Post-marketing Surveillance of Mepolizumab Use in Patients with Eosinophilic Granulomatosis with Polyangiitis in Japan : Interim Analysis

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ABSTRACT

Objectives : This post-marketing surveillance study assessed the real-world safety of mepolizumab in Japanese patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Methods : This ongoing all-case study (GSK ID : 208505) commenced in May 2018 ; here we report a 48-week interim analysis using data up to March 23, 2020. Patient data were collected for the 4 weeks preceding and up to 48 weeks following mepolizumab initiation for the treatment of EGPA. Patients with data at Week 12 were included ; Week 48 data were included where available. Adverse events (AEs) and serious AEs following mepolizumab initiation were identified using case report forms. In particular, important

Key words : Eosinophilic granulomatosis with polyangiitis, Mepolizumab, Anti-neutrophil cytoplasmic antibody, Safety, Post-marketing surveillance

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potential risks for mepolizumab identified by the Japanese Risk Management Plan were assessed.

Results：Of the 321 included patients, 58.6%（*n*＝188）were female and 60.1%（*n*＝193）were ＜65 years of age；72.3%（*n*＝232）of patients had a disease duration ≦5 years and 60.7%（*n*＝195）had a disease severity grading of III（range I–V）. AEs were reported in 24.0%（*n*＝77）of patients and were serious in 12.8%（*n*＝41）of patients. The most common AEs were infections, reported in 7.5%（*n*＝24）of patients；3.4%（*n*＝11）of patients had serious infections and infestations. Hypersensitivity reactions were reported in 5.3%（*n*＝17）of patients and 2.2%（*n*＝7）of patients had serious hypersensitivity reactions. No malignancy was observed. Mepolizumab was discontinued in three patients with AEs；three deaths were reported（thalamus haemorrhage, capillary leak syndrome, pneumonia aspiration）.

Conclusions：This interim analysis of the post-marketing surveillance study in Japan showed mepolizumab was well-tolerated in patients with EGPA.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis（EGPA）is a rare systemic necrotizing vasculitis linked with anti-neutrophil cytoplasmic antibodies（ANCA）and extravascular granulomas[1–6]. Patients with EGPA have preceding asthma and high eosinophil counts, and approximately 40% of patients with EGPA have an ANCA-positive status[4]. The clinical and disease characteristics of EGPA are thought to differ depending on ANCA status[4,7–10] and as such, multiple organ systems can be affected[2,4,11], including the peripheral nervous system and respiratory system and cutaneous system[2,4].

Glucocorticoids（GC）are the cornerstone of EGPA treatment[12], and most patients with EGPA require long-term GC to help control their EGPA-associated comorbidities[9]. Importantly, the risks associated with long-term GC use have been well studied[13–15] and despite patients with EGPA having a high dependency on GC, disease relapse is still common[12,16]. As such, the EGPA Consensus Task Force for Europe and the USA recommends tapering GC doses over the first 6 months of therapy[12], and while the clinical practice guidelines of the Japan Research Committee of the Ministry of Health, Labour and Welfare（MHLW）found insufficient evidence to support GC tapering, their statements, albeit weakly, recommend GC use in conjunction with other immunosuppressants[17]. In the absence of unified guidance, it is clear that additional treatment options for EGPA are needed[12,17].

Interleukin（IL）-5 is a key cytokine responsible for the proliferation, maturation, activation, and recruitment of eosinophils, making the IL-5 pathway as an evident therapeutic target for the treatment of eosinophilic inflammation[18]. Mepolizumab is a targeted, humanized monoclonal antibody that binds to and inactivates IL-5, preventing it from binding to its receptor on eosinophils, and blocking eosinophil survival and proliferation[19,20]. Mepolizumab is indicated for the treatment of EGPA in several countries, including Japan[21–23]. Data from the Phase III MIRRA clinical trial, which assessed the impact of subcutaneous mepolizumab 300 mg in patients with refractory EGPA, demonstrated that mepolizumab had an acceptable safety profile and was associated with greater accrued time in remis-

sion, reduced annualized relapse rates and a reduced GC dose in patients with relapsing EGPA[16,24]. In order to investigate the safety of mepolizumab for the treatment of EGPA in real-world clinical practice, we conducted a post-marketing surveillance study of mepolizumab-treated patients in Japan ; here we report the safety profile of mepolizumab and describe clinical observations using data from an interim analysis.

TARGET AND METHOD

1 Study design

This ongoing 96-week all-case surveillance study in Japan commenced in May 2018 (GSK ID : 208505) ; we report an interim analysis, with data locked on March 23, 2020. For the purposes of this analysis, patient data were collected using pre-defined, standardized case report forms (CRFs), during the 12 weeks following the first administration of mepolizumab for the treatment of EGPA (observation period). Data for Week 12 and for the 4 weeks preceding the first injection of mepolizumab (baseline period) were collected at Week 12 ; where patient data were available, a subsequent 48-Week time point was also included. In total, 398 institutes participated in this study. This study was conducted in accordance with the Japanese Good Post-marketing Study Practice (GPSP, Ordinance of MHLW No. 171 of December 20, 2004). Informed consent was collected from the patients included in this analysis ; rules of personal data confidentiality were adhered to and all participating institutions agreed to the publication of the study results. Institutional Review Board approval was granted as needed, in accordance with the regulations of each participating institution.

2 Patients

All patients who commenced mepolizumab treatment for EGPA were enrolled in this study, including those who had previously used mepolizumab for the treatment of bronchial asthma. EGPA was diagnosed by investigator's assessment. Patients were excluded from the analysis if their CRF did not contain the relevant data.

3 Mepolizumab safety profile

Safety data, including adverse events (AEs), serious AEs, and AEs considered to be possibly or probably related to mepolizumab (adverse drug reactions[ADRs]), were assessed throughout the observation period. Serious AEs were defined as events that met at least one of the following criteria : required in-patient hospitalization or prolonged existing hospitalization to enable treatment ; was considered to be a medically significant condition ; caused a persistent or significant disability/incapacity ; resulted in a congenital anomaly or birth defect ; resulted in death or was considered life-threatening ; or was listed in the European Medicines Agency's important medical event term list[25].

