Longterm Prognosis of 121 Patients with Eosinophilic Granulomatosis with Polyangiitis in Japan

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ABSTRACT. ***Objective.*** We investigated the risk factors for relapse or prognosis of eosinophilic granulomatosis with polyangiitis (EGPA) in Japanese patients presenting to our hospital.

Methods. From June 1999 through March 2015, we retrospectively recruited 121 patients with EGPA according to the American College of Rheumatology criteria. Frequent relapse was defined as disease occurrence at least once every 2 years after a period of initial remission. The study endpoint was the last examination performed. We used multiple logistic regression to analyze risk factors for relapse or survival in EGPA.

Results. Gastrointestinal (GI) involvement with both abnormalities on endoscopy and biopsy ($p < 0.01$) and symptoms; myocardial involvement with both abnormalities on 1 or more cardiac investigations and symptoms ($p < 0.01$); and treatment at initial or maintenance with immunosuppressants ($p < 0.01$) or administration of intravenous immunoglobulin (IVIG; $p < 0.01$) were associated significantly more often with frequent relapse than with infrequent. Overall 5-, 10-, and 20-year survival rates were 91.1%, 83.7%, and 68.6%, respectively. Survival in EGPA was associated with age of onset < 65 years. Age at onset of EGPA was the only significant predictor of survival ($p < 0.01$). Myocardial or GI tract involvement did not affect mortality risk.

Conclusion. Patients with myocardial or GI tract involvement had frequent relapses, but these conditions were not reflected in increased mortality. Treatment with immunosuppressants or IVIG in addition to corticosteroids might have improved the prognosis in Japanese patients with EGPA. (First Release June 1 2017; J Rheumatol 2017;44:1206–15; doi:10.3899/jrheum.161436)

Key Indexing Terms:

CHURG–STRAUSS SYNDROME
EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS
MORTALITY
INTRAVENOUS IMMUNOGLOBULIN
FIVE FACTOR SCORE
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Eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome) is a rare disease characterized by the presence of allergic granulomatosis and necrotizing vasculitis. Development of the condition is preceded by peripheral blood eosinophilia and eosinophilic tissue infiltration[1]. The mortality rate and prognosis of EGPA are related to disease severity as assessed by using the 2009-revised Five Factor Score [FFS2009; age ≥ 65 yrs, severe cardiac involvement, severe gastrointestinal (GI) tract involvement, severe renal insufficiency, and status without sinusitis[2]]. The vasculitis itself is the main cause of death in patients with EGPA, accounting for almost 47.6% of deaths[3]. Patients with systemic vasculitis, including those with EGPA with FFS2009 ≥ 2, have a poorer prognosis than those with FFS2009 = 0[2]. Of the 5 factors, severe cardiac involvement[4,5] or GI tract involvement[4] are independent risk factors for mortality in EGPA. First-year mortality largely results from uncontrolled vasculitis (66%) in patients with various combinations of cardiac, renal, and GI involvement[6].

Prognosis and mortality rates have improved because of better diagnosis in accordance with the American College of Rheumatology (ACR) criteria since 1994[7] and improvements in appropriate treatments over the last 20 years. The 5-, 10-, and 20-year survival rates reported in 2011 by Guillevin, *et al* were about 90%, 75%, and 45%, respectively[2], whereas those reported in 2013 by Moosig, *et al* were 97%, 89%, and 72%, respectively[8]. However, FFS2009 values of 0, 1, and 2 are associated with respective 5-year mortality rates of 9%, 21%, and 40%; despite improvements in the prognosis of EGPA, disease with FFS2009 ≥ 2 has a poor prognosis[2].

The mainstay of treatment for EGPA is systemic cortico-

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steroid therapy; some patients receive additional treatment with immunosuppressive agents such as cyclophosphamide (CYC) and azathioprine (AZA)[9]. Corticosteroid and CYC therapy significantly prolongs survival in patients with FFS1996 of ≥ 2[10]. However, combined therapy with corticosteroids and CYC affords little benefit in some EGPA patients with mononeuritis multiplex or heart failure[11]. Patients with systemic vasculitis (including those with EGPA and mononeuritis multiplex) treated without add-on treatments such as cytotoxic agents, biotherapy, intravenous immunoglobulin (IVIG), or plasma exchange have a poor prognosis[12]. IVIG therapy has been used to treat the initial phases of various diseases, including microscopic polyangiitis (MPA), granulomatosis with polyangiitis, and other antineutrophil cytoplasmic autoantibody (ANCA)-associated systemic vasculitides (AAV)[13]. IVIG have also induced complete remissions in relapsed AAV[14]. We previously showed that IVIG therapy was effective against severe mononeuritis multiplex or heart failure in patients with EGPA who did not respond to corticosteroid–CYC treatment[15]. However, whether IVIG treatment affects relapse rates and prognosis in EGPA is unknown.

Once EGPA remission has been achieved, the relapse rate is high, and many patients remain glucocorticoid-dependent[16]. There have been many multicenter joint studies of prognosis in EGPA[2,3,4,10,17], but few have accumulated patients at a single center[8]. Here, we retrospectively investigated risk factors for relapse or mortality in EGPA in 121 Japanese patients who presented to our hospital, and we analyzed the relationships between these risk factors and clinical manifestations or treatments.

MATERIALS AND METHODS

Patients. We recruited 121 patients with EGPA at the Department of Allergy and Respirology, National Hospital Organization, Sagamihara, Kanagawa, Japan, from June 1999 through March 2015. The presence of EGPA was diagnosed according to the allergic granulomatosis angiitis (Churg–Strauss syndrome) criteria[18] and classified by using the ACR criteria[7]. In brief, for patients with EGPA, inclusion criteria were the presence of at least 4 of the 6 following: asthma, eosinophilia, polyneuropathy, pulmonary infiltrate, paranasal sinus abnormality, and extravascular eosinophils. We collected all patient data retrospectively from medical records.

