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RAPID COMMUNICATIONS

# Issues associated with the Ministry of Health, Labour and Welfare diagnostic criteria for antineutrophil cytoplasmic antibody-associated vasculitides: Reclassification of patients in the prospective cohort study of Remission Induction Therapy in Japanese patients with ANCA-associated vasculitides according to the MHLW criteria

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**History**

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Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), have been grouped into the antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides (AAV) that are characterized by necrotizing small-vessel inflammation and high prevalence of ANCA positivity. In 1990, the American College of Rheumatology (ACR) proposed classification criteria for GPA and EGPA [1,2]. In 1994, the Chapel Hill Consensus Conference (CHCC) produced definitions for vasculitis [3]. These criteria and definitions have been used for the entry criteria in clinical trials of AAV patients, but there are some drawbacks. The ACR has not published criteria for MPA, the ACR criteria for EGPA and GPA do not include ANCA positivity, and the CHCC definitions require histological findings. Recently, Watts et al. proposed a new consensus algorithm for the classification of primary systemic vasculitides, including AAV and polyarteritis nodosa (PAN), for epidemiological studies, now known as the European Medicines Agency (EMEA) algorithm [4]. In the algorithm, EGPA is first classified using the ACR or Lanham's criteria, followed successively by GPA, MPA, and PAN. GPA is classified by means of the ACR criteria, the CHCC histological definitions, or histology or ANCA positivity plus surrogate clinical markers for GPA. Subsequently, MPA is classified using the clinical and histological features or ANCA positivity plus surrogate clinical markers for renal vasculitis.

The Ministry of Health, Labour and Welfare (MHLW) criteria for the diagnosis of AAV was proposed in 1998 and are now widely used in Japan, but these criteria have never been formally validated [5](Supplementary1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.982270).

We previously conducted a nation-wide, prospective cohort study of Remission Induction Therapy in Japanese patients with ANCA-associated vasculitides (RemIT-JAV) to characterize Japanese patients with AAV, and to evaluate the effectiveness and safety of remission induction therapy for AAV in Japan (UMIN000001648). A total of 156 patients, receiving a diagnosis of active AAV and requiring immunosuppressive treatment based on the discretion of the site investigators, were enrolled in the study. By applying the EMEA algorithm, 14, 33, and 78 patients were classified as EGPA, GPA, and MPA, respectively, but 31 patients remained unclassifiable (Supplementary 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.982270) [6].

In the present study, a cohort of patients in the RemIT-JAV study was reclassified according to the MHLW criteria. The MHLW scheme classified 13 patients as definite and 2 patients as probable EGPA, 57 as definite and 91 as probable GPA, and 37 as definite and 84 as probable MPA, respectively (Supplementary 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.982270). When the EMEA algorithm was used as a gold standard, the sensitivity, specificity and accuracy of the MHLW definite criteria were 85.7%, 99.2%, and 98.1% for EGPA; 54.5%, 68.3%, and 65.4% for GPA; and 38.5%, 91.0%, and 64.7% for MPA, respectively. These measures of the MHLW probable criteria were 100%, 99.2%, and 99.4% for EGPA; 97.0%, 5.7%, and 25% for GPA; and 91.0%, 35.9% and 63.5% for MPA, respectively (Table 1).

The MHLW definite criteria for GPA showed a lower specificity. Of 57 patients with MHLW-definite GPA, 5, 54, and 9 patients fulfilled the definite criteria (i), (ii), and (iii), respectively, and several patients simultaneously fulfilled two or more of these criteria; 1, 1, and 8 patients fulfilled (i)+(ii)+(iii), (i)+(ii),

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Table 1. Classification capabilities of the Ministry of Health, Labour and Welfare (MHLW) criteria for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides with the prospective cohort study of Remission Induction Therapy in Japanese patients with ANCA-associated vasculitides (RemIT-JAV) in comparison with the European Medicines Agency (EMEA) algorithm.

a) Eosinophilic granulomatosis with polyangiitis (EGPA).