Important potential risks for mepolizumab, identified by the Japanese Risk Management Plan (hypersensitivity reactions [including anaphylaxis], infections and infestations, malignancies)[26], were also assessed. AEs and ADRs were further analysed by age and EGPA disease duration at baseline to determine whether these patient characteristics were associated with increased susceptibility to AEs. AE and ADR outcomes were also recorded. Safety data were classified by the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms[27] ; ADRs were determined according to the investigator's assessment for each patient.

4 Clinical observations

Clinical observations included : the proportion of patients with clinical symptoms, overall and by ANCA status ; the cumulative proportion of patients with no clinical symptoms ; blood

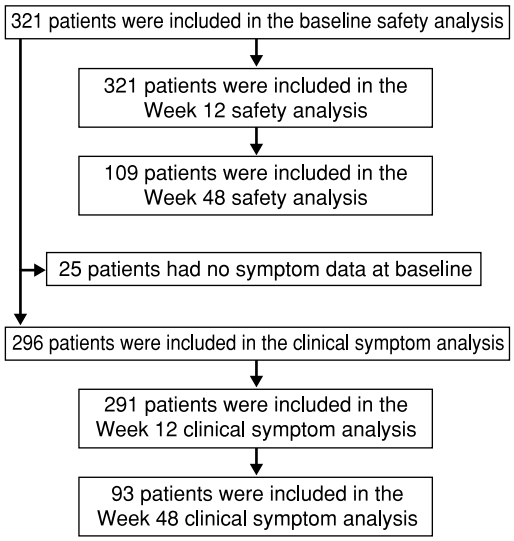

Fig. 1 Patient disposition

eosinophil count, white blood cell (WBC) count; the proportion of patients with an ANCA-positive status; the proportion of patients receiving GC or immunosuppressants and mean GC dose (mg/day). In the overall surveillance study, clinical observation data were recorded at baseline and at Weeks 12, 24, 36, 48 and 96. In this interim analysis, all clinical observations were assessed at baseline and at Weeks 12 and 48, except for the proportion of patients receiving GC or immunosuppressants (for which, data were shown for baseline and Week 48 only) and the cumulative proportion of patients with no clinical symptoms (for which, data were shown for baseline and Weeks 12, 24, 36 and 48).

The presence of clinical symptoms was assessed by the investigator. Clinical symptom categories, excerpted from the Birmingham Vasculitis Activity Score (a clinical index of vasculitis[28]), were: general, cutaneous, mucous membranes/eyes, ear, nose and throat, chest, cardiovascular, abdominal, renal, and nervous system (**e-Table 1**).

5 Sample size and statistical analysis

The sample size was estimated based on a risk of serious infection incidence threshold of 6%[16]. To account for a risk of at least double 6%, 277 patients were required to be included in the safety analysis. The mean and standard deviation (SD) were reported for continuous variables and the counts and percentages were reported for the nominal or categorical variables, including the overall data available for each time point and endpoint.

RESULTS

1 Patient population

Of the 321 patients included in the interim analysis, data from all patients were included in the safety analysis, and data from 296 patients were included in the clinical symptom analysis; 25 patients had no symptom data (**Fig. 1**). By Weeks 12 and 48, 321 and 109 patients were included in the safety analysis, respectively, and 291 and 93 patients were included in the clinical symptom analysis, respectively (**Fig. 1**).

Overall, 58.6% (n=188) of patients were female and 60.1% (n=193) of patients were < 65 years of age (**Table 1**). Most patients had a disease duration of ≦5 years (n=232, 72.3%), with a mean (SD) disease duration of 3.6 (3.9) years (**Table 1**). Only 2.2% (n=7) and 0.9% (n=3) of patients had either the mildest (grade I) or most severe (grade V) disease severity grading, respectively, with 60.7% (n=195) of patients categorized with a disease severity grading of III (**Table 1**). At baseline, the mean (SD) blood eosinophil count was 1211.9 (4380.7) cells/μL, with 44.9% (n=144) of patients having a blood eosinophil count ≧300 cells/μL (**Table 1**). Of the 54.2% (n=174) of patients with ANCA data, 20.7% (n=36) had an ANCA-positive status (equivalent to 11.2% of patients in the total population); among these, 91.7% (n=33) were

Table 1　Patient baseline demographics and disease characteristics

	Patient population (n=321)
Sex, n (%)	
Female	188 (58.6)
Male	133 (41.4)
Age, years, mean [SD]	59.3 [15.5]
Age, years, categories, n (%)	
<65	193 (60.1)
≧65	128 (39.9)
Disease duration, years, mean [SD]	3.6 [3.9]
Disease duration, years, categories, n(%)	
≦2	145 (45.2)
>2–5	87 (27.1)
>5–10	49 (15.3)
>10	26 (8.1)
Unknown	14 (4.4)
EGPA disease severity grading*, categories, n (%)	
I	7 (2.2)
II	88 (27.4)
III	195 (60.7)
IV	28 (8.7)
V	3 (0.9)
Blood eosinophil count, cells/μL, mean [SD]	1211.9 [4380.7]
Blood eosinophil count, cells/μL, categories, n (%)	
<150	122 (38.0)
150–<300	34 (10.6)
≧300	144 (44.9)
>1000	50 (15.6)
Unknown	21 (6.5)
CRP, mg/dL, categories, n (%)	
<0.3	276 (86.0)
≧0.3	18 (5.6)
Unknown	27 (8.4)
ANCA status, categories, n (%)	
Positive	36 (11.2)
MPO only†	25 (69.4)
PR3 only†	3 (8.3)
MPO & PR3†	8 (22.2)
Negative	138 (43.0)
Unknown	147 (45.8)
Patients with prior mepolizumab therapy‡, n (%)	
Yes	50 (15.6)
No	271 (84.4)
Comorbidity, n (%)	
Osteoporosis	86 (26.8)
Dyslipidaemia§	83 (25.9)
Hypertension	74 (23.1)
Diabetes mellitus#	64 (19.9)
Gastroesophageal reflux disease	53 (16.5)
Constipation	45 (14.0)
Insomnia	43 (13.4)

The baseline period was defined as the 4 weeks before the start of mepolizumab treatment. Due to data rounding, percentages may not total 100%.

