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RAPID COMMUNICATION

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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RESEARCH ARTICLE Open Access

Different responses to treatment across classified diseases and severities in Japanese patients with microscopic polyangiitis and granulomatosis with polyangiitis: a nationwide prospective inception cohort study

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Abstract

Introduction: This study aims to elucidate the prognosis and the effectiveness of current treatments for Japanese patients with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA).

Methods: Patients with newly diagnosed MPA and GPA were enrolled in a nationwide, prospective, inception cohort study from 22 tertiary Japanese institutions, and treatment patterns and responses were evaluated for 24 months. Primary outcome measures were rates of remission (Birmingham Vasculitis Activity Score, 0) and remission with low-dose glucocorticoids (GC) (prednisolone ≤ 10 mg) (GC remission).

Results: Of 156 enrolled patients, 78 MPA patients and 33 GPA patients were included. Concomitant cyclophosphamide (CY) was used in 24 MPA (31 %) and 20 GPA (60 %) patients during the initial 3 weeks of treatment. After 6 months, remission was achieved in 66 MPA (85 %) and 29 GPA (87 %) patients, while GC remission was obtained in only 31 MPA (40 %) and 13 GPA (39 %) patients. During the 24-month period, 14 MPA patients and 2 GPA patients died; end stage renal disease (ESRD) was noted in 13 MPA patients but no GPA patients. Patients with severe disease, according to the European Vasculitis Study Group (EUVAS) classification, showed poorer ESRD-free and overall survival rates than those with generalized disease ($p < 0.0001$). There were no differences in relapse-free survival rates between GPA and MPA, among EUVAS-defined disease severity categories, and between anti-neutrophil cytoplasmic antibody subspecialties.

Conclusions: The majority of Japanese patients with MPA and GPA received treatment with high-dose GC and limited CY use, and showed high remission and relapse-free survival rates but low GC remission rates in clinical practice.

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

Keywords: Antineutrophil cytoplasmic antibody-associated vasculitis, Cyclophosphamide, Glucocorticoid, Granulomatosis with polyangiitis, Inception cohort, Microscopic polyangiitis, Prospective cohort

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by blood vessel inflammation with few or no immune deposits and the presence of ANCA positivity. Recently, the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides classified AAV into four clinically relevant subsets: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal-limited AAV (RLV), considered an organ-specific variant of MPA [1]. Watts et al. [2] proposed an epidemiological classification algorithm (the European Medicines Agency (EMEA) algorithm), which classifies primary systemic vasculitis into EGPA, GPA, MPA/RLV, and polyarteritis nodosa, with no overlaps between the categories. Significant differences in clinical characteristics and ANCA serology of AAV between European and Asian patients have been suggested [3]. A European epidemiologic study showed a dominance of GPA over MPA [4], while our prospective study [5] and two retrospective studies from China [6] and Japan [3] that applied the EMEA algorithm found perinuclear/myeloperoxidase (MPO)-ANCA-positive MPA to be the most common form of AAV in Asia.

The guidelines of the British Society of Rheumatology (BSR) and the European League Against Rheumatism (EULAR) recommended assessment for treatment with high-dose glucocorticoids (GC) and concomitant cyclophosphamide (CY) or rituximab as the first-line option for all patients with newly diagnosed AAV, in principle [7, 8]. These recommendations are based on several randomized controlled trials (RCTs) enrolling more patients with GPA than with MPA [9–11]. Since patients with MPA were older and tended to exhibit higher levels of creatinine than those with GPA in our cohort of Japanese patients [5], these recommendations should be applied to Asian patients with caution in terms of safety.

Recently, Ozaki et al. [12] have reported the treatment effectiveness stratified by disease severity for Japanese patients with MPO-ANCA-positive MPA in a prospective observational study. However, differences in treatment effectiveness between MPA and GPA patients and across the spectrum of disease severity remain to be clarified.

We have previously reported the demographic and baseline clinical characteristics of Japanese patients with AAV who were enrolled in a nationwide, prospective, inception cohort study of Remission Induction Therapy in Japanese patients with ANCA-associated Vasculitides (RemIT-JAV). In the present study, we aimed to elucidate and compare treatment and its effectiveness in terms of remission, survival, and relapse rates in clinical practice in Japanese patients with MPA and GPA using the RemIT-JAV cohort database.