A state of remission was defined as the absence of clinical signs or symptoms of active vasculitis after initial treatment. A state of relapse was defined as the recurrence after remission of vasculitis symptoms and signs, excluding an exacerbation of asthma or sinusitis (with or without an increase in the proportion of eosinophils among white blood cells), that required the resumption of immunosuppressive therapy or an increased dose of immunosuppressant. A large increase in tissue eosinophilia might be correlated with an increase in the severity of vasculitis signs and symptoms, but this criterion was not considered in our definition of relapse. Frequent relapse was defined as disease occurrence at least once every 2 years after a period of initial remission. Infrequent relapse was defined as relapse less than once every 2 years[19].

Mononeuritis multiplex as motor nerve dysfunction was evaluated using the manual muscle test (MMT) and the Medical Research Council scale (0 to 5), as well as by electromyographic examination. Sensory nerve dysfunction was assessed subjectively based on symptoms and physical examination. Lung involvement was defined as consolidation, ground glass opacity, nodules within the ground glass opacity, interlobular septal thickening[20,21], bronchial wall thickening, lymph node enlargement[22,23], pleural effusion (as identified by high-resolution computed tomography[20,24]), or infiltration by eosinophils (as detected by lung biopsy). Cardiac involvement was defined as cardiac symptoms (as assessed as chest pain, chest discomfort, back pain, or palpitations) or abnormal signs (as assessed by cardiac echocardiography, Holter electrocardiogram, plasma B-type natriuretic peptide level analysis, or myocardial imaging using 123I-metaiodobenzylguanidine). GI involvement was defined as symptoms of epigastralgia, abdominal pain, diarrhea or constipation or positive endoscopic signs, and GI eosinophil infiltration or colonic submucosal edematous change[25], as detected by biopsy. Skin involvement was defined as purpura, erythema, livedo, ulceration, acrocyanosis, nodule formation, or eosinophil infiltration, as detected by biopsy. Central nervous system involvement was defined as headache, visual disorder, abnormal visual sensation, cerebral infarction, bleeding, or cranial nerve dysfunction. Cardiac involvement or GI involvement with and without symptoms or abnormalities on 1 or more cardiac investigations, or abnormalities on endoscopy and biopsy, or both, was analyzed. Renal involvement was defined by the presence of any of the following: eosinophils in the urine, glomerulonephritis, nephrosis (proteinuria > 3.5 g/day), renal dysfunction (i.e., creatinine level elevated to over 20% of baseline), or proteinuria (> 0.5 g/day or 50 mg/dl). Otitis media was diagnosed by an otorhinolaryngologist. Disease severity in all patients with EGPA was evaluated using the FFS1996[4] or FFS2009[2]. Organs compromised by asthma or sinusitis were not included in the total number of organs involved. Disease activity was assessed at onset and at first relapse by using the Birmingham Vasculitis Activity Score (BVAS)[26]. The BVAS evaluates symptoms and signs within 9 categories (systemic, cutaneous, mucous membranes and eyes, ENT, chest, heart and vessels, GI tract, renal system, and nervous system). The maximum number of possible points in each category is 7, and the maximum score is 63.

White blood cell and eosinophil counts in whole blood and myeloperoxidase (MPO)-ANCA, proteinase 3 (PR3)-ANCA, and immune complex levels in serum were assayed at the onset of EGPA. Treatment of all patients with pulsed steroids, initial doses of prednisolone, immunosuppressants in the initial or maintenance stage, or IVIG (Venilon; 400 mg/kg daily for 5 days) was determined from the medical records.

Our study endpoint was the last examination performed within the study period. We confirmed whether the patient was alive or dead, the cause of death, the disease state (remission or relapse), and treatment at the last examination.

The Ethics Committee of our hospital approved the study, and written informed consent was obtained from all patients themselves or from their legal representatives. The ethics approval number was No. 16 in 2012 at the National Hospital Organization Sagamihara Hospital and R2016-14 at the National Hospital Organization Saitama Hospital.

Statistical analysis. All values are expressed as means ± SD unless otherwise specified. Statistical comparisons among groups were achieved by using 2-way ANOVA according to a repeated-measures algorithm, followed by posthoc comparisons using the Newman–Keuls test. The 2 mean values obtained by this process were compared by using the Wilcoxon matched-pairs t test. Correlation coefficients were obtained using Spearman rank correlation test. Kaplan–Meier analysis was performed using a log-rank test and the Wilcoxon test. A multiple logistic regression analysis was used to calculate risk factor coefficients; p values of < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS for Windows, version 20 (SPSS Inc.).

RESULTS

Clinical findings and treatments. Thirty-four of 115 patients (29.6%) were positive for MPO-ANCA, 7 of 113 patients (6.2%) were positive for PR3-ANCA, and 19 of 73 patients (26.0%) were positive for immune complexes at the time of disease onset (Table 1). During followup, more than 90% of

Table 1. Characteristics of 121 patients with EGPA. Values are mean ± SD unless otherwise specified.