*Defined by the Japan Intractable Diseases Information Center[29], †percentages are based on total number of patients with an ANCA positive status, ‡for the treatment of bronchial asthma, §includes hypercholesterolemia, dyslipidaemia, lipid metabolism disorder, and hyperlipidaemia, #includes diabetes mellitus, type 2 diabetes mellitus, steroid diabetes and glycosuria.

ANCA：anti-neutrophil cytoplasmic antibodies, CRP：C-reactive protein, EGPA：eosinophilic granulomatosis with polyangiitis, MPO：myeloperoxidase, PR3：proteinase 3, SD：standard deviation

myeloperoxidase (MPO)-ANCA-positive (**Table 1**). Osteoporosis (n=86/321, 26.8%) and dyslipidaemia (n=83/321, 25.9%) were the most common comorbidities (**Table 1**).

2　Mepolizumab safety profile

AEs were reported in 24.0% (n=77) of patients and serious AEs were reported in 12.8% (n=41) of patients (**Table 2**). AEs and serious AEs that were considered to be ADRs were reported in 7.2% (n=23) and 2.2% (n=7) of patients, respectively (**Table 2**). Hypersensitivity reactions and serious hypersensitivity reactions (both including anaphylaxis) were reported in 5.3% (n=17) and 2.2% (n=7) of patients,

Table 2　Patients with AEs and ADRs, by MedDRA system organ class and preferred term（1）

	Patient population（n=321）			
Number of patients, n（%）	Patients with AEs*（n=77）	Patients with serious AEs（n=41）	Patients with ADRs*（n=23）	Patients with serious ADRs（n=7）
Infections and infestations	24（7.5）	11（3.4）	3（0.9）	1（0.3）
Bronchitis	4（1.2）	1（0.3）	—	—
Pneumonia	3（0.9）	3（0.9）	—	—
Herpes zoster	2（0.6）	—	1（0.3）	—
Influenza	2（0.6）	—	—	—
Nasopharyngitis	2（0.6）	—	—	—
Pharyngitis	2（0.6）	—	—	—
Pyelonephritis	2（0.6）	2（0.6）	—	—
Pneumonia bacterial	2（0.6）	2（0.6）	—	—
Periodontitis	1（0.3）	1（0.3）	—	—
Pneumonia cytomegaloviral	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Sepsis	1（0.3）	1（0.3）	—	—
Respiratory tract infection	1（0.3）	1（0.3）	—	—
Acute sinusitis	1（0.3）	—	—	—
Cystitis	1（0.3）	—	1（0.3）	—
Sinusitis	1（0.3）	—	—	—
Oral herpes	1（0.3）	—	—	—
Respiratory, thoracic and mediastinal disorders	17（5.3）	10（3.1）	2（0.6）	1（0.3）
Asthma	12（3.7）	8（2.5）	1（0.3）	—
Eosinophilic pneumonia	2（0.6）	1（0.3）	—	—
Interstitial lung disease	1（0.3）	1（0.3）	—	—
Pneumonia aspiration	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Eosinophilic pneumonia chronic	1（0.3）	1（0.3）	—	—
Sputum increased	1（0.3）	—	—	—
Upper respiratory tract inflammation	1（0.3）	—	—	—
Chronic eosinophilic rhinosinusitis	1（0.3）	—	—	—
Skin and subcutaneous tissue disorders	17（5.3）	3（0.9）	8（2.5）	2（0.6）
Acne	2（0.6）	—	1（0.3）	—
Drug eruption	2（0.6）	—	1（0.3）	—
Purpura	2（0.6）	—	1（0.3）	—
Rash	2（0.6）	—	1（0.3）	—
Urticaria	2（0.6）	—	1（0.3）	—
Haemorrhage subcutaneous	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Panniculitis	1（0.3）	1（0.3）	—	—
Pustular psoriasis	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Dermal cyst	1（0.3）	—	—	—
Eczema	1（0.3）	—	1（0.3）	—
Eczema asteatotic	1（0.3）	—	1（0.3）	—

All percentages are expressed using the total patient population（n=321）as the denominator. Several symptoms may be reported per patient. *Reported AEs and ADRs include serious AEs and serious ADRs, respectively.
ADR：adverse drug reaction, AE：adverse event, MedDRA：Medical Dictionary for Regulatory Activities

Table 2　Patients with AEs and ADRs, by MedDRA system organ class and preferred term（2）

Number of patients, *n*（%）	Patient population（*n*＝321）			
	Patients with AEs*（*n*＝77）	Patients with serious AEs（*n*＝41）	Patients with ADRs*（*n*＝23）	Patients with serious ADRs（*n*＝7）
Skin and subcutaneous tissue disorders	17（5.3）	3（0.9）	8（2.5）	2（0.6）
Hyperhidrosis	1（0.3）	—	—	—
Pruritus	1（0.3）	—	1（0.3）	—
Skin exfoliation	1（0.3）	—	—	—
Urticaria chronic	1（0.3）	—	—	—
Nervous system disorders	13（4.0）	7（2.2）	3（0.9）	2（0.6）
Hypoesthesia	2（0.6）	—	1（0.3）	—
Mononeuropathy multiplex	2（0.6）	1（0.3）	—	—
Neuropathy peripheral	2（0.6）	2（0.6）	—	—
Cognitive disorder	2（0.6）	1（0.3）	1（0.3）	1（0.3）
Cerebral atrophy	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Cerebral infarction	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Loss of consciousness	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Syncope	1（0.3）	1（0.3）	—	—
Pachymeningitis	1（0.3）	1（0.3）	—	—
Thalamus haemorrhage	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Dizziness postural	1（0.3）	—	—	—
Dysaesthesia	1（0.3）	—	1（0.3）	—
Peripheral sensory neuropathy	1（0.3）	—	1（0.3）	—
Cerebral ventricle dilatation	1（0.3）	—	1（0.3）	—
Cervical radiculopathy	1（0.3）	—	—	—
Central nervous system lesion	1（0.3）	—	1（0.3）	—
General disorders and administration site conditions	11（3.4）	4（1.2）	3（0.9）	1（0.3）
Malaise	3（0.9）	1（0.3）	1（0.3）	—
Oedema peripheral	3（0.9）	—	—	—
Asthenia	2（0.6）	1（0.3）	2（0.6）	1（0.3）
Pyrexia	2（0.6）	2（0.6）	—	—
Gait disturbance	1（0.3）	1（0.3）	—	—
Condition aggravated	1（0.3）	—	—	—
Oedema	1（0.3）	—	—	—
Immune system disorders	7（2.2）	6（1.9）	0（0.0）	0（0.0）
EGPA	5（1.6）	5（1.6）	—	—
Anaphylactic shock	1（0.3）	1（0.3）	—	—
Contrast media allergy	1（0.3）	—	—	—