| | MHLW-EGPA definite | MHLW-EGPA probable | MHLW-EGPA unclassified | Total |
|---|---|---|---|---|
| EMEA-EGPA (+) | 12 | 2 | 0 | 14 |
| EMEA-EGPA (−) | 1 | 0 | 141 | 142 |
| Total | 13 | 2 | 141 | 156 |

When the EMEA algorithm was used as a gold standard, the sensitivity, specificity and accuracy of the MHLW definite criteria were 85.7%, 99.2%, and 98.1%. These measures of the MHLW probable criteria were 100%, 99.2%, and 99.4%.

b) Granulomatosis with polyangiitis (GPA).

| | MHLW-GPA definite | MHLW-GPA probable | MHLW-GPA unclassified | Total |
|---|---|---|---|---|
| EMEA-GPA (+) | 18 | 14 | 1 | 33 |
| EMEA-GPA (−) | 39 (EMEA-EGPA 1, EMEA-MPA 37) | 77 (EMEA-EGPA 13, EMEA-MPA 40) | 7 | 123 |
| Total | 57 | 91 | 8 | 156 |

The sensitivity, specificity and accuracy of the MHLW definite criteria were 54.5%, 68.3%, and 65.4%. These measures of the MHLW probable criteria were 97.0%, 5.7%, and 25%.

c) Microscopic polyangiitis (MPA).

| | MHLW-MPA definite | MHLW-MPA probable | MHLW-MPA unclassified | Total |
|---|---|---|---|---|
| EMEA-MPA (+) | 30 | 41 | 7 | 78 |
| EMEA-MPA (−) | 7 (EMEA-EGPA 0, EMEA-GPA 6) | 43 (EMEA-EGPA 7, EMEA-GPA 10) | 28 | 78 |
| Total | 37 | 84 | 35 | 156 |

The sensitivity, specificity and accuracy of the MHLW definite criteria were 38.5%, 91.0%, and 64.7%. These measures of the MHLW probable criteria were 91.0%, 35.9% and 63.5%.

and (ii)+(iii), respectively. In 39 patients with MHLW-definite GPA who failed to meet the EMEA classification for GPA, 3, 33 and 2 patients fulfilled the MHLW GPA definite criteria (i), (ii), and (ii)+(iii), respectively, which indicates that the major disagreement between the two classification methods is due to the MHLW GPA definite criteria (ii) (Supplementary 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.982270). Since "L symptoms" of the MHLW GPA criteria do not include granulomatous inflammation of the respiratory tract or GPA-related pulmonary lesions such as nodules, infiltrations, and cavities, patients with typical MPA who have K symptoms and pauci-immune, crescentic glomerulonephritis could be classified as GPA if "L symptoms", that is bloody sputa, cough, and dyspnea, are present. Replacement of current "L symptoms" with "granulomatous histology and GPA-related pulmonary manifestations" may improve the diagnostic capability of the MHLW criteria. In 24 patients fulfilling both of the MHLW definite criteria for GPA and MPA, only 4 patients were classified as GPA and 20 patients were classified as MPA by the EMEA algorithm. The specificity and accuracy of the MHLW-GPA criteria could be increased by excluding patients with MHLW-definite EGPA and MPA from MHLW-GPA classification (Supplementary 3 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.982270). These results suggest that introduction of such a hierarchical classification system to the MHLW diagnosis criteria may improve their classification capabilities.

Sensitivity of the MHLW criteria appeared to be limited for MPA. Of 78 patients with EMEA-defined MPA, 48 patients did not satisfy the MHLW definite criteria for MPA. However, 41 of this 48 patient population fulfilled the MHLW probable criteria (ii). On the other hand, additional 43 patients with probable MPA were classified by the criteria (ii). By the EMEA algorithm, they were classified as having EMEA-EGPA in 7 patients, EMEA-GPA in 10 patients, and unclassifiable vasculitis in 26 patients. Of these 43 patients, 1 of 7 EMEA-EGPA patients, none of 10 EMEA-GPA patients, and 18 of 26 unclassifiable patients had interstitial lung disease (ILD). These findings indicate that exclusion of ILD from major symptoms of the MHLW MPA criteria and transfer of probable criteria (ii) to the definite criteria, or inclusion of ILD in the EMEA algorithm could increase the sensitivity of the MHLW definite criteria for MPA. Although ILD is presumably an essential clinical manifestation in Asian AAV patients [6], further investigation is required for determining the significance of ILD in MPA classification. The predominance of MPA and MPO-ANCA positivity in Japanese patients over patients in Europe and the United States also could contribute to the discordance in classifying MPA. The EMEA surrogate markers for GPA should be cautiously applied in Japan and other Asian countries, where MPA is more prevalent than GPA [6].