Characteristics	All Patients with EGPA
Current age, yrs	61.2 ± 16.7
Male/female, n	42/79
Age at onset of asthma, yrs	43.4 ± 16.4
Age at onset of EGPA, yrs	53.3 ± 17.0
Duration from onset asthma to EGPA, yrs	9.4 ± 10.9
Atopic/nonatopic	55/57
Length of observation, yrs	7.8 ± 6.6
At onset of EGPA	
WBC, /ml	15,772 ± 7623
Blood eosinophils, /ml	8528 ± 6764
MPO-ANCA, %, n = 115	29.6
PR3-ANCA, %, n = 113	6.2
IC > 1.5 mg/ml, %, n = 73	26.0
Cumulative manifestations during followup, %	
Asthma	98.3
Paranasal sinusitis	91.2
Multiple polyneuropathy	98.3
Minimum MMT score	3.50 ± 0.90
Pulmonary infiltrates	67.6
Myocardial involvement	
Symptoms or abnormalities on 1 or more cardiac investigations	73.9
Symptoms and abnormalities on 1 or more cardiac investigations	42.6
Abnormalities on 1 or more cardiac investigations without symptoms	31.3
Symptoms without abnormalities on 1 or more cardiac investigations	0
Gastrointestinal tract	
Symptoms or abnormalities on endoscopy and biopsy	78.6
Symptoms and abnormalities on endoscopy and biopsy	41.7
Abnormalities on endoscopy and biopsy without symptoms	23.3
Symptoms without abnormalities on endoscopy and biopsy	13.6
Liver, gall bladder, pancreas	17.3
Renal involvement‡	35.2
Proteinuria, 0.5 g/day or > 50 mg/dl	22.7
Eosinophils in urine	41.5
Nephritis, nephrosis, or renal failure	15.1
Skin involvement	67.9
Arthralgia	46.7
Myalgia	22.6
CNS involvement	29.2
Otitis media	24.2
No. organs involved	
Cumulative organ involvement, n‡‡	4.6 ± 1.8
Five factor score 1996	1.0 ± 0.9
Five factor score 2009	1.2 ± 1.1
BVAS at onset	31.5 ± 9.0
ACR criteria 4/6, 5/6, 6/6	39/28/54
Initial treatment	
PSL as initial dose, mg	42.6 ± 13.0
mPSL pulse, yes/no (%)	69/42 (62.1)
Immunosuppressant at initial treatment, yes/no (%)	85/36 (70.2)
CYC/AZA/CSA/MTX/RTX, n	68/6/9/2/0
Immunosuppressant at maintenance, yes/no (%)	62/55 (53.0)
CYC/AZA/CSA/MTX/RTX, n	12/18/20/12/0
IVIG, yes/no (%)	76/45 (62.8)
PSL as maintenance dose, mg	8.3 ± 5.4

‡ Renal involvement including proteinuria or eosinophils in urine or glomerular nephritis or nephrosis or renal dysfunction. ‡‡ Cumulative organ involvement, excluding asthma and sinusitis. EGPA: eosinophilic granulomatosis with polyangiitis; WBC: white blood cells; MPO-ANCA: myeloperoxidase-specific antineutrophil cytoplasmic antibody; PR3: protein 3; IC: immune complex; MMT: manual muscle test; CNS: central nervous system; BVAS: Birmingham Vasculitis Activity Score; ACR: American College of Rheumatology; PSL: prednisolone; mPSL: methylprednisolone; CYC: cyclophosphamide; AZA: azathioprine; CSA: cyclosporine; MTX: methotrexate; RTX: rituximab; IVIG: intravenous immunoglobulin.

all patients with EGPA had asthma, paranasal sinusitis, or multiple polyneuropathy. Only 42.6% of patients had both laboratory findings and symptoms of myocardial involvement; 73.9% of patients had either laboratory findings or symptoms, and 31.3% had laboratory findings but no symptoms.

Overall, 78.6% of patients had GI tract involvement with either abnormalities on endoscopy and biopsy or symptoms, whereas 41.7% had both abnormalities on endoscopy and biopsy and symptoms, 23.3% had abnormalities on endoscopy and biopsy but no symptoms, and 13.6% had symptoms but no abnormalities on endoscopy and biopsy during followup (Table 1). Sixty-nine of 111 patients (62.1%) received pulsed methylprednisolone and 85 of 121 patients (70.2%) were treated initially with an immunosuppressant; CYC was also given to 68 of these 85 patients (80.0%). Seventy-six of 121 patients (62.8%) were given IVIG until they achieved remission.

Sixteen of 121 patients (13.2%) were excluded from the analysis of relapse rate because they had a short duration of EGPA from onset (< 2 yrs). Thirty-five of 105 patients (33.3%) who experienced frequent relapse and 70 who experienced infrequent relapse were analyzed for risk factors for relapse. Patients with EGPA with frequent relapse had significantly higher rates of myocardial involvement with either abnormalities on 1 or more cardiac investigations or symptoms ($p < 0.05$) or both abnormalities on 1 or more cardiac investigations and symptoms ($p < 0.01$); significantly higher rates of GI tract involvement with both abnormalities on endoscopy and biopsy and symptoms ($p < 0.01$); significantly higher rates of proteinuria ($p < 0.05$) than patients with infrequent relapse during followup (Table 2). These numbers were all significantly higher in EGPA patients with frequent relapse than in those with infrequent relapse ($p < 0.01$; Table 2): the percentage of patients given an immunosuppressant in the initial phase (91.4% in the frequent group, 67.1% in the infrequent group) or during maintenance (frequent 79.4%, infrequent 45.6%), the percentage given IVIG (frequent 88.6%, infrequent 57.4%), the number of times IVIG was given (mean: frequent 3.4 ± 3.0 times, infrequent 1.5 ± 2.1 times), and the mean maintenance dose of prednisolone (frequent 11.6 ± 6.2 mg, infrequent 6.6 ± 4.9 mg).