Methods

Settings and patient population

Database

Details regarding the RemIT-JAV study protocol have been reported previously [5]. Twenty-two tertiary care institutions participated in this study and enrolled 156 consecutive patients with newly diagnosed AAV from April 2009 to December 2010. The criteria for enrolment included a diagnosis of AAV made by the site investigators that fulfilled the criteria for primary systemic vasculitis proposed by the EMEA algorithm: symptoms and signs characteristic of or compatible with a diagnosis of AAV or polyarteritis nodosa; at least one of histological proof of vasculitis, positive serology for ANCA, specific investigations strongly suggestive of vasculitis and/or granuloma, or eosinophilia; and no other diagnosis to account for symptoms/signs [2]. "Specific investigations" included neurophysiological tests for mononeuritis multiplex, conventional or magnetic resonance angiography, and thoracic or neck magnetic resonance imaging/computed tomography imaging, depending on the signs and symptoms of the patients. The site investigators excluded patients with malignancy, infection, drug-induced vasculitis, secondary vasculitis, other types of vasculitides, vasculitis mimics, sarcoidosis, and other nonvasculitic granulomatous disease. Of the 156 patients enrolled, 78, 33, and 14 were classified as MPA, GPA, and EGPA, respectively. The present study included all patients with MPA or GPA from the RemIT-JAV study, but not those with EGPA. The RemIT-JAV study was conducted according to the Declaration of Helsinki and the ethical guidelines for epidemiologic research in Japan. Written informed consent was obtained from each participant, and the study protocol was approved by the ethics committees at each participating institution (refer to Acknowledgements). The RemIT-JAV study was registered to the University Hospital Medical Information Network Clinical Trials Registry (UMIN000001648).

Data collection

Each patient's baseline data included demographic information, comorbidities, laboratory data, Birmingham Vasculitis Activity Score (BVAS), imaging data, and respiratory function data. Patients were evaluated at 3, 6, 12, 18, and 24 months after diagnosis and at relapse, and the following data were collected: vital status, BVAS, laboratory data, treatments, and adverse events. Organ involvement was defined according to BVAS system. Disease severity was determined by the categorization system developed by the European Vasculitis Study Group (EUVAS) [13]. The Vascular Damage Index (VDI) was also collected at 6, 12, and 24 months. Chest radiography, thoracic computed tomography, arterial blood gas analysis, and respiratory function data were collected at

12 and 24 months in patients with pulmonary involvement. Because the RemIT-JAV study was an observational study, a treatment protocol was not provided. Selection and dosage of immunosuppressants, dosage of GC, and concomitant usage of plasmapheresis were determined at the discretion of the attending physicians. Observation was completed in March 2013, and the baseline characteristics have been described previously [5].

Site investigators filled out the electronic case report forms for each patient and submitted them to the RemIT-JAV data center at the Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Primary and secondary outcomes

The primary effectiveness outcome of the present study was the remission rate. We analyzed two types of remission in this study. The first type of remission was determined systematically by a BVAS of 0 on two occasions at least 1 month apart according to EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis [13]. The second type of remission was defined as BVAS of 0 plus a daily prednisolone (PSL) dose of ≤10 mg (designated as "GC remission" hereafter). GCs other than PSL were converted to an equivalent dose of PSL.

Secondary effectiveness outcomes included cumulative overall end-stage renal disease (ESRD)-free and relapse-free survival rates. ESRD was defined as dependence on dialysis or an irreversible increase in serum creatinine level of >5.6 mg/dl (500 μmol/l). Based on the aforementioned EULAR recommendations, relapse was defined as the reoccurrence or new onset of disease activity attributable to active inflammation. Major relapse was defined as a relapse with organ-threatening or life-threatening disease activity, and other relapses were classified as minor [13].

The safety outcome was the type and incidence of serious infections (SIs). Our definition of SIs was based on an International Conference on Harmonisation report [14]. Bacterial infections that required intravenous antibiotic administration and opportunistic infections were regarded as SIs. The diagnosis of infection was based on the attending physicians' clinical diagnosis, using a comprehensive evaluation of physical findings, laboratory data, and imaging data.

