prevalence of ILD in Japanese patients with AAV. These patients were categorised as having a milder form (that is, more early systemic and less generalised or severe diseases) and lower disease activity according to the BVAS (Table 5), partially because ILD is not included in these definitions. Investigation of the clinical courses and prognoses of patients with ILD will shed more light on the relevance of ILD in the severity and activity of AAV.

We identified 16 unclassifiable AAV patients with ILD who were eligible for the EMEA algorithm because they were MPO-ANCA-positive, had symptoms and signs compatible with AAV such as general symptoms, and could not be diagnosed as having other diseases. A previous study reported that MPO-ANCA seroconversion from negative to positive occurred in 10% of patients with ILD in their clinical courses and that some patients with MPO-ANCA and ILD eventually developed typical MPA [29]. On the other hand, vasculitis was proven in five of 15 biopsy specimens of MPO-ANCA-positive patients with pulmonary fibrosis [13]. These data indicate that patients with unclassifiable AAV and ILD could be classified as having MPA. Further investigation is required to pursue this possibility.

This study has some limitations. The number of patients evaluated was limited, and the patient data were collected from the university and referral hospitals in large cities in Japan, which might cause tertiary care biases for the relative frequency of AAV diseases.

Conclusions

MPO-ANCA-positive MPA/RLV is the most common component of AAV in the Japanese population, and more than one-half of patients with GPA are also positive for MPO-ANCA. ILD is an important clinical manifestation in Japanese patients with AAV. Unclassifiable vasculitis with MPO-ANCA positivity and ILD may represent a novel variant of MPA. These data confirm the substantial difference in clinical and ANCA serological features of AAV between western countries and Asian countries, including Japan, and indicate that further investigation and discussion are required from a global perspective for a better AAV classification system that can be applied to all geographic areas and ethnicities.

Consent

This study was approved by the following ethical committees: Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences; Medical Research Ethics Committee of Tokyo Medical and Dental University; Kyoto University Ethics Committee Review Board; Ethics Committee of Kagawa University; Ethics Committee of Juntendo University School of Medicine; Ethics Committee University of Tsukuba Hospital; Ethics Committee of St. Marianna University School of Medicine; Kanazawa University Ethical Committee; Ethics Committee of the University of Tokyo; Ethics Committee of Kyorin University School of Medicine; Saitama Medical Center Hospital Ethics Committee; Research Ethics Committee of the University of Miyazaki; Local Ethics Committee of Toho University; Ethics Committee of Kobe University Hospital; Ethics Committee of Kitano Hospital, The Tazuke Kofukai Medical Research Institute; Shimane University Institutional Committee on Ethics; Ethics Review Committee of Nagoya City University Graduate School of Medical Sciences; Ethics Committee of Ehime University Graduate School of Medicine; Ethics Committee of Jichi Medical University; Ethics Committee of Kyoto Prefectural University School of Medicine; Ethics Committee of Tokyo Medical University Hachioji Medical Center; Ethics Committee of Kitasato University Hospital; and Ethics Committee of Hamamatsu University School of Medicine.

Appendix

Research Committee of Intractable Vasculitis Syndrome of the Ministry of Health, Labour, and Welfare of Japan: in addition to the authors, the following investigators and institutions participated in this study: Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University (Koichi Amano); Department of Nephrology, Faculty of Medicine, University of Tsukuba (Kunihiro Yamagata); Department of Hemovascular and Artificial Organs, Faculty of Medicine, University of Miyazaki (Shouichi Fujimoto); Department of Respiratory Medicine, Toho University Omori Medical Center (Sakae Homma); Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine (Shunichi Kumagai); Center for Nephrology and Urology, Division of Nephrology and Dialysis, Kitano Hospital, Tazuke Kofukai Medical Research Institute (Eri Muso); Department of Rheumatology, Shimane University Faculty of Medicine (Yohko Murakawa); Division of Rheumatology, Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Science (Shogo Banno); Department of Bioregulatory Medicine, Ehime University Graduate School of Medicine (Hitoshi Hasegawa); Division of Nephrology, Department of Internal Medicine, Jichi Medical University (Wako Yumura); Department of Cardiovascular Medicine, Kyoto Prefectural University School of Medicine (Hiroaki Matsubara); Division of Nephrology, Tokyo Medical University Hachioji Medical Center (Masaharu Yoshida); Department of Dermatology, Kitasato University School of Medicine (Kensei Katsuoka); and Third Department of Internal Medicine, Division of Immunology and Rheumatology, Hamamatsu University School of Medicine, Hamamatsu (Noriyoshi Ogawa).