GI tract involvement with both abnormalities on endoscopy and biopsy during followup and symptoms ($p < 0.05$) or myocardial involvement with both abnormalities on 1 or more cardiac investigations during followup and symptoms ($p < 0.01$) were predictors of frequent relapse (Table 3).

Of 121 patients, 114 (94.2%) were followed for a mean of 8.2 ± 5.8 years after diagnosis; the remaining 7 patients (5.8%) were lost to followup by the end of our study. Overall, 5-, 10-, and 20-year survival rates in the 114 patients were 91.1%, 83.7%, and 68.6%, respectively (Figure 1A). Age at time of onset of asthma or EGPA was significantly younger in patients who were alive at the end of the study than in those who had died (alive: 40.1 ± 15.8 yrs at asthma onset, dead: 55.4 ± 10.4 yrs, $p < 0.01$; alive: 49.3 ± 16.3 yrs at EGPA onset, dead: 69.2 ± 9.2 yrs, $p < 0.01$; Table 4). Patients with EGPA who had died by the end of the study had significantly lower minimum MMT scores ($p < 0.01$), significantly higher rates of nephritis, nephrosis, or renal failure ($p < 0.05$), significantly higher FFS2009 ($p < 0.01$), and higher total number of relapses of vasculitis per year than those who were still alive. Survival rates did not differ significantly between patients with and without myocardial involvement (Figure 1B) or with and without GI tract involvement (data not shown). Treatment with daily dose of prednisolone in the initial phase, use of steroid pulsing, use of an immunosuppressant in the initial phase or in maintenance, use of IVIG, and daily dose of prednisolone used for maintenance did not differ among the 2 groups (Table 4).

Seventeen patients (9 women) died at a mean age of 74.4 ± 9.4 years, at a mean of 6.2 ± 5.0 years after diagnosis. The daily prednisolone dose at the endpoint in those who died was a mean of 10.3 ± 7.1 mg. Only 6 of 17 patients were being treated with an immunosuppressant at the time of death (3 patients, CYC; 2 patients, cyclosporine; 1 patient, AZA). Eleven patients (6 women) died of infection (bacterial pneumonia, pneumocystis, sepsis). Two women and 1 man died of chronic heart failure, and 1 man died of cardiomyopathy. Other patients died of cholangiocarcinoma (n = 1) or interstitial pneumonia (n = 1). Only in the patient with cardiomyopathy was there direct evidence of active vasculitis associated with cardiac involvement of EGPA.

Survival was not influenced by baseline myocardial involvement, renal failure, GI tract involvement, minimum MMT score, or presence of sinusitis. Age at onset of EGPA was the only significant predictor of survival in EGPA ($p < 0.01$; Table 5). The survival rate was significantly lower in patients with age of onset ≥ 65 years than in those with age of onset < 65 years ($p < 0.01$; Figure 1C).

DISCUSSION

Before the use of corticosteroids, the mortality rate in EGPA was about 50% within 3 months of diagnosis[3,10]. Pre-1990 reports suggest 5-year survival rates for EGPA of 62%–80%[4,10,27]. Patients with EGPA, polyarteritis nodosa, or MPA diagnosed after 1990 had higher survival rates 50 months after diagnosis than those diagnosed between 1953 and 1989[28]. The mortality rate of patients with EGPA diagnosed after 1996 was lower than that of those diagnosed before 1996[29]. Increased adoption of the ACR classification of EGPA[7] might have improved the prognosis of patients with EGPA[2,8,30]. Remission rates in EGPA range from 81%–91%, and relapse rates vary from 20%–81.1%[5,17,31]. In 1 study, 67 of 72 patients with EGPA (93%) with FFS1996 = 0 achieved remission with corticosteroids alone, but 35 of 72 patients (49%) relapsed during the first year of treatment[6].

Table 2. Characteristics and therapy of patients with EGPA with and without frequent relapse. Values of $p < 0.05$ were considered statistically significant. Values are mean ± SD unless otherwise specified.