Statistical analysis

We used baseline and follow-up data at 3, 6, 12, 18, and 24 months from the patients with MPA and GPA enrolled in this study. The cumulative remission, overall survival, ESRD-free survival, and relapse-free survival rates were analyzed using the Kaplan–Meier method and the log-rank test. p <0.05 was considered significant for statistical analyses between two categories. When comparing three or four categories, statistical significance was determined by p <0.05/3 or p <0.05/4 by Bonferroni correction to avoid multiplicity. When no patients in a group achieved an endpoint, the group was excluded from the long-rank test. As such, the patients with limited type disease, as defined by EUVAS categorization [13], were excluded from the analysis of survival and ESRD-free survival, and patients with early systemic type disease were excluded from the analysis of ESRD-free survival.

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

Patient characteristics

Of the 156 patients with AAV enrolled in the RemIT-JAV study, 78 patients with MPA/RLV and 33 patients with GPA were included in the present study. The mean (median) observation periods were 559 (730) days in MPA patients and 653 (730) days in GPA patients, respectively. At 24 months, 52 patients with MPA and 28 patients with GPA remained in the cohort (Fig. 1). Selected patient characteristics and treatment of these patients are summarized in Table 1; details regarding patient characteristics have been described in our previous report [5].

Treatment patterns

Changes in treatment over time in patients with MPA and GPA are presented in Table 1 as observed data. The mean initial daily PSL dose was 41 mg in MPA patients and 40 mg in GPA patients. Concomitant CY was used during the initial 3 weeks of remission induction therapy in 24 of 78 (31 %) MPA patients and 20 of 33 (60 %) GPA patients. One GPA patient and three MPA patients were treated with plasma exchange. Hemodialysis was implemented at any time point during the initial 3 months in 13 of 78 (14 %) MPA patients and 2 of 33 (6 %) GPA patients. At 3 months, the daily PSL dose was tapered down to ≤15 mg in 29 of 67 (43 %) MPA patients and 10 of 32 (31 %) GPA patients.

At 6 months, the mean daily PSL dose was 12 mg in MPA patients and 13 mg in GPA patients, and 10 of 62 MPA patients (16 %) and 8 of 30 GPA patients (27 %) were receiving concomitant azathioprine. Data regarding treatment were not obtained in one patient with MPA. The mean daily PSL dose decreased gradually thereafter in both groups.