All percentages are expressed using the total patient population（*n*＝321）as the denominator. Several symptoms may be reported per patient. *Reported AEs and ADRs include serious AEs and serious ADRs, respectively.
ADR：adverse drug reaction, AE：adverse event, EGPA：eosinophilic granulomatosis with polyangiitis, MedDRA：Medical Dictionary for Regulatory Activities

Table 2　Patients with AEs and ADRs, by MedDRA system organ class and preferred term（3）

Number of patients, *n*（%）	Patient population（*n*＝321）			
	Patients with AEs*（*n*＝77）	Patients with serious AEs（*n*＝41）	Patients with ADRs*（*n*＝23）	Patients with serious ADRs（*n*＝7）
Gastrointestinal disorders	7（2.2）	2（0.6）	0（0.0）	0（0.0）
Stomatitis	2（0.6）	—	—	—
Colitis ischemic	1（0.3）	1（0.3）	—	—
Enterocolitis	1（0.3）	1（0.3）	—	—
Abdominal discomfort	1（0.3）	—	—	—
Angular cheilitis	1（0.3）	—	—	—
Nausea	1（0.3）	—	—	—
Gastrointestinal angiectasia	1（0.3）	—	—	—
Investigations	7（2.2）	4（1.2）	2（0.6）	1（0.3）
Blood immunoglobulin G decreased	1（0.3）	1（0.3）	1（0.3）	—
C-reactive protein increased	1（0.3）	1（0.3）	—	—
Eosinophil count increased	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Immunoglobulins decreased	1（0.3）	1（0.3）	1（0.3）	—
Pulmonary function test decreased	1（0.3）	1（0.3）	—	—
Blood creatine phosphokinase increased	1（0.3）	—	—	—
Blood creatinine increased	1（0.3）	—	—	—
White blood cell count decreased	1（0.3）	—	1（0.3）	—
Imaging procedure abnormal	1（0.3）	—	—	—
Musculoskeletal and connective tissue disorders	5（1.6）	3（0.9）	1（0.3）	1（0.3）
Osteonecrosis	2（0.6）	2（0.6）	1（0.3）	1（0.3）
Arthralgia	1（0.3）	1（0.3）	—	—
Pain in extremity	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Pathological fracture	1（0.3）	1（0.3）	—	—
Arthritis	1（0.3）	—	—	—
Chondrocalcinosis pyrophosphate	1（0.3）	—	—	—
Injury, poisoning and procedural complications	5（1.6）	2（0.6）	0（0.0）	0（0.0）
Fall	2（0.6）	—	—	—
Fractured sacrum	1（0.3）	1（0.3）	—	—
Tendon rupture	1（0.3）	1（0.3）	—	—
Skin abrasion	1（0.3）	—	—	—
Rib fracture	1（0.3）	—	—	—
Upper limb fracture	1（0.3）	—	—	—
Metabolism and nutrition disorders	4（1.2）	2（0.6）	0（0.0）	0（0.0）
Dehydration	1（0.3）	1（0.3）	—	—
Diabetes mellitus	1（0.3）	1（0.3）	—	—
Hypophosphataemia	1（0.3）	—	—	—
Dyslipidaemia	1（0.3）	—	—	—

All percentages are expressed using the total patient population（*n*＝321）as the denominator. Several symptoms may be reported per patient. *Reported AEs and ADRs include serious AEs and serious ADRs, respectively.
ADR：adverse drug reaction, AE：adverse event, MedDRA：Medical Dictionary for Regulatory Activities

Table 2　Patients with AEs and ADRs, by MedDRA system organ class and preferred term（4）

Number of patients, *n*（%）	Patient population（*n*＝321）			
	Patients with AEs*（*n*＝77）	Patients with serious AEs（*n*＝41）	Patients with ADRs*（*n*＝23）	Patients with serious ADRs（*n*＝7）
Eye disorders	4（1.2）	2（0.6）	1（0.3）	0（0.0）
Cataract	1（0.3）	1（0.3）	—	—
Conjunctival haemorrhage	1（0.3）	1（0.3）	—	—
Erythema of eyelid	1（0.3）	—	—	—
Ocular hyperaemia	1（0.3）	—	1（0.3）	—
Periorbital swelling	1（0.3）	—	1（0.3）	—
Vascular disorders	4（1.2）	3（0.9）	2（0.6）	1（0.3）
Capillary leak syndrome	1（0.3）	1（0.3）	—	—
Circulatory collapse	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Deep vein thrombosis	1（0.3）	1（0.3）	—	—
Hot flush	1（0.3）	—	1（0.3）	—
Hepatobiliary disorders	4（1.2）	2（0.6）	1（0.3）	0（0.0）
Cholecystitis	2（0.6）	2（0.6）	—	—
Liver disorder	2（0.6）	—	1（0.3）	—
Blood and lymphatic system disorders	2（0.6）	0（0.0）	0（0.0）	0（0.0）
Anaemia	1（0.3）	—	—	—
Hypochromic anaemia	1（0.3）	—	—	—
Renal and urinary disorders	2（0.6）	1（0.3）	1（0.3）	1（0.3）
Renal impairment	1（0.3）	1（0.3）	1（0.3）	1（0.3）
Pollakiuria	1（0.3）	—	—	—
Endocrine disorders	1（0.3）	1（0.3）	0（0.0）	0（0.0）
Hypothyroidism	1（0.3）	1（0.3）	—	—
Psychiatric disorders	1（0.3）	0（0.0）	0（0.0）	0（0.0）
Depressive symptom	1（0.3）	—	—	—
Cardiac disorders	1（0.3）	1（0.3）	0（0.0）	0（0.0）
Cardiac failure	1（0.3）	1（0.3）	—	—
Surgical and medical procedures	1（0.3）	1（0.3）	0（0.0）	0（0.0）
Tooth extraction	1（0.3）	1（0.3）	—	—