The MHLW diagnostic criteria are established mainly to define patients who can apply for exemption of medical expenses, while the EMEA classification algorithm was developed for epidemiological studies. Thereby, it is difficult to compare the utility and superiority of these two methods in AAV classification. Nonetheless, it is considered as important to understand their concordance and discordance when evaluating the evidence from Western countries in comparison with Japanese evidence.

In conclusion, the MHLW definite criteria had a similar sensitivity and specificity for EGPA but showed a lower sensitivity and specificity for GPA and a lower sensitivity for MPA in comparison with the EMEA algorithm, in a cohort of the RemIT-JAV study. A multi-national clinical study is underway to establish new diagnostic and classification criteria for vasculitides [7]. Comparison of the MHLW criteria with international diagnostic criteria will provide important information for future modification of the MHLW criteria.

EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

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## Conflict of interest

MH has research grants and/or honoraria from Abbvie 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 Abbvie 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 is a consultant for AbbVie, Astellas and Teijin, receives speaker honoraria from Astellas, Boehringer-ingelheim, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Kyowa Hakko Kirin, MSD, Novartis, Pfizer, Takeda, and Tanabe Mitsubishi, and receives grant support from Astellas, Boehringer-ingelheim, Daiichi Sankyo, Dainippon Sumitomo, Kyowa Hakko Kirin, Mochida,MSD, Novartis, Novo Nordisk, Pfizer, Takeda, and Tanabe Mitsubishi.

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## Supplementary material available online

Supplementary 1–3.

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ORIGINAL ARTICLE

# A nationwide survey on the epidemiology and clinical features of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in Japan

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**Abstract**

*Objective.* We conducted a cross-sectional nationwide survey to determine eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) prevalence and clinical features in Japan.
*Methods.* Data for EGPA patients in 2008 were collected from 1,564 hospitals. In total, 965 patients were reported from 365 departments. In a second survey, clinical data for 473 patients were obtained.
*Results.* We estimated that 1,866 (95% CI: 1,640–2,092) patients have EGPA in Japan (prevalence, 17.8/1,000,000). Of the 473 patients in the second survey, 315 fulfilled American College of Rheumatology (ACR) criteria or Lanham's criteria for EGPA. The mean age (± SD) of the 315 at onset was 55 ± 14 years, male to female ratio 1:2. 93% of patients had neurological manifestations, which were the organ system most frequently involved. Among 277 patients tested for myeloperoxidase (MPO)-/p anti-neutrophil cytoplasmic antibody (ANCA), 139 (50%) were positive, while only 6 of 238 were positive for proteinase3 (PR3)-/cANCA. MPO-ANCA-positive patients had renal involvement, mucous membrane or ophthalmological symptoms, and ENT symptoms more frequently, whereas cutaneous lesions and cardiovascular involvement were less common.
*Conclusion.* The prevalence of EGPA and the frequency of MPO-/p-ANCA-positivity in Japanese EGPA patients were mostly similar to those of Western countries. However, female predominance and a high frequency of neurological manifestations characterized Japanese patients.

**Keywords**

Anti-neutrophil cytoplasmic antibodies, Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA), Epidemiology, Vasculitis

**History**

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## Introduction

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA), originally described as allergic granulomatosis and angiitis, is characterized by pulmonary and systemic small-vessel vasculitis, extravascular granulomatous, and hypereosinophilia, and occurs in individuals with asthma and allergic rhinitis [1]. EGPA is a rare vasculitis, and its prevalence in the USA and Europe ranges from 10.7 to 13 per 1,000,000 adults, depending on the classification criteria used [2–4]. In most epidemiological studies, ACR criteria [5] and Lanham's clinical criteria [6] have been used for classification of EGPA. The epidemiology and clinical features of EGPA in Japan have been reported by limited institutions; however, no nationwide studies based on these classification criteria have been performed at present.