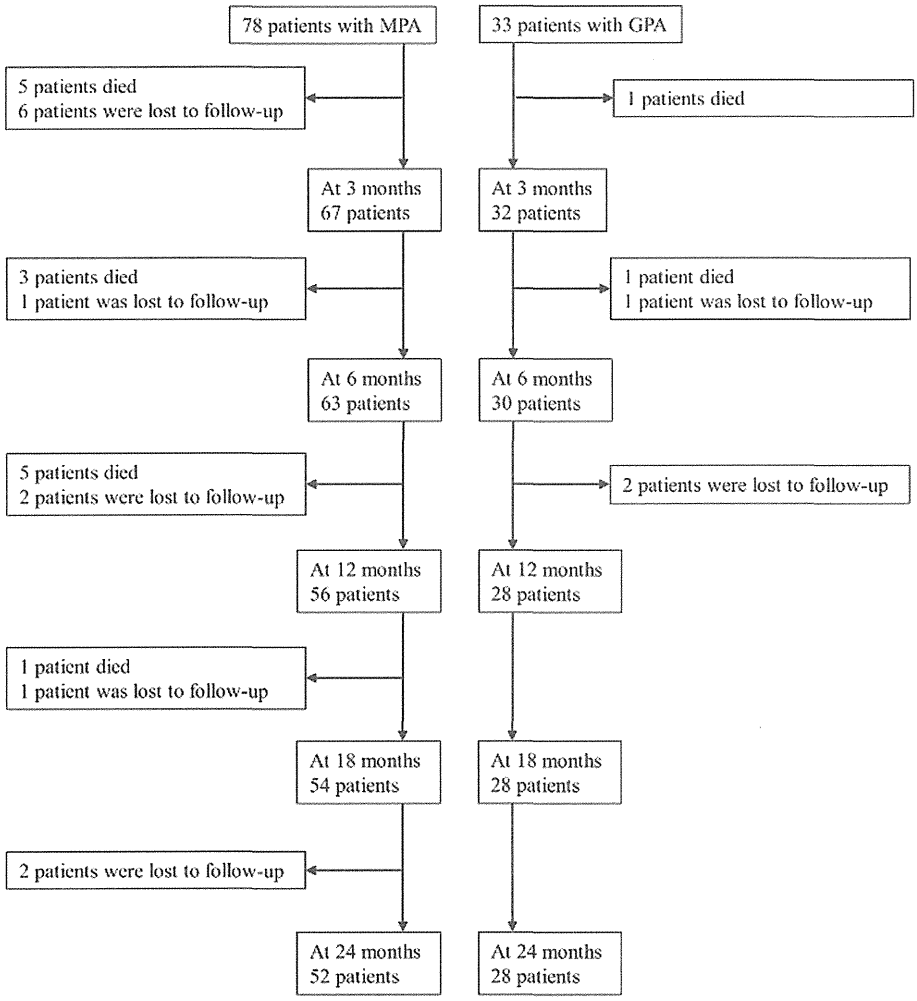

Fig. 1 Flow chart of the enrolled patients. *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis

Remission

No statistically significant differences in remission rates were found between MPA and GPA patients (Fig. 2a). By 6 months, 66 of 78 MPA patients (85 %) and 29 of 33 GPA patients (87 %) achieved remission, as defined by BVAS of 0 on two occasions at least 1 month apart. However, only 31 of 78 MPA patients (40 %) and 13 of 33 GPA patients (39 %) satisfied the definition of GC remission; that is, BVAS of 0 remission plus a daily PSL dose of ≤10 mg.

When both patients with MPA and those with GPA were classified into four different types (i.e. limited, early systemic, generalized, and severe) according to the EUVAS-defined disease severity, there were no significant differences in remission rates across the spectrum of disease severity (Fig. 2b). Remission and GC remission were obtained by 6 months in four (100 %) and three (75 %) of four patients with the limited type, in 18 (90 %) and 10 (50 %) of 20 patients with the early systemic type, in 58 (89 %) and 24 (37 %) of 65 patients with the generalized type, and in 15 (68 %) and 7 (32 %) of 22 patients with the severe type, respectively.

No significant differences in remission and GC remission rates at 6 months were noted between MPO-ANCA-positive and peroxidase-3 (PR3)-ANCA-positive patients, or between patients with or without interstitial lung disease (ILD).

Overall survival

Sixteen deaths were reported during the observation period (14 MPA patients and two GPA patients). Causes of death reported by site investigators were vasculitis itself (five patients), infection (six patients), and other or unknown (five patients: completely unknown in two patients, cardiac failure in one patient, intracerebral hemorrhage in one patient, and hyperkalemia in one patient). Of the five cases of death caused by vasculitis itself, all patients were treated with GC without

Table 1 Patient characteristics and treatments

	MPA ($n = 78$)	GPA ($n = 33$)
Age (years), mean ± SD	71 ± 10	64 ± 13
Sex (male:female)	35:43	12:21
Disease severity, *n*		
Limited	0	4
Early systemic	15	5
General	47	18
Severe	16	6
MPO-ANCA, *n* (%)	76 (97)	18 (55)
PR3-ANCA, *n* (%)	2 (3)	15 (46)
Serum creatinine (mg/dl), mean ± SD	2.46 ± 2.18	1.51 ± 1.32
BVAS, mean ± SD	18 ± 7	20 ± 7
Initial treatments (within 3 weeks)		
Maximum daily dose of PSL (mg/day), mean ± SD	41 ± 15	40 ± 15
mPSL pulse use, *n* (%)	34 (44)	13 (39)
Cyclophosphamide, *n* (%)	24 (31)	20 (60)
Oral:intravenous	3:21	7:13
Cumulative dose for 6 months (g), mean ± SD	2.6 ± 2.8	4.3 ± 3.6
Methotrexate, *n* (%)	0 (0)	2 (6)
Azathioprine, *n* (%)	0 (0)	0 (0)
Treatments at 6 months		
	$n = 62$	$n = 30$
Minimum daily dose of PSL (mg/day), mean ± SD	12 ± 5	13 ± 6
Cyclophosphamide, *n*	20	16
Methotrexate, *n*	0	3
Azathioprine, *n*	10	8
Treatments at 12 months		
	$n = 56$	$n = 28$
Minimum daily dose of PSL (mg/day), mean ± SD	9 ± 5	9 ± 6
Cyclophosphamide, *n*	9	7
Methotrexate, *n*	0	4
Azathioprine, *n*	11	11
Treatments at 24 months		
	$n = 52$	$n = 28$
Minimum daily dose of PSL (mg/day), mean ± SD	7 ± 5	6 ± 3
Cyclophosphamide, *n*	4	5
Methotrexate, *n*	0	4
Azathioprine, *n*	10	5