All percentages are expressed using the total patient population（*n*＝321）as the denominator. Several symptoms may be reported per patient. *Reported AEs and ADRs include serious AEs and serious ADRs, respectively.
ADR：adverse drug reaction, AE：adverse event, MedDRA：Medical Dictionary for Regulatory Activities

respectively；EGPA was the most common event in this category（*n*＝5 patients each for AE and serious AE；**Table 3**）. Infections and infestations were reported in 7.5%（*n*＝24）of patients, with bronchitis being the most common（*n*＝4 patients；**Table 3**）. Serious infections and infestations were reported in 3.4%（*n*＝11）of patients, with pneumonia being the most common event in this category（*n*＝3 patients；**Table 3**）. No malignancy was reported（**Table 3**）. Of the AEs that were considered to be ADRs, hypersensitivity reactions（including anaphylaxis）were

Table 3 Important potential risks associated with mepolizumab treatment

	Patient population (*n*=321)			
Number of patients, *n* (%)	Patients with AEs* (*n*=77)	Patients with serious AEs (*n*=41)	Patients with ADRs* (*n*=23)	Patients with serious ADRs (*n*=7)
Hypersensitivity reactions including anaphylaxis	17 (5.3)	7 (2.2)	6 (1.9)	1 (0.3)
EGPA	5 (1.6)	5 (1.6)	—	—
Drug eruption	2 (0.6)	—	1 (0.3)	—
Rash	2 (0.6)	—	1 (0.3)	—
Urticaria	2 (0.6)	—	1 (0.3)	—
Anaphylactic shock	1 (0.3)	1 (0.3)	—	—
Contrast media allergy	1 (0.3)	—	—	—
Periorbital swelling	1 (0.3)	—	1 (0.3)	—
Circulatory collapse	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Chronic eosinophilic rhinosinusitis	1 (0.3)	—	—	—
Eczema	1 (0.3)	—	1 (0.3)	—
Urticaria chronic	1 (0.3)	—	—	—
Infections and infestations	24 (7.5)	11 (3.4)	3 (0.9)	1 (0.3)
Bronchitis	4 (1.2)	1 (0.3)	—	—
Pneumonia	3 (0.9)	3 (0.9)	—	—
Pyelonephritis	2 (0.6)	2 (0.6)	—	—
Pneumonia bacterial	2 (0.6)	2 (0.6)	—	—
Herpes zoster	2 (0.6)	—	1 (0.3)	—
Influenza	2 (0.6)	—	—	—
Nasopharyngitis	2 (0.6)	—	—	—
Pharyngitis	2 (0.6)	—	—	—
Pneumonia cytomegaloviral	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Periodontitis	1 (0.3)	1 (0.3)	—	—
Respiratory tract infection	1 (0.3)	1 (0.3)	—	—
Sepsis	1 (0.3)	1 (0.3)	—	—
Cystitis	1 (0.3)	—	1 (0.3)	—
Acute sinusitis	1 (0.3)	—	—	—
Sinusitis	1 (0.3)	—	—	—
Oral herpes	1 (0.3)	—	—	—
Malignancies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

All percentages are expressed using the total patient population (*n*=321) as the denominator. Several symptoms may be reported per patient. *Reported AEs and ADRs include serious AEs and serious ADRs, respectively.
ADR：adverse drug reaction, AE：adverse event, EGPA：eosinophilic granulomatosis with polyangiitis

reported in 1.9% (*n*=6) of patients, and infections and infestations were reported in 0.9% (*n*=3) of patients (**Table 3**). The proportion of patients experiencing AEs or those considered to be ADRs was similar regardless of age or disease duration at baseline (**e-Table 2**).

Mepolizumab treatment was discontinued in 3/77 patients：the first patient experienced pachymeningitis due to EGPA, the second patient experienced panniculitis due to obesity, and the third patient experienced non-serious ocular hyperaemia and periorbital swelling that

were considered to be an allergic reaction associated with mepolizumab. All AEs were either resolved or recovering after mepolizumab discontinuation.

AE outcomes were reported for 74/77 patients experiencing AEs. Of the 74 patients with AE outcomes reported, three patients died (deaths reported for serious AEs of thalamus haemorrhage, capillary leak syndrome, and pneumonia aspiration). Osteonecrosis was reported as a serious sequela in one patient, and seven patients did not recover from their AEs during the interim analysis period ; mepolizumab treatment was continued in all seven of these patients. Four patients reported a total of seven unrecovered serious AEs, which included pneumonia, neuropathy peripheral, cognitive disorder, cardiac failure, arthralgia, gait disturbance, and pyrexia. Three of the unrecovered AEs (eczema, eczema asteatotic, and cognitive disorder) were considered to be ADRs.

3 Clinical observations

1) Clinical symptoms

Of the 291 or 93 patients included in the clinical symptom analyses at Week 12 or 48, respectively, reductions from baseline in the proportion of patients experiencing clinical symptoms were seen for all nine clinical symptom categories (**Fig. 2**). In all nine clinical symptom categories, the decrease that was seen in the proportion of patients with clinical symptoms over the observation period was irrespective of ANCA status (**e-Fig. 1**). The proportion of patients with no clinical symptoms increased from 10.8% (n=32/296) at baseline to 31.2% (n=29/93) by Week 48 (**e-Fig. 2**).