Abbreviations
AAV: antineutrophil cytoplasmic antibody-associated vasculitis; ACR: American College of Rheumatology; ANCA: antineutrophil cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score; CHCC: Chapel Hill Consensus Conference; EGPA: eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); EMEA: European Medicines Agency; GPA: granulomatosis with polyangiitis (Wegener's granulomatosis); ILD: interstitial lung disease; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase-3; RemIT-JAV: Remission Induction Therapy in Japanese Patients with ANCA-associated Vasculitides; RLV: renal-limited vasculitis.

Competing interests
MH has received research grants and/or honoraria from Abbott Japan Co., Ltd, Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd, Eisai Co., Ltd, Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Santen Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Teijin Pharma, Ltd, and Pfizer Japan Inc. TF has received research grants from Abbott Japan Co., Ltd, Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd, Daiichi-Sankyo Pharmaceutical Co. Ltd, Eisai Co., Ltd, Mitsubishi Tanabe Pharma Co, Takeda Pharmaceutical Co., Ltd, and Pfizer Japan Inc. HM serves as a consultant to AbbVie Inc., Astellas Pharma Inc., and Teijin Pharma Ltd; received honoraria from Astellas Pharma Inc., MSD K.K., Takeda Pharmaceutical Co., Ltd, and Mitsubishi Tanabe Pharma Co.; and received research funding from Astellas Pharma Inc., Daiichi Sankyo Inc., Dainippon Sumitomo Pharma Co., Ltd, MSD K.K., Novo Nordisk Pharma Ltd, and Takeda Pharmaceutical Co., Ltd.

Authors' contributions
KS was responsible for conception and design, data collection and analysis, and manuscript writing. MY, MH, and TF were responsible for conception and design, data collection and analysis, and critical revision. HD, YT, SI, HY, TW, and JH were responsible for data collection and interpretation, and critical revision. YA and HM were responsible for conception and design, data collection and analysis, and critical revision. All authors read and approved the final manuscript.

Acknowledgements
This work was supported by grants from Research on Rare and Intractable Diseases, the Ministry of Health, Labour and Welfare, Japan (nannti-ippann-004). The authors thank Keiko Hongo, Kumiko Muraki, Eri Katsuyama, Takayuki Katsuyama, Haruki Watanabe, Mariko Narazaki, Noriko Toyota, Yoshinori Matsumoto, Ryutaro Yamanaka, and Kouichi Sugiyama for their great assistance in data management.

Author details
[1]Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. [2]Center for Rheumatology, Okayama Saiseikai General Hospital, 1-17-18 Ifuku-cho, Kita-ku, Okayama 700-8511, Japan. [3]Department of Pharmacovigilance and Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. [4]Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. [5]Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Department of Internal Medicine, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan. [6]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan. [7]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. [8]Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan. [9]Division of Nephrology, Department of Laboratory Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Faculty of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan. [10]Department of Nephrology and Endocrinology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. [11]First Department of Internal Medicine, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan.