Variables	Frequently Relapsing EGPA, n = 35	Infrequently Relapsing EGPA, n = 70	Univariate Analysis, p	Risk Ratio	95% CI
Current age, yrs	59.4 ± 17.0	62.8 ± 14.8	NS†		
Male/female, n	15/20	22/48	NS††		
Atopic/nonatopic	17/18	27/35	NS††		
Age at onset of asthma, yrs	44.2 ± 15.6	43.5 ± 16.0	NS†		
Age at onset of EGPA, yrs	52.5 ± 19.4	54.6 ± 15.0	NS†		
Duration from asthma onset to EGPA, yrs	8.4 ± 11.1	10.2 ± 10.8	NS†		
Total no. relapses of vasculitis	5.4 ± 4.8	1.5 ± 1.8	< 0.01†		
Total no. relapses of vasculitis per yr	1.03 ± 0.95	0.16 ± 0.16	< 0.01†		
Length of observation, yrs	7.3 ± 7.8	8.9 ± 5.6	NS†		
At onset of EGPA					
WBC, /ml	16,621 ± 7980	15,725 ± 7923	NS†		
Blood eosinophils, /ml	9192 ± 6630	8771 ± 7027	NS†		
MPO-ANCA, positive/negative, n	12/22	17/48	NS††		
PR3-ANCA, positive/negative, n	2/32	3/60	NS††		
IC > 1.5 mg/ml, positive/negative, n	9/15	7/32	NS††		
BNP, pg/ml	182.4 ± 437.2	88.3 ± 178.8	NS†		
Clinical manifestations of EGPA, %					
Asthma	97.1	100	NS††		
Paranasal sinusitis	90.9	90.6	NS††		
Multiple polyneuropathy	100	98.6	NS††		
Minimum MMT score	3.3 ± 1.0	3.4 ± 0.8	NS†		
Pulmonary infiltrates	78.1	67.2	NS††		
Myocardial involvement, %					
Symptoms or abnormalities on 1 or more cardiac investigations	91.4	71.9	< 0.05††	2.872	0.974–8.464
Symptoms and abnormalities on 1 or more cardiac investigations	68.6	35.9	< 0.01††	2.414	1.332–4.375
Abnormalities on 1 or more cardiac investigations without symptoms	22.9	35.9	NS††		
Symptoms without abnormalities on one or more cardiac investigations	0	0	NS††		
Gastrointestinal tract, %					
Symptoms or abnormalities on endoscopy and biopsy	90.0	73.8	NS††		
Symptoms and abnormalities on endoscopy and biopsy	63.3	32.8	< 0.01††	2.303	1.244–4.263
Abnormalities on endoscopy and biopsy without symptoms	10.0	24.6	NS††		
Symptoms without abnormalities on endoscopy and biopsy	16.7	16.4	NS††		
Liver, gall bladder, pancreas	25.0	15.3			
Renal involvement, %*	45.2	30.3	NS††		
Proteinuria, 0.5 g/day or > 50 mg/dl	37.9	14.8	< 0.05††	2.058	1.190–3.561
Eosinophils in urine	50.0	33.3	NS††		
Nephritis, nephrosis, or renal failure	23.3	9.4	NS††		
Skin involvement	77.4	65.6	NS††		
Arthralgia	58.1	42.4	NS††		
Myalgia	20.6	26.3	NS††		
CNS involvement	20.0	32.3	NS††		
Otitis media	31.4	24.3	NS††		
No. organs involved					
Cumulative organ involvement**	5.1 ± 1.6	4.4 ± 1.9	NS†		
Five factor score 1996	1.5 ± 0.9	0.9 ± 0.8	< 0.01†		
Five factor score 2009	1.8 ± 1.1	1.0 ± 1.0	< 0.01†		
BVAS at onset	37.3 ± 8.8	30.4 ± 7.3	< 0.01†		
ACR criteria 4/6, 5/6, 6/6, n	8/9/18	24/15/31	NS††		
Initial treatment					
PSL as initial dose, mg	43.9 ± 15.1	43.1 ± 11.9	NS†		
Steroid pulse, yes/no (%)	24/10 (70.6)	38/25 (60.3)	NS††		
Immunosuppressant at initial phase, yes/no (%)	32/3 (91.4)	47/23 (67.1)	< 0.01†		
CYC/AZA/CSA/MTX/RTX, n	25/2/5/0/0	38/3/4/2/0	NS††		
CYC at initial phase, yes/no (%)	26/9 (74.2)	41/27 (60.3)	NS††		
Immunosuppressant as maintenance use, yes/no (%)	27/7 (79.4)	31/37 (45.6)	< 0.01††		
CYC/AZA/CSA/MTX/RTX, n	8/12/3/4/0	2/5/17/7/0	< 0.01††		
IVIG, yes/no (%)	31/4 (88.6)	40/30 (57.4)	< 0.01††		
No. times IVIG administered	3.4 ± 3.0	1.5 ± 2.1	< 0.01†		
PSL as maintenance dose, mg	11.6 ± 6.2	6.6 ± 4.9	< 0.01†		

* Renal involvement including proteinuria or eosinophils in urine or glomerular nephritis or nephrosis or renal dysfunction. ** Cumulative organ involvement, excluding asthma and sinusitis. † Two-way ANOVA with repeated measures between 2 groups. †† Chi-square test revealed no significant differences in frequency between the 2 groups. EGPA: eosinophilic granulomatosis with polyangiitis; WBC: white blood cells; MPO-ANCA: myeloperoxidase-specific antineutrophil cytoplasmic antibody; PR3: protein 3; IC: immune complex; BNP: B type natriuretic peptide; MMT: manual muscle test; CNS: central nervous system; BVAS: Birmingham Vasculitis Activity Score; ACR: American College of Rheumatology; PSL: prednisolone; CYC: cyclophosphamide; AZA: azathioprine; CSA: cyclosporine; MTX: methotrexate; RTX: rituximab; IVIG: intravenous immunoglobulin; NS: not significant.

Table 3. Logistic regression model of baseline factors predictive of relapse frequency in EGPA. Values of p < 0.05 were considered statistically significant.

Variables	Exponent	95% CI	p
Age at onset EGPA, yrs	0.979	0.946–1.012	0.2
GI tract with both symptoms and abnormalities on endoscopy and biopsy	3.961	1.251–12.536	< 0.05
Myocardial involvement with both symptoms and abnormalities on 1 or more cardiac investigations	5.805	1.901–17.729	< 0.01
Central nervous system involvement	0.683	0.205–2.279	0.54
Otitis media	2.008	0.589–6.840	0.27
Minimum MMT score	0.668	0.343–1.300	0.24
MPO-ANCA at onset, yes/no	0.818	0.254–2.633	0.74