2) Blood eosinophil count, WBC count, and ANCA status

Mean (SD) blood eosinophil count reduced from 1211.9 (4380.7) cells/μL during the baseline period to 50.3 (146.0) cells/μL by Week 12 ; this reduction was sustained to Week 48 (mean [SD] 97.7 [408.9] cells/μL) (**e-Fig. 3A**). Likewise, WBC count decreased during the observation period, from a baseline mean (SD) value of 9383.4 (7919.8) cells/μL to 6349.1 (2174.7) cells/μL at Week 48 (**e-Fig. 3B**). The proportion of patients with an ANCA-positive status was similar at baseline (n=36/174, 20.7%) and at Week 48 (n=5/29, 17.2%) (**e-Fig. 3C**).

3) GC and immunosuppressant use

At baseline, 96.3% (n=309/321) of patients used GC ; by Week 48, the proportion of patients using GC was reduced to 81.7% (n=85/104) (**e-Fig. 4A**). Additionally, the mean (SD) GC dose was reduced from 13.2 (12.5) mg/day at baseline to 5.2 (4.3) mg/day by Week 48 (**e-Fig. 4B**). The proportion of patients using immunosuppressants was consistent between baseline (n=107/321 [33.3%]) and Week 48 (n=29/104 [27.9%]) (**e-Fig. 4A**).

DISCUSSION

This is the first real-world study to assess the clinical safety of mepolizumab in patients with EGPA in Japan. Data from this interim analysis showed that mepolizumab was well-tolerated in patients with EGPA with up to 48 weeks of follow-up data.

In the current analysis, AEs were reported in 77/321 patients ; while the risk of experiencing an AE was small, those most frequently reported were infections, mirroring the findings of the Phase III MIRRA clinical trial[16]. Several studies have suggested a role of IL-5 and eosinophils in infection control[30-37]. Given mepolizumab's mechanism of action, it is therefore reasonable to assume that mepolizumab treatment might be associated with an increased risk of infections. However, while we, and others, have shown that mepolizumab reduces peripheral blood eosinophil counts[16,38,39], the results of this

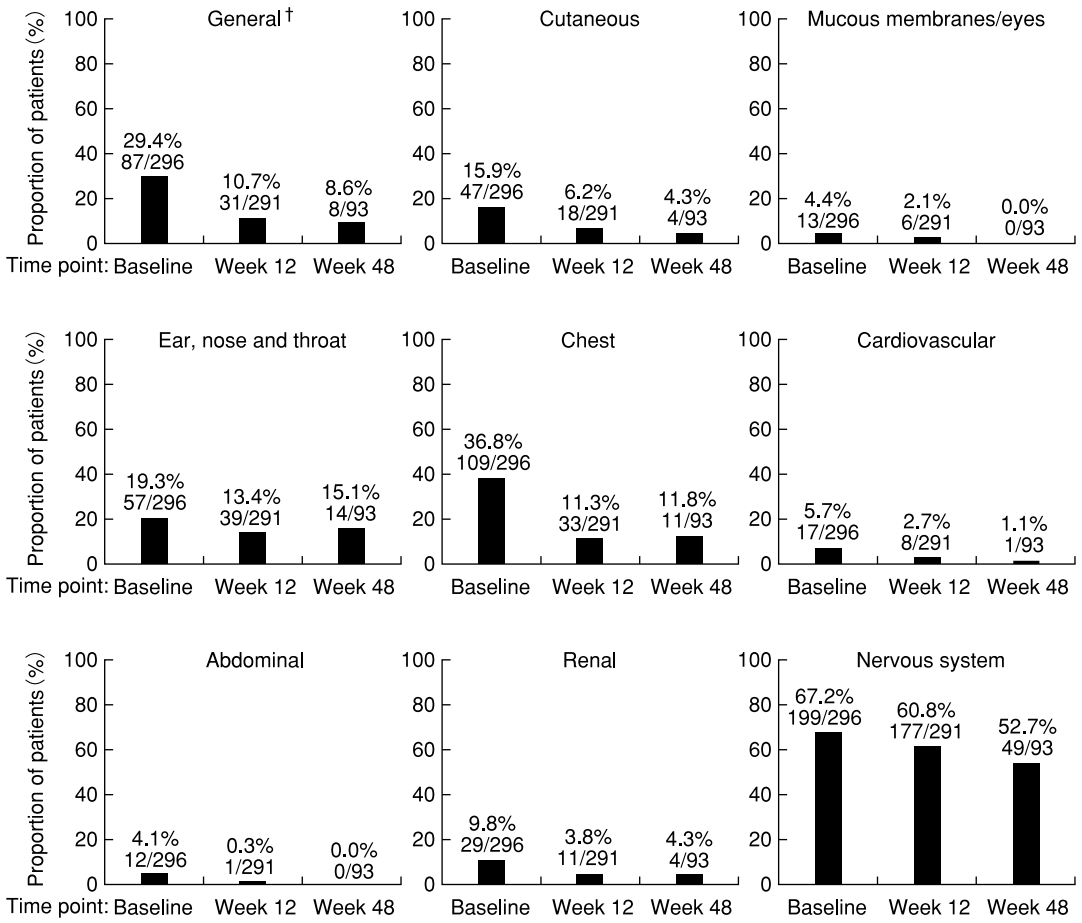

Fig. 2 Proportion of patients with clinical symptoms* before and during mepolizumab treatment
Analyses were performed using data from patients in the clinical symptom analysis population who presented with at least one clinical symptom at baseline ; more than one symptom was recorded for some patients. *Clinical vasculitis symptoms were selected based on the symptoms used for calculating the Birmingham Vasculitis Activity Score (a clinical index of vasculitis[28]). 'Baseline' values represent the 4 weeks before the start of mepolizumab treatment. †General symptoms included myalgia, arthralgia/arthritis, fever and weight loss.

interim analysis do not suggest that mepolizumab treatment increases the risk of infections. Indeed, the infection rates observed in this interim analysis are consistent with those reported for the general EGPA population in Japan[40]. The available evidence suggests that concomitant use of GC and/or immunosuppressants may play a role in infection risk[13,40-42]. Nonetheless, all infections should continue to be closely observed in clinical practice as a potential risk. With regards to hypersensitivity, AEs deemed to be hypersensitivity reactions were reported in 17/321 patients. The most frequent serious hypersensitivity event was worsening of EGPA disease characteristics, occurring in five patients. While our data suggest that these serious AEs were not related to mepolizumab treatment, the criteria for assessing ADRs were not standardized in this study ; ADRs were solely assessed subjectively by the investigator, and as

such, ADRs reported in this study should be interpreted with caution.