EGPA is often associated with the presence of ANCAs that are mostly targeting MPO, whereas other pathogenic mechanisms are also involved in the pathogenesis of EGPA [7]. In the USA and Europe, less than 50% of patients have circulating MPO-ANCA [8]. Recent studies have suggested the existence of different disease subsets in EGPA; for example, ANCA-positive patients have more clinical and histopathological features of small-vessel vasculitis, whereas ANCA-negative patients show tissue infiltration of eosinophils [8]. Previous reports showed that microscopic polyangiitis (MPA) with positive MPO-ANCA was more common in Japan, while granulomatosis with polyangiitis (Wegener's) (GPA) with positive PR3-ANCA was more common in the UK [9]. Although the predominance of ANCA-positivity in Asian patients with EGPA remains to be determined, this could have an effect on the clinical features of their disease progression.

Here, we report the results of a cross-sectional nationwide survey, conducted in 2009, describing the prevalence and clinical features of Japanese patients with EGPA.

## Materials and methods

This survey was designed in the form of two sequential investigations. The first survey was for the epidemiological study, which investigated only the number of patients with EGPA who were treated at hospitals in Japan during 2008, and the second survey was for the clinical study in which a questionnaire was sent to only the departments that had treated EGPA patients during 2008.

The list of all hospitals in Japan was obtained from the Ministry of Health and Welfare. The hospitals were categorized according

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to the institution type and the number of hospital beds. Hospitals were randomly selected from these categories; sampling rates were determined as approximately 5%, 10%, 20%, 40%, 80%, and 100% for the stratum of general hospitals with 20–99 beds, 100–199 beds, 200–299 beds, 300–399 beds, 400–499 beds, and 500 or more beds, respectively [10]. From this selection, 2,599 hospitals were selected. Then, in January 2009, the first questionnaire was sent mainly to the department of internal medicine, rheumatology, and neurology at the 2,599 hospitals asking only the number of patients with EGPA treated during 2008. A total of 1,564 hospitals responded to the questionnaire, reporting having treated 965 patients with EGPA in 365 medical departments.

Next, the second survey questionnaire asking for detailed clinical features of each patient was sent only to the departments that reported treating patients with EGPA in 2008. In this study, EGPA was classified by ACR and Lanham's criteria, based on the European Medicines Agency algorithm for the classification of ANCA-associated vasculitis and polyarteritis nodosa [11], and these criteria were used to evaluate the clinical manifestation of EGPA. The following information was examined in the questionnaire: age, sex, history of allergic diseases, previous treatment for allergic diseases, existence of typical clinical course (manifestations of small-vessel vasculitis developed within several years after the onset of allergic diseases), histological information, Birmingham Vasculitis Activity Score (BVAS) [12] at the onset of the disease and the last visit, eosinophil number, ANCA positivity, and treatment information. Details of clinical manifestations and organ involvements were recorded with a corresponding date using the nine items listed on the BVAS form [12] (Supplementary Appendix to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.857582). From the initial 965 patients, clinical data on 475 patients from the second questionnaire were returned. However, two patients were excluded due to insufficient data, leaving a total of 473 patients who were enrolled in this study. The Ethical Board of Jichi Medical University approved this survey (October 2008, No. 08-35).

All statistical analyses were performed using the JMP Statistical Package for Windows software, version 8.0 (SAS Institute Inc., Cary, NC, USA). All results were expressed as means ± SD.

We estimated the prevalence of EGPA from results of the first survey. The estimation was based on the assumption that the responses of the departments were independent of the frequency of patients [13]. The estimation of prevalence of EGPA was computed as

$$\check{a}k = \frac{1}{SRT_k RRT_k}\sum_i iN_{ki} = \frac{1}{\frac{NS_k}{n_k}\frac{N_k}{NS_k}}\sum_i iN_{ki} = \frac{n_k}{N_k}\sum_i iN_{ki}$$

where $SRT_\kappa$, $RRT_\kappa$, $NS_\kappa$, $n_\kappa$, $N_\kappa$, and $N_{\kappa l}$ denote the sampling rate, response rate, the number of sampling departments, the total number of departments, the number of responding departments, and the number of departments with $i$ patients in stratum $k$, respectively [14].