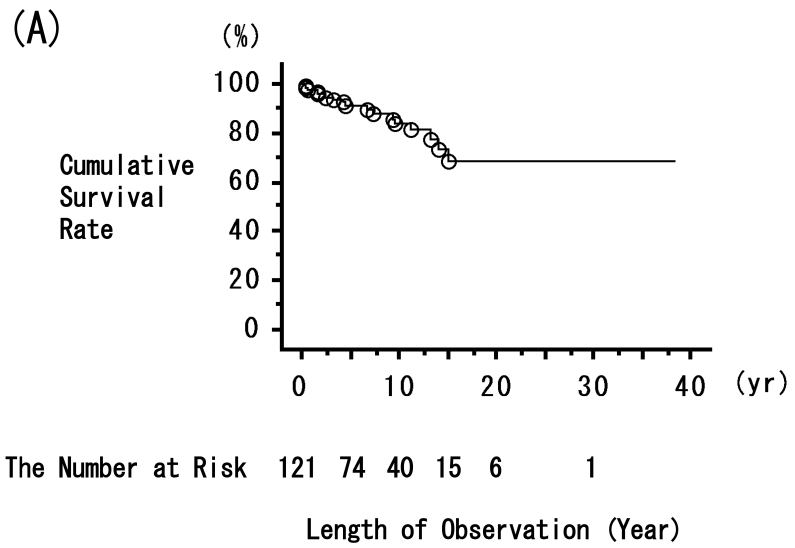
EGPA: eosinophilic granulomatosis with polyangiitis; MMT: manual muscle test; MPO-ANCA: myeloperoxidase-specific antineutrophil cytoplasmic antibody; GI: gastrointestinal.

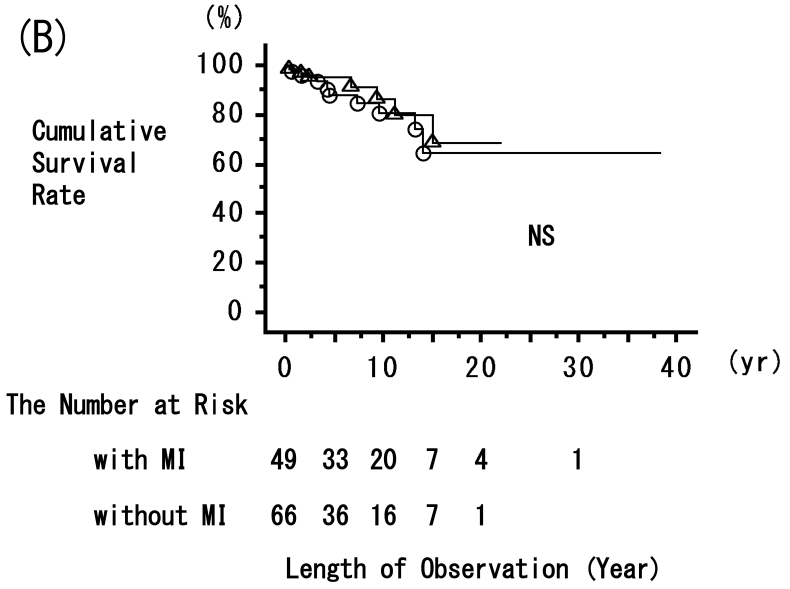
Although survival rates of EGPA have increased, the relapse rate after initial remission is high[16,31]. Factors previously determined to be predictive of relapse are low eosinophil count in the peripheral blood at diagnosis[29,32], MPO-ANCA positivity[31,32], and GI involvement[31]. We previously reported that cardiac sympathetic nerve function is damaged in EGPA patients with cardiac involvement and that 123I-metaiodobenzylguanidine scintigraphy or measurement of B-type natriuretic peptide is useful for detecting cardiac involvement and predicting relapse due to cardiac events[33].

The risk factors found here to be predictors of relapse after remission were GI tract involvement with both abnormalities and symptoms on endoscopy and biopsy, and myocardial involvement with both abnormalities and symptoms on 1 or more cardiac investigations. For GI tract or myocardial involvement, we analyzed 4 combinations: the presence of either abnormalities or symptoms on examination, both abnormalities and symptoms on examination, abnormalities on examination but no symptoms, and symptoms but no abnormalities on examination. In other published series, 62%–92% had GI involvement and 52%–54% had cardiac involvement[1,34]. We found that none of these affected relapse, and in our logistic regression the only combination critical to managing relapse prevention in EGPA was both abnormalities and symptoms on examination.

In our previous study, the FOXP+ regulatory T cell count was significantly lower, and the percentage of CD80+, CD27+, or CD95+–positive B cells was significantly higher in patients with frequently relapsing EGPA than in those with few relapses. The increased percentages of activated B cells might induce apoptosis of B cells and thus reduce serum immunoglobulin G (IgG) concentrations in patients with frequent relapse[19]. We considered an appropriate classification of frequent relapse to be disease occurrence at least once every 2 years after a period of initial remission. Significantly more patients with frequent relapse had received an immunosuppressant in the initial and maintenance phases, or IVIG, than had patients with few relapses. Most of the patients with frequent relapse had received IVIG treatment several times.