There are no large-scale real-world effectiveness data reported for mepolizumab in patients with EGPA in Japan. Therefore, although safety was the focus of this interim analysis, we have also reported clinical observations for patients receiving mepolizumab therapy. Notably, the proportion of patients using GC and the mean daily GC dose decreased with mepolizumab ; these results align with data from the Phase III MIRRA clinical trial[16]. Long-term GC use is associated with several adverse effects, including increased risk of osteoporosis[13-15]. Likewise, previous observational studies have shown dyslipidaemia in patients receiving GC for the treatment of asthma, rheumatoid arthritis, and connective tissue disorders[43], however, evidence from the overall literature regarding the association between chronic GC use and dyslipidaemia is conflicting[14,15]. In this interim analysis, osteoporosis and dyslipidaemia were the most frequently reported baseline comorbidities, and as such, reductions in GC dose after the initiation of mepolizumab may be of benefit to patients with EGPA. Improvements in clinical symptoms were seen irrespective of ANCA status, despite several studies associating ANCA status with differing clinical and disease features of EGPA[4,7-10]. As such, these data may suggest a role for mepolizumab in reducing clinical symptoms across a spectrum of disease characteristics, which will be assessed in more detail in the 96-week analysis of our study.

There are several limitations to this study. The comparative approach used in this study compares each patient's outcome between the baseline period and observational period, and accounts for time-fixed confounding factors, but does not account for time-varying confounding factors, therefore, this study is prone to bias from temporal trends in the outcomes[44]. As this study was non-interventional, data collection was limited to those outcomes assessed as part of daily medical care. Likewise, patients were included irrespective of their previous or baseline therapies, including prior treatment with mepolizumab for bronchial asthma. In addition, all treatment decisions were at the investigator's discretion, which complicates analysis of effectiveness and safety. This study was limited to patients with completed CRFs, therefore, these data may not be a full reflection of patients with EGPA treated with mepolizumab in a real-world setting. Finally, as the study is ongoing, it is possible that later findings may differ as a result of further data retrieval and analysis.

CONCLUSION

This interim analysis of real-world data in Japan showed that mepolizumab was well-tolerated in patients with EGPA. These results suggest that the safety findings of previous clinical studies of mepolizumab in patients with EGPA translate into routine clinical practice.

CONFLICTS of INTERESTS

TF received research grants and/or speaker fees from AbbVie GK, Asahi Kasei Pharma Co., Chugai Pharmaceutical Co. Ltd, Eisai Co. Ltd, GlaxoSmithKline K.K., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, and ONO Pharmaceutical Co. Ltd. TA received research grants from Astellas Pharma Inc., Takeda Pharmaceutical Co. Ltd, Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co. Ltd, Daiichi Sankyo Co. Ltd, Otsuka Pharmaceutical Co. Ltd, Pfizer Inc., Alexion Inc., ONO Pharmaceutical Co. Ltd, Teijin Pharma Ltd, speaker fees from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co. Ltd, Astellas Pharma Inc., Takeda Pharmaceutical Co. Ltd, Pfizer Inc., AbbVie GK, Eisai Co. Ltd, Daiichi Sankyo Co. Ltd, Bristol-Myers Squibb Co. Ltd, UCB Japan Co. Ltd, Eli Lilly Japan K.K., Novartis Pharma K.K., Kyowa Kirin Co. Ltd, Taiho Pharmaceutical Co. Ltd, and consultancy fees from AstraZeneca plc, Medical & Biological Laboratories Co. Ltd, Pfizer

Inc., AbbVie GK, ONO Pharmaceutical Co. Ltd, Novartis Pharma K.K., and Nippon Boehringer Ingelheim Co. Ltd. NO declares no conflicts. NoT received speaker fees from Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., AbbVie GK, Eisai Co. Ltd, Chugai Pharmaceutical Co. Ltd, Bristol-Myers Squibb Co. Ltd, Janssen Pharmaceutical K.K., Astellas Pharma Inc., Asahi Kasei Pharma Co., and Eli Lilly Japan K.K.. NaT received research grants and/or speaker fees from AbbVie GK, Astellas Pharma Inc., Ayumi Pharmaceutical Co., Bristol-Myers Squibb Co. Ltd, GlaxoSmithKline K.K., Chugai Pharmaceutical Co. Ltd, Eisai Co. Ltd, Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Kyowa Kirin Co. Ltd, Mitsubishi Tanabe Pharma Co., and Novartis Pharma K.K. AtN declares no conflicts. AyN received research grants from Chugai Pharmaceutical Co. Ltd, Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc. ; speaker fees from AbbVie GK, Actelion Pharmaceuticals Japan Ltd, Asahi Kasei Pharma Co., Astellas Pharma Inc., Ayumi Pharmaceutical Co., Bristol-Myers Squibb Co. Ltd, Chugai Pharmaceutical Co. Ltd, Eisai Co. Ltd, Eli Lilly Japan K.K., GlaxoSmithKline K.K., Hisamitsu Pharmaceutical Co. Inc., Kyorin Pharmaceutical Co. Ltd, Mitsubishi Tanabe Pharma Co., Otsuka Pharmaceutical Co. Ltd, Pfizer Japan Inc., and Teijin Pharma Ltd. HM declares no conflicts. MK received consulting fees, speaker fees, and/or research grants from AbbVie GK, Astellas Pharma Inc., Asahi Kasei Pharma Co., Bayer, Boehringer Ingelheim Co. Ltd, Chugai Pharmaceutical Co. Ltd, Corbus Pharmaceuticals Holdings, Inc., Eisai Co. Ltd, GlaxoSmithKline K.K., Janssen Pharmaceutical K.K., Medical & Biological Laboratories Co. Ltd., Mochida Pharmaceutical Co. Ltd, Nippon Shinyaku Co. Ltd, ONO Pharmaceutical Co. Ltd, Pfizer Japan Inc., and Mitsubishi Tanabe Pharma Co. MT declares no conflicts. TT received research grants from Chugai Pharmaceutical Co. Ltd, speaker or consulting fees from Chugai Pharmaceutical Co. Ltd, and GlaxoSmithKline K.K. IM, AI, and KA are employees of GlaxoSmithKline K.K.