Received: 16 August 2013 Accepted: 9 April 2014
Published: 23 April 2014

References

1. Jennette J, Falk R, Bacon P, Basu N, Cid M, Ferrario F, Flores-Suarez L, Gross W, Guillevin L, Hagen E, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA: **Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.** *Arthritis Rheum* 2013, **65**:1–11.
2. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG, McCluskey RT, Sinico RA, Rees AJ, van Es LA, Waldherr R, Wiik A: **Nomenclature of systemic vasculitides. Proposal of an international consensus conference.** *Arthritis Rheum* 1994, **37**:187–192.
3. Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, Hashimoto H, Nunoi H: **Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K.** *Rheumatology (Oxford)* 2011, **50**:1916–1920.
4. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D: **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**:222–227.
5. Liu LJ, Chen M, Yu F, Zhao MH, Wang HY: **Evaluation of a new algorithm in classification of systemic vasculitis.** *Rheumatology (Oxford)* 2008, **47**:708–712.
6. Watts RA, Mooney J, Skinner J, Scott DG, Macgregor AJ: **The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis.** *Rheumatology (Oxford)* 2012, **51**:926–931.
7. Goupil R, Brachemi S, Nadeau-Fredette AC, Deziel C, Troyanov Y, Lavergne V, Troyanov S: **Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis.** *Clin J Am Soc Nephrol* 2013, **8**:416–423.
8. Ozaki S, Atsumi T, Hayashi T, Ishizu A, Kobayashi S, Kumagai S, Kurihara Y, Kurokawa MS, Makino H, Nagafuchi H, Nakabayashi K, Nishimoto N, Suka M, Tomino Y, Yamada H, Yamagata K, Yoshida M, Yumura W, Amano K, Arimura Y, Hatta K, Ito S, Kikuchi H, Muso E, Nakashima H, Ohsone Y, Suzuki Y, Hashimoto H, Koyama A, Matsuo S, *et al*: **Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study.** *Mod Rheumatol* 2012, **22**:394–404.
9. Chen M, Yu F, Zhang Y, Zhao MH: **Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients.** *Medicine (Baltimore)* 2008, **87**:203–209.
10. Ahn JK, Hwang JW, Lee J, Jeon CH, Cha HS, Koh EM: **Clinical features and outcome of microscopic polyangiitis under a new consensus algorithm of ANCA-associated vasculitides in Korea.** *Rheumatol Int* 2012, **32**:2979–2986.
11. Arulkumaran N, Periselneris N, Gaskin G, Strickland N, Ind PW, Pusey CD, Salama AD: **Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study.** *Rheumatology (Oxford)* 2011, **50**:2035–2043.
12. Bhanji A, Karim M: **Pulmonary fibrosis-an uncommon manifestation of anti-myeloperoxidase-positive systemic vasculitis?** *NDT Plus* 2010, **3**:351–353.
13. Homma S, Matsushita H, Nakata K: **Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides.** *Respirology* 2004, **9**:190–196.
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: **Toxicity and response criteria of the Eastern Cooperative Oncology Group.** *Am J Clin Oncol* 1982, **5**:649–655.
15. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, Savage C, Adu D: **Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis.** *QJM* 1994, **87**:671–678.
16. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, Jayne D, Mahr A, Merkel PA, Raspe H, Scott DG, Witter J, Yazici H, Luqmani RA: **EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis.** *Ann Rheum Dis* 2007, **66**:605–617.

17. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P: **The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort.** *Medicine (Baltimore)* 2011, **90**:19–27.
18. Watts RA, Lane SE, Bentham G, Scott DG: **Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom.** *Arthritis Rheum* 2000, **43**:414–419.
19. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH: **Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease.** *Clin J Am Soc Nephrol* 2012, **7**:240–247.
20. Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DG: **Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe.** *Ann Rheum Dis* 2001, **60**:170–172.
21. Watts RA, Lane SE, Scott DG, Koldingsnes W, Nossent H, Gonzalez-Gay MA, Garcia-Porrua C, Bentham GA: **Epidemiology of vasculitis in Europe.** *Ann Rheum Dis* 2001, **60**:1156–1157.
22. Gibson A, Stamp LK, Chapman PT, O'Donnell JL: **The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a Southern Hemisphere region.** *Rheumatology (Oxford)* 2006, **45**:624–628.
23. Mahr A, Katsahian S, Varet H, Guillevin L, Hagen EC, Hoglund P, Merkel PA, Pagnoux C, Rasmussen N, Westman K, Jayne DR, French Vasculitis Study Group (FVSG); European Vasculitis Society (EUVAS): **Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis.** *Ann Rheum Dis* 2013, **72**:1003–1010.
24. Walsh M, Flossmann O, Berden A, Westman K, Hoglund P, Stegeman C, Jayne D: **Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis.** *Arthritis Rheum* 2012, **64**:542–548.
25. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, Baslund B, Brenchley P, Bruchfeld A, Chaudhry AN, Cohen Tervaert JW, Deloukas P, Feighery C, Gross WL, Guillevin L, Gunnarsson I, Harper L, Hrušková Z, Little MA, Martorana D, Neumann T, Ohlsson S, Padmanabhan S, Pusey CD, Salama AD, Sanders JS, Savage CO, Segelmark M, Stegeman CA, Tesař V, *et al.*: **Genetically distinct subsets within ANCA-associated vasculitis.** *N Engl J Med* 2012, **367**:214–223.
26. Hauer HA, Bajema IM, van Houwelingen HC, Ferrario F, Noel LH, Waldherr R, Jayne DR, Rasmussen N, Bruijn JA, Hagen EC: **Renal histology in ANCA-associated vasculitis: differences between diagnostic and serologic subgroups.** *Kidney Int* 2002, **61**:80–89.
27. Foulon G, Delaval P, Valeyre D, Wallaert B, Debray MP, Brauner M, Nicaise P, Cadranel J, Cottin V, Tazi A, Aubier M, Crestani B: **ANCA-associated lung fibrosis: analysis of 17 patients.** *Respir Med* 2008, **102**:1392–1398.
28. Hervier B, Pagnoux C, Agard C, Haroche J, Amoura Z, Guillevin L, Hamidou MA: **Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature.** *Ann Rheum Dis* 2009, **68**:404–407.
29. Ando M, Miyazaki E, Ishii T, Mukai Y, Yamasue M, Fujisaki H, Ito T, Nureki S, Kumamoto T: **Incidence of myeloperoxidase anti-neutrophil cytoplasmic antibody positivity and microscopic polyangitis in the course of idiopathic pulmonary fibrosis.** *Respir Med* 2013, **107**:608–615.

doi:10.1186/ar4550
Cite this article as: Sada *et al.*: Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study. *Arthritis Research & Therapy* 2014 **16**:R101.

Ⅴ. プログラム・抄録

厚生労働科学研究費補助金　難治性疾患等政策研究事業

難治性血管炎に関する調査研究班

平成 26 年度　第 1 回班会議

プ　ロ　グ　ラ　ム

平成 26 年 9 月 14 日（日）10：00～17：00

於 都市センターホテル 6 階　601 会議室

研究代表者　有村　義宏

難治性血管炎に関する調査研究班
平成26年度　第1回班会議　プログラム

平成26年9月14日（日）

1. 厚生労働省より基調講演　10：00－10：10
厚生労働省　健康局疾病対策課　松倉　遊

2. 今年度の活動目標　10：10－10：30
研究代表者　有村　義宏

3. 今年度の研究分担者・研究協力者紹介／研究計画／進捗状況報告

Ⅰ．大型血管炎臨床分科会活動計画　10：30－10：50
分科会長　磯部　光章

Ⅱ．中・小型血管炎臨床分科会活動計画　10：50－11：15
分科会長　針谷　正祥

Ⅲ．臨床病理分科会活動計画　11：15－11：35
分科会長　石津　明洋

Ⅳ．国際協力分科会活動計画　11：35－11：55
分科会長　藤元　昭一

Ⅴ．横断協力分科会活動計画　11：55－12：15
分科会長　髙崎　芳成

Ⅵ．総合討論　12：15－12：30

～　お　昼　休　憩　～　12：30－13：30

4. ガイドライン作成について　講演　13：30－14：30
研究分担者　中山　健夫
（日本医療機能評価機構：Minds）

5. ガイドライン作成に関する具体的検討　14：30－15：20
研究分担者　中山　健夫
（日本医療機能評価機構：Minds）

6. 事務局より連絡　15：20－15：30
研究分担者　駒形　嘉紀

7. 各分科会小委員会　15：30－17：00

大型血管炎臨床分科会	603会議室
臨床病理分科会	604会議室
中・小型血管炎臨床分科会	601会議室
国際協力分科会	607会議室
横断協力分科会	608会議室