The mean 5-, 10-, and 20-year mortality rates at our hospital were 91.7%, 83.7%, and 68.6%, respectively. This result is similar to that in a report by Moosig, *et al* in Germany[8]. The rate of GI involvement with both abnormalities on endoscopy and biopsy and symptoms was 41.7% in our study — more than 28.7% in Moosig, *et al*'s study or 23.2% in Comarmond, *et al*'s study[29], but the rate of cardiac involvement with both abnormalities on 4 or more cardiac investigations and symptoms was similar (42.6% in our study; 46.7% in Moosig, *et al*'s study; 27.4% in Comarmond, *et al*'s study). There were no differences in the mortality rate of patients with GI involvement or those with unknown prognosis, or mortality from EGPA with or without GI involvement, among 3 studies. Cardiac involvement did not affect the mortality rate in our study, but patients with heart failure showed significantly increased mortality rates in the studies by Moosig, *et al* and Comarmond, *et al*[8,29]. Seventy-six of the entire set of our 121 patients (62.8%) received IVIG treatment in addition to corticosteroids, with or without an immunosuppressant. However, in other studies, only 5 of 150 patients (3.3%) with EGPA (reported by Moosig, *et al*[8]) and 3 of 75 patients (4.0%) with EGPA, polyarteritis nodosa, or MPA[12] were treated with IVIG. In Europe and the United States, unlike in our hospital, IVIG is used in only small numbers of patients with EGPA. At our hospital, 14 of 17 patients (82.4%) who had died by the end of the study period and 31 of 35 patients (88.6%) with frequent relapse had received IVIG. Moreover, by demonstrating an increase in the concentration of regulatory T cells as FOXP3+CD4+ T cells in the peripheral blood, we have confirmed the longterm efficacy of IVIG in EGPA patients with severe mononeuritis multiplex or heart failure; with IVIG treatment, we have been able to reduce the maintenance corticosteroid dose compared with that in patients not given IVIG[35]. In our study, myocardial involvement did not affect the mortality rate. Age of EGPA onset was the only predictor of survival. The presence of signs or symptoms of vasculitis and myocardial or GI tract involvement was not directly related to the risk of death. The fact that cardiac and GI involvement did not predict mortality could not have been related to the relatively few deaths compared with living patients. Only 1 patient died because of cardiac involvement of EGPA, and none of the causes of death of the 17 who died were directly related to GI involvement. One limitation of our study was that it was retrospective. Moreover, more than half of our patients (62.8%) received IVIG treatment. There were no significant differences in mortality rates between patients who did and did not receive IVIG, but the treatment intervals and numbers of treatments differed among





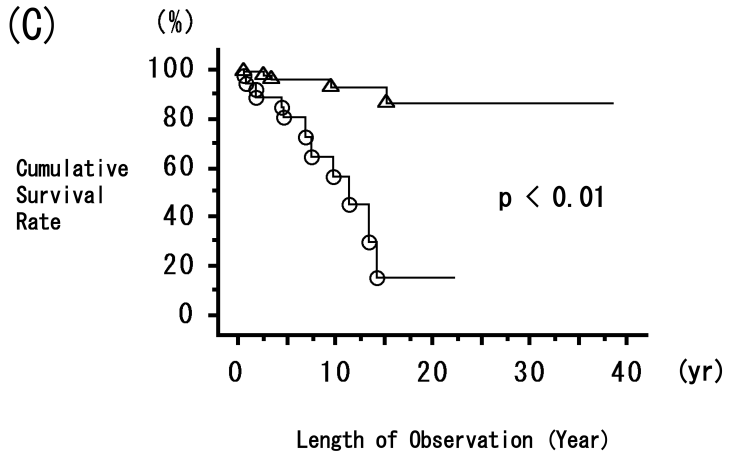


Figure 1. (A) Kaplan-Meier overall survival curve of 121 patients with EGPA. (B) Survival curve according to the presence (open circles) or absence (open triangles) of MI. (C) Survival curve according to age ≥ 65 years (open circles) or < 65 years (open triangles) at onset of EGPA. Data were censored after a maximum of 38.1 years of followup. P value determined using log-rank tests and the Wilcoxon test. EGPA: eosinophilic granulomatosis with polyangiitis; MI: myocardial involvement; NS: not significant.

Table 4. Univariate analysis of survival in EGPA. Values are mean ± SD unless otherwise specified.