ANCA antineutrophil cytoplasmic antibody, *BVAS* Birmingham Vasculitis Activity Score, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *MPO* myeloperoxidase, *mPSL* methylprednisolone, *PR3* proteinase 3, *PSL* prednisolone, *SD* standard deviation

concomitant CY and two patients were treated with plasma exchange. Renal manifestations developed in all five cases and ESRD developed in two of five cases. Lung manifestations developed in four of five patients including pulmonary hemorrhage and ILD in one case, ILD in one case, pleuritis in one case, and pulmonary infiltration in one case.

In terms of overall survival rates, MPA patients tended to have a worse prognosis than GPA patients, although the difference did not reach statistical significance (Fig. 3a; $p = 0.12$). In the spectrum of EUVAS disease severity, there were significant differences in overall survival rates among the four different types (Fig. 3b; $p = 0.0003$). Patients with severe disease, showing the lowest survival rate of 56 % at 24 months, had a markedly poorer prognosis, even compared with those with generalized type disease ($p < 0.0001$).

On the other hand, significant differences in survival rates were undetectable between MPO-ANCA-positive and PR3-ANCA-positive patients (82 % versus 92 % at month 24) or between patients with and without ILD (87 % versus 83 % at month 24).

ESRD-free survival

Thirteen cases of ESRD developed during the observation period in MPA patients, but none occurred in GPA patients. Hence, the ESRD-free survival rate of MPA patients was significantly lower than that of GPA patients, decreasing to 81 % at 24 months (Fig. 4a; $p = 0.012$). In the spectrum of EUVAS disease severity, there were significant differences in ESRD-free survival rates (Fig. 4b; $p < 0.0001$). Patients with severe type disease showed the lowest ESRD-free survival rate of 51 % at 24 months, which was much lower than that of patients with generalized type disease ($p < 0.0001$).

MPO-ANCA-positive patients tended to have lower ESRD-free survival rates than PR3-ANCA-positive patients (84 % versus 100 % at 24 months), although this difference was not statistically significant. No significant difference in ESRD-free survival rates was detectable between patients with and without ILD (90 % versus 85 % at 24 months).

Relapse

Of the 98 patients who achieved remission by 6 months, 23 relapsed during the total observation period, including 18 MPA and five GPA patients, with a mean duration for the remission period of 566 days. Of the 23 relapses, 11 were major relapses and 12 were minor. There were no significant differences in relapse rates between MPA and GPA patients (Fig. 5a; 29 % versus 15 % at month 18) or among patients with the four different types of EUVAS disease severity (Fig. 5b) (0 %, 42 %, 21 %, and 28 % at month 18 for limited, early systemic,