※尚、昼食時に603会議室にて「血管炎登録・ガイドライン作成・普及推進委員会」（研究代表者・各分科会長・事務局）を開催いたします。

大型血管炎分科会活動計画

分科会長

磯部光章　東京医科歯科大学大学院循環制御内科学

研究分担者

小室一成　東京大学大学院医学系研究科循環器内科学
杉原毅彦　東京都健康長寿医療センター　膠原病リウマチ科
種本和雄　川崎医科大学心臓血管外科
中岡良和　大阪大学大学院 医学系研究科循環器内科学
長谷川　均　愛媛大学大学院医学系研究科　血液・免疫・感染症内科学
山田秀裕　聖マリアンナ医科大学　リウマチ膠原病アレルギー内科
吉藤　元　京都大学大学院医学研究科　臨床免疫学

研究協力者

井上芳徳　東京医科歯科大学　食道・一般外科（血管外科）
内田治仁　岡山大学大学院医歯薬学総合研究科 腎・免疫・内分泌代謝内科学講座
重松邦広　東京大学医学部　血管外科
宮田哲郎　山王病院・山王メディカルセンター　血管病センター
渡部芳子　川崎医科大学生理学１

大型血管炎分科会では、高安動脈炎と巨細胞性血管炎の診療の質向上に資するため、臨床的諸問題を解決するなかで標準的診療ガイドラインの作成を目指す。いずれも比較的稀少な疾患ではあるが、特に前者は本邦で発見され、日本人の医学研究者の名を冠した疾患であり、これまで我が国の医学者が研究の主翼を担ってきた疾患である。

高安動脈炎については、前研究班での前向き登録研究をさらに進めることで、本疾患の臨床的特徴、最近の画像診断法の進歩が診断効率の向上に寄与しているか、免疫抑制剤とくに生物学的製剤が本疾患の寛解導入、生命予後改善に有効であるか、を明らかにする。また最近本邦にて GWAS で明らかにされたリスク遺伝子と病型の関連を明らかにし、新しい診療体系の確立とそれに基づくガイドラインの作成を目指す。

巨細胞性血管炎については本邦における信頼に足る新しいデータベースが乏しい。まず、後ろ向きに患者登録を進め、我が国における本疾患の実態を把握する。同時に高安動脈炎と同じ前向き登録研究を継続する。もってエビデンスに基づくガイドライン作成を目指す。特に両疾患の臨床像は欧米における臨床像と異なることが示唆されており、疾患概念についても議論があるところである。新しいガイドラインでは、この点について明らかにするなかで国際的にも通用する理論を構築したい。

Clinical Questions

1）高安動脈炎に対する中等量(20-30mg) のステロイド投与はより高容量 (40-60mg または 0.8-1mg/kg) のステロイド投与より有効と言えるか？

2）高安動脈炎に、免疫抑制剤投与は投与しない場合に比べて、生命予後、血管合併症の改善に有効か？

3）高安動脈炎で、新しい画像診断で得られる情報に基づく病型診断は、予後改善に有効か？

4）高安動脈炎におけるリスク遺伝子の診断に基づく治療法の選択は予後改善に有効か？

5）高安動脈炎における血管狭窄に対して行われる血管内治療は予後改善に有効か？

6）巨細胞性血管炎(GCA)と高安動脈炎の疫学的調査は、両者の病態の違いを明らかにするか、さらにGCAの寛解導入療法・維持療法の向上に有効か？

中・小型血管炎分科会活動計画

難治性血管炎に関する調査研究―中・小型血管炎臨床分科会

分科会長：針谷正祥（東京医科歯科大学大学院医歯学総合研究科 薬害監視学講座）

研究分担者

本間　栄	東邦大学医学部内科学講座呼吸器内科学分野
佐田　憲映	岡山大学大学院医歯薬学総合研究科腎・免疫・内分泌代謝内科学
和田　隆志	金沢大学医薬保健研究域医学系血液情報統御学
伊藤　聡	新潟県立リウマチセンターリウマチ科
土橋　浩章	香川大学医学部内分泌代謝・血液・免疫・呼吸器内科
堀田　哲也	北海道大学大学院医学研究科内科学講座（免疫・代謝内科学）
駒形　嘉紀	杏林大学医学部第一内科（腎臓・リウマチ膠原病内科）
中山　健夫	京都大学大学院医学研究科健康管理学講座（健康情報学）
勝又　康弘	東京女子医科大学附属膠原病リウマチ痛風センター
天野　宏一	埼玉医科大学総合医療センターリウマチ・膠原病内科