Variables	Alive at Study Endpoints, n = 97	Death, n = 17	p
Current age or age at death, yrs	56.8 ± 16.4	74.4 ± 9.4	< 0.01†
Male/female, n	33/64	8/9	NS††
Atopic/nonatopic, n	48/42	7/10	NS††
Age at onset of asthma, yrs	40.1 ± 15.8	55.4 ± 10.4	< 0.01†
Age at onset of EGPA, yrs	49.3 ± 16.3	69.2 ± 9.2	< 0.01†
Duration from onset asthma to EGPA, yrs	8.8 ± 10.7	12.9 ± 13.3	NS†
Total no. relapses of vasculitis	2.5 ± 3.7	2.6 ± 2.4	NS†
Total no. relapses of vasculitis per yr	0.33 ± 0.42	0.84 ± 1.36	< 0.01†
Length of observation, yrs	8.5 ± 6.9	6.2 ± 5.0	NS†
At onset of EGPA			
WBC, /ml	15,615 ± 7954	14,899 ± 5899	NS†
Blood eosinophils, /ml	8213 ± 6877	8974 ± 5902	NS†
MPO-ANCA, positive/negative, n	27/66	5/11	NS††
PR3-ANCA, positive/negative, n	7/84	0/16	NS††
IC > 1.5 mg/ml, positive/negative, n	17/45	1/8	NS††
BNP, pg/ml	106.8 ± 319.3	234.6 ± 406.9	NS†
Clinical manifestations of EGPA, %			
Asthma	97.9	100	NS††
Paranasal sinusitis	92.3	87.5	NS††
Multiple polyneuropathy	97.9	100	NS††
Minimum MMT score	3.6 ± 0.8	2.8 ± 1.1	< 0.01†
Pulmonary infiltrates	64.2	81.3	NS††
Myocardial involvement, %			
Symptoms or abnormalities on 1 or more cardiac investigations	74.1	81.3	NS††
Symptoms and abnormalities on 1 or more cardiac investigations	43.0	56.3	NS††
Abnormalities on 1 or more cardiac investigations without symptoms	31.2	25.0	NS††
Symptoms without abnormalities on 1 or more cardiac investigations	0	0	NS††
Gastrointestinal tract, %			
Symptoms or abnormalities on endoscopy and biopsy	77.6	64.3	NS††
Symptoms and abnormalities on endoscopy and biopsy	41.2	42.9	NS††
Abnormalities on endoscopy and biopsy without symptoms	25.9	0	< 0.05††
Symptoms without abnormalities on endoscopy and biopsy	10.6	21.4	NS††
Liver, gall bladder, pancreas	15.5	23.5	NS††
Renal involvement, %*	29.1	53.8	NS††
Proteinuria, 0.5 g/day or > 50 mg/dl	17.7	41.7	NS††
Eosinophils in urine	31.3	66.7	NS††
Nephritis, nephrosis, or renal failure	10.0	30.8	< 0.05††
Skin involvement	67.8	60.0	NS††
Arthralgia	49.4	26.7	NS††
Myalgia	24.1	13.3	NS††
CNS involvement	30.0	17.6	NS††
Otitis media	26.6	11.8	NS††
No. organs involved			
Cumulative organ involvement**	4.5 ± 1.6	4.6 ± 1.6	NS†
Five factor score 1996	1.2 ± 1.1	0.9 ± 0.8	NS†
Five factor score 2009	1.0 ± 0.9	2.2 ± 1.5	< 0.01†
BVAS at onset	30.8 ± 9.2	35.5 ± 7.9	NS†
ACR criteria 4/6, 5/6, 6/6, n	29/22/43	3/6/8	NS†
Treatment			
PSL as initial dose, mg	43.3 ± 12.6	42.1 ± 14.9	NS†
Steroid pulse, yes/no (%)	55/35 (61.1)	11/6 (64.7)	NS††
Immunosuppressant at initial phase, yes/no (%)	69/28 (71.1)	13/4 (76.5)	NS††
CYC/AZA/CSA/MTX/RTX, n	53/6/8/2/0	12/0/1/0/0	NS††
CYC at initial phase, yes/no (%)	55/41 (57.3)	12/5 (70.6)	NS††
Immunosuppressant as maintenance use, yes/no (%)	56/40 (58.3)	6/11 (35.3)	NS††
CYC/AZA/CSA/MTX/RTX, n	9/17/18/12/0	3/1/2/0/0	NS††
IVIG, yes/no (%)	59/38 (60.8)	14/3 (82.4)	NS††
No. times IVIG administered	2.0 ± 2.34	2.7 ± 2.9	NS†
PSL as maintenance dose, mg	8.0 ± 5.0	10.3 ± 7.1	NS†

* Renal involvement including proteinuria or eosinophils in urine or glomerular nephritis or nephrosis or renal dysfunction. ** Cumulative organ involvement, excluding asthma and sinusitis. † Two-way ANOVA with repeated measures between 2 groups. †† Chi-square test revealed no significant differences in frequency between the 2 groups. EGPA: eosinophilic granulomatosis with polyangiitis; WBC: white blood cells; MPO-ANCA: myeloperoxidase-specific antineutrophil cytoplasmic antibody; PR3: protein 3; IC: immune complex; BNP: B type natriuretic peptide; MMT: manual muscle test; CNS: central nervous system; BVAS: Birmingham Vasculitis Activity Score; ACR: American College of Rheumatology; PSL: prednisolone; CYC: cyclophosphamide; AZA: azathioprine; CSA: cyclosporine; MTX: methotrexate; RTX: rituximab; IVIG: intravenous immunoglobulin; NS: not significant.

Table 5. Logistic regression model of baseline factors predictive of survival in EGPA.

Variable	Exponent	95% CI	p
Age at EGPA onset, yrs	0.850	0.772–0.936	< 0.01
GI tract involvement	1.466	0.168–12.787	0.73
Myocardial involvement	2.725	0.474–15.676	0.26
Nephritis, nephrosis, or renal failure	1.991	0.258–15.346	0.51
Paranasal sinusitis	0.178	0.010–3.028	0.23
Minimum MMT score	1.544	0.558–4.271	0.40

EGPA: eosinophilic granulomatosis with polyangiitis; MMT: manual muscle test; GI: gastrointestinal.

individuals. It is unknown whether the timing of administration (during initial treatment or at relapse after remission) or the types and frequencies of previous treatments affect the clinical and immunologic efficacy of IVIG. Nevertheless, we reported previously that an increase in the numbers of FOXP3+CD4+ regulatory T cells in the blood 1 month after IVIG treatment indicated a need for additional IVIG[36]. Moreover, the IgG4 immune response is positively associated with EGPA disease activity[37]. The mean IgG4 level was 282.8 mg/dl in 7 patients in our study. A deficiency of Fcγ-receptor 3B copy number variation as 1 of the IgG receptors might contribute to the risk of EGPA — especially purpura, renal dysfunction, peripheral neuropathy, or the presence of vasculitis[38]. The immune response mediated by the Fcγ-receptor 3B or IgG4 might be found in future to contribute to the mechanism of action of IVIG.

Patients who develop EGPA at age ≥ 65 years have a poor prognosis and more frequently develop severe adverse events after treatment with CYC[39]. Using a low dose of intravenous CYC might lead to remission without severe adverse events[39]. We expect in future that treatment with a combination of low-dose intravenous CYC and IVIG might achieve remission and reduce mortality rates in patients with older onset EGPA. IVIG treatment of patients with refractory or relapsing EGPA might bring clinical benefits[40].

Here, we analyzed the prognosis of patients with EGPA at our hospital. Patients with myocardial or GI tract involvement had frequent relapses, but these complications were not associated with mortality. Treatment with immunosuppressants or IVIG in addition to corticosteroids may have positively influenced the disease prognosis. Randomized prospective trials of IVIG are needed to confirm these findings in future.

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