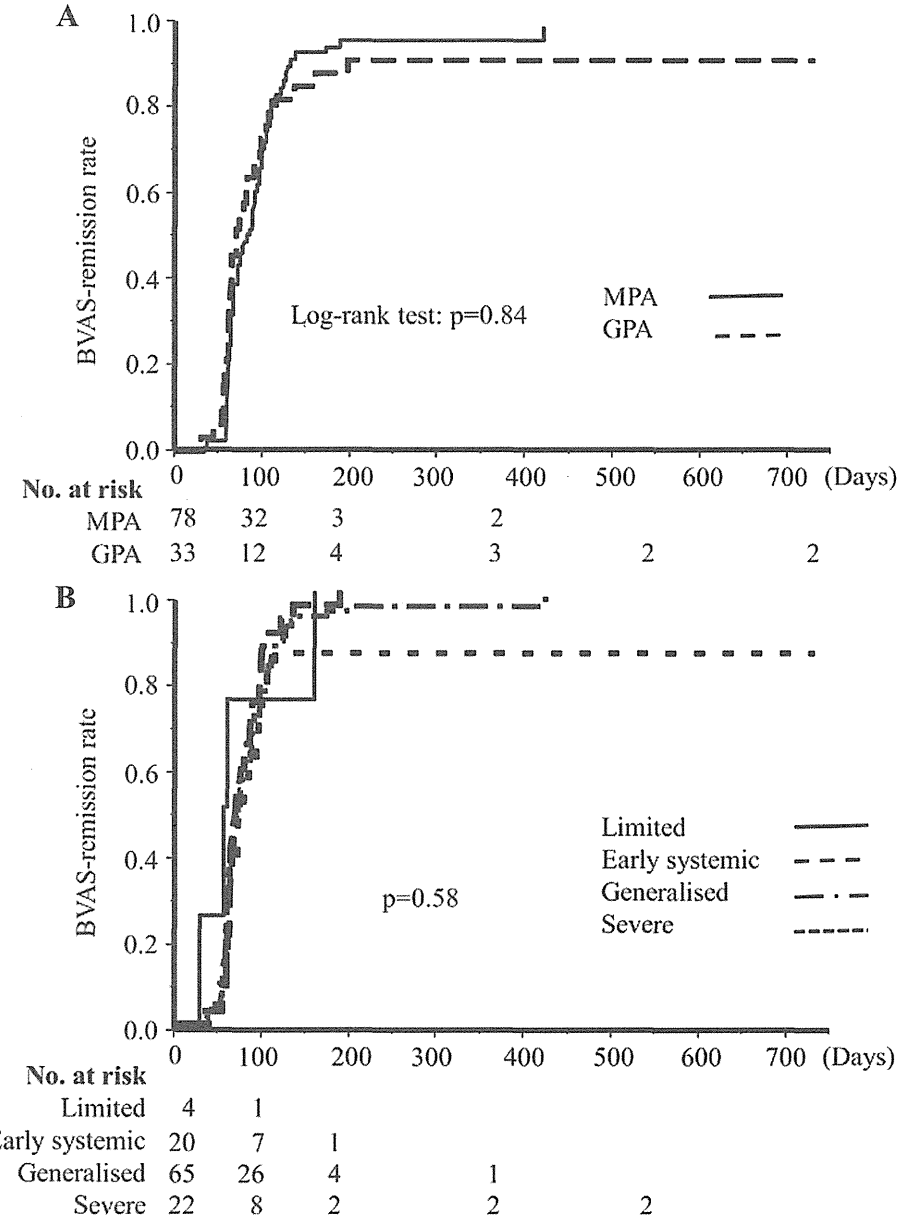

Fig. 2 Cumulative remission rates in MPA and GPA patients and among the four EUVAS-defined disease severity types. **a** Remission rates in MPA and GPA patients. **b** Remission rates among patients with the four types of EUVAS disease severity. *BVAS* Birmingham Vasculitis Activity Score, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis

generalized, and severe types, respectively). In addition, there were no significant differences in relapse rates between MPO-ANCA-positive and PR3-ANCA-positive patients (25 % versus 21 % at month 18) or between patients with or without ILD (34 % versus 18 % at month 18).

SI and VDI

During the 2-year follow-up period, 76 SIs were reported in 46 patients (41.4 %). The number of SIs decreased over time, from 43 in 27 patients in the first 6 months to 20 in 18 patients in the second 6 months, nine in seven patients in the third 6 months, and four in four patients in the last 6 months of follow-up. The most frequent site of SI was the respiratory system (41 events), followed by skin and subcutaneous tissue (12 events). Frequently reported types of opportunistic infections were deep mycoses (14 events), cytomegalovirus infection (10 events), and herpes zoster (nine events).

The mean (standard deviation) total VDI score of MPA patients and GPA patients were 1.95 (1.55) and 1.64 (1.57) at 12 months and 2.13 (1.56) and 2.11 (1.79) at 24 months, respectively.