Differences in clinical features between MPO-/p-ANCA-positive and -negative patients in categorical variables were determined by Fisher's exact test. The prevalence ratios (PRs) of organ involvement and the associated 95% CIs were also determined. *P*-values of less than 0.05 were considered significant for all statistical analyses.

## Results

### Prevalence of EGPA in Japan

Of the 2,599 hospitals selected from all over Japan, 1,564 responded to the first questionnaire concerning the number of EGPA patients treated during 2008. A total of 965 patients from 365 medical departments were reported to have been treated for EGPA. Therefore, the annual number of patients treated for EGPA was 1,866 (95% CI: 1,640–2,092). From these results, we calculated the prevalence to be 17.8 per 1,000,000.

Table 1. Demographic data and clinical characteristics of 315 patients with eosinophilic granulomatosis with polyangiitis.

| | |
|---|---|
| N | 315 |
| Age at onset (years) | 55 ± 14 |
| Male/Female | 103/209 |
| Asthma, N (%) | 308 (98) |
| Allergic rhinitis, N (%) | 41 (13) |
| Treatment employed before the presentation of vasculitic manifestations | |
| Glucocorticoid therapy, N (%) | 215 (68) |
| Oral corticosteroids, N | 82 |
| Inhaled corticosteroids, N | 183 |
| Leukotriene receptor antagonists, N (%) | 132 (48) |
| Typical clinical course before onset*, N (%) | 207 (66) |
| Eosinophil number (/μL) | 11494 ± 9172 |
| MPO-/p-ANCA positive, N (%) | 139/277 (50) |
| PR3-/c-ANCA positive, N (%) | 6/238 (3) |
| Tissue biopsy performed, N (%) | 206 (65) |
| Skin, N | 120 |
| Peripheral nerve, N | 60 |
| Kidney, N | 19 |
| Gastrointestinal tract, N | 14 |
| Muscle, N | 13 |
| Lung, N | 11 |
| Paranasal sinus, N | 4 |
| Others, N | 6 |

ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, peroxidase-3.

Eosinophilic granulomatosis with polyangiitis was defined by ACR and Lanham's criteria for all 315 patients.

*Typical clinical course means symptoms due to vasculitis follow allergic disease and eosinophilia.

### Patients' characteristics

Of the 473 patients whose clinical data was made available from the second survey, 315 (67%) patients fulfilled the ACR criteria or Lanham's clinical criteria for EGPA. The clinical characteristics of 315 patients fulfilled the ACR criteria or Lanham's clinical criteria for EGPA are shown in Table 1. The mean age (± SD) was 55 ± 14 years, and the male to female ratio was 1:2. Among the 277 patients tested for MPO-/p-ANCA, 139 (50%) patients were positive for MPO-/p-ANCA at diagnosis, while 138 patients were negative. On the other hand, PR3-/c-ANCA tests were positive in only 6 (3%) of the 238 patients who were tested for PR3-/c-ANCA.

The biopsy of 206 of 315 EGPA patients showed eosinophilic infiltration in 139 patients (67%), necrotizing vasculitis in 58 patients (28%), and extravascular granulomas in 17 patients (8%).

The clinical manifestations of EGPA in 315 patients are shown in Table 2. Overall, 93% of patients had neurological manifestations, which was the most common system involved. In addition, systemic, skin, respiratory system, and renal involvements were found in 76%, 51%, 60%, and 39% of patients, respectively. In contrast, ENT symptoms and cardiovascular involvement were reported in only 23% and 16% of patients, respectively.

A total of 303 (96%) patients were treated with glucocorticoids (mean dosage of prednislone: 46 ± 13 mg/day), and 94 (30%) of these patients were treated with a combination of glucocorticoids and immunosuppressive agents. Patients responded well to these treatments, and organ manifestations had mostly improved by the final visit. However, neurological manifestations, defined by the persistence of BVAS, still remained in 42% of patients. Cardiovascular and renal manifestations were 15% and 12%, respectively.