研究協力者

臼井　丈一	筑波大学医学医療系臨床医学域腎臓内科学
小川　法良	浜松医科大学第三内科
川上　　純	長崎大学大学院医歯薬学総合研究科展開医療科学講座
川口　鎮司	東京女子医科大学リウマチ科
栗原　泰之	聖路加国際病院放射線科
黒崎　敦子	公益財団法人結核予防会　複十字病院放射線診断科
小松田　敦	秋田大学医学部血液・腎臓・膠原病内科
坂野　章吾	愛知医科大学腎臓・リウマチ膠原病内科
田中　良哉	産業医科大学第一内科学講座
川嶋　聡子	杏林大学第一内科　腎臓・リウマチ膠原病内科
萩野　　昇	帝京大学ちば総合医療センター 血液・リウマチ内科
板橋美津代	東京女子医科大学第四内科

原　章規	金沢大学　医薬保健研究域医学系　未来医療研究人材養成拠点形成事業　プログラムマネージメント室
中野　正明	新潟大学医学部 保健学科 臨床生体情報学
中屋　来哉	岩手県立中央病院腎臓内科
林　　太智	筑波大学 医学医療系 内科　(膠原病・リウマチ・アレルギー)
難波　大夫	名古屋市立大学大学院医学研究科　生体総合医療学講座　呼吸器・免疫アレルギー内科
本間　則行	新潟県立新発田病院内科
村川　洋子	島根大学医学部内科学講座内科学第三内科
山村　昌弘	岡山済生会総合病院内科/リウマチ・膠原病センター
竹田　慎一	黒部市民病院内科
長坂　憲治	東京医科歯科大学大学院医歯学総合研究科 薬害監視学講座
南郷　栄秀	公益社団法人地域医療振興協会　東京北医療センター　総合診療科

中・小型血管炎の主要疾患である抗好中球細胞質抗体（ANCA）関連血管炎（顕微鏡的多発血管炎、多発血管炎性肉芽腫症、好酸球性多発血管炎性肉芽腫症）は、血清中のANCA出現と多臓器病変を特徴とする難治性再発性疾患であり、複数科の専門家がその診断・治療に携わっている。難治性血管炎調査研究班は昨年度までに、ANCA関連血管炎に関連する２班と共同で、ANCA関連血管炎の診療ガイドラインを作成・改訂し、全国レベルでの診断・治療の標準化に寄与してきた。本分科会では、ANCA関連血管炎患者のアウトカムをさらに向上させるために、最新の診療ガイドライン作成手法にもとづき、同ガイドラインの全面的な改訂を行い、併せて、その後の定期的なガイドラインの改訂に必要な研究を実施する。平成26年度は以下の研究課題に取り組む。

1) ANCA 関連血管炎の診療ガイドライン作成

同ガイドライン（2014 年改訂版）を全面改訂し、平成 28 年度末の出版を目指す。医療情報サービス Minds が提案する最新のガイドライン作成手法等を参考に、ANCA 関連血管炎の診療に携わる各領域の専門家を含めたガイドライン作成グループ、システマティックレビュー（SR）チームを形成し、改訂作業を進める。平成 26 年度は、診療アルゴリズム案を作成し、重要臨床課題を決定し、それらに基づいたクリニカルクエスチョン（CQ）を決定し、SR を開始する。ガイドラインの作成にあたっては、ANCA 関連血管炎に関連する既存のガイドラインとの整合性も十分検討する。平成 26 年 6 月 4 日に第 1 回分科会を開催し、ガイドライン作成の目的・方法・基本方針等を討議した。