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e–Table 1　List of clinical symptoms by category

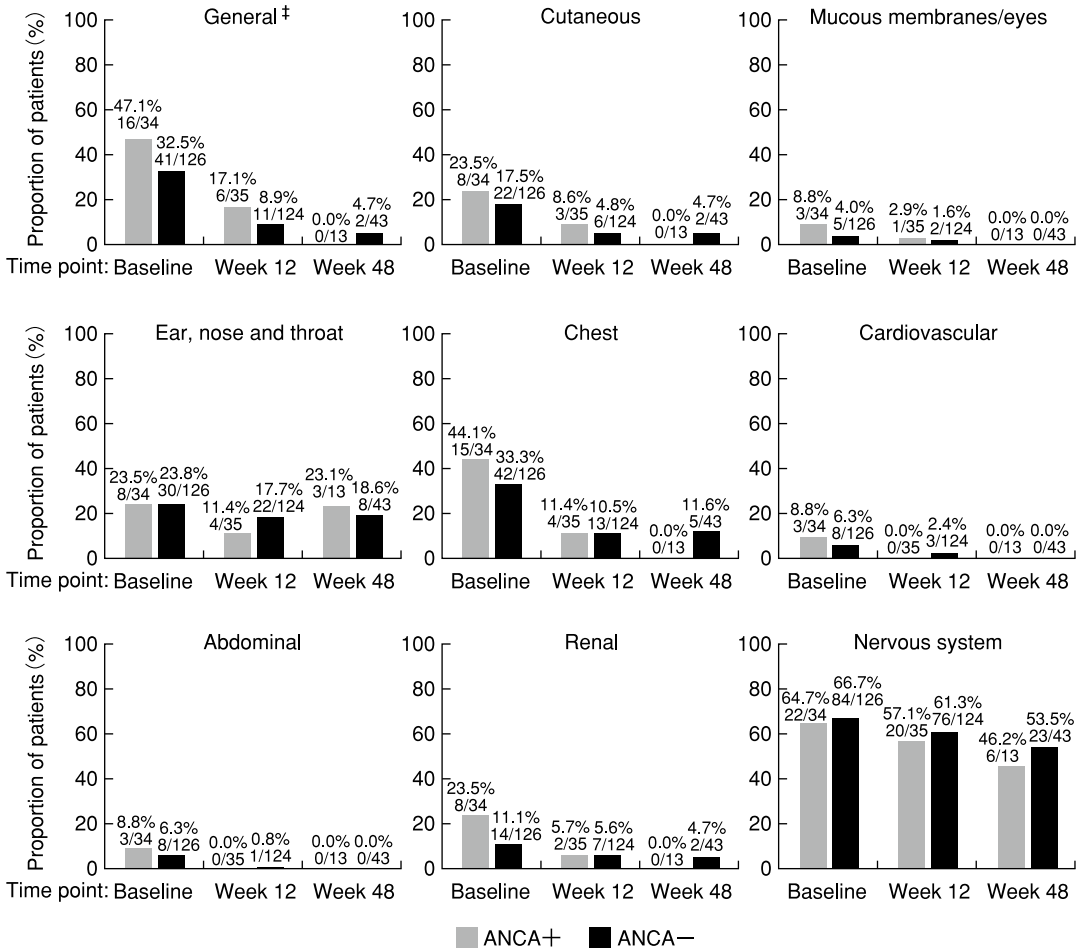
Clinical symptom category	Symptoms included
General	Myalgia, arthralgia/arthritis, fever, weight loss
Cutaneous	Infarct, purpura, ulcer, gangrene, other skin vasculitis
Mucous membranes/eyes	Mouth ulcers, genital ulcers, adnexal inflammation, significant proptosis, scleritis/episcleritis, conjunctivitis/blepharitis/keratitis, blurred vision, sudden visual loss, uveitis, retinal changes
Ear, nose and throat	Bloody nasal discharge/crusts/ulcers/granulomata, paranasal sinus involvement, subglottic stenosis, conductive hearing loss, sensorineural hearing loss
Chest	Wheeze, nodules or cavities, pleural effusion/pleurisy, infiltrate, endobronchial involvement, massive haemoptysis/alveolar haemorrhage, respiratory failure
Cardiovascular	Loss of pulses, valvular heart disease, pericarditis, ischaemic cardiac pain, cardiomyopathy, congestive cardiac failure
Abdominal	Peritonitis, bloody diarrhoea, ischaemic abdominal pain
Renal	Hypertension, proteinuria, haematuria, SCr：1.4–2.79 mg/dL, 2.8–5.69 mg/dL, ≧5.7 mg/dL or rise（>30%）, fall in CCr（>25%）
Nervous system	Headache, meningitis, organic confusion, seizures（not hypertensive）, cerebrovascular accident, spinal cord lesion, cranial nerve palsy, sensory peripheral neuropathy, mononeuritis multiplex

Clinical symptom categories were selected based on the symptoms used for calculating the Birmingham Vasculitis Activity Score（a clinical index of vasculitis[28]）.
CCr：creatinine clearance, SCr：serum creatinine

e–Table 2　Baseline age and disease duration in patients with AEs and ADRs

	Patients with AEs (*n*=77)	Patients with ADRs (*n*=23)
Age, years, mean［SD］	61.5［15.2］	62.5［14.3］
Age, years, categories, *n*（%）		
<65（*n*=193）	42（21.8）	12（6.2）
≧65（*n*=128）	35（27.3）	11（8.6）
Disease duration, years, mean［SD］	3.7［4.3］	3.7［3.8］
Disease duration, years, *n*（%）		
≦2（*n*=145）	38（26.2）	11（7.6）
>2–5（*n*=87）	18（20.7）	6（6.9）
>5–10（*n*=49）	13（26.5）	3（6.1）
>10（*n*=26）	7（26.9）	2（7.7）
Unknown（*n*=14）	1（7.1）	1（7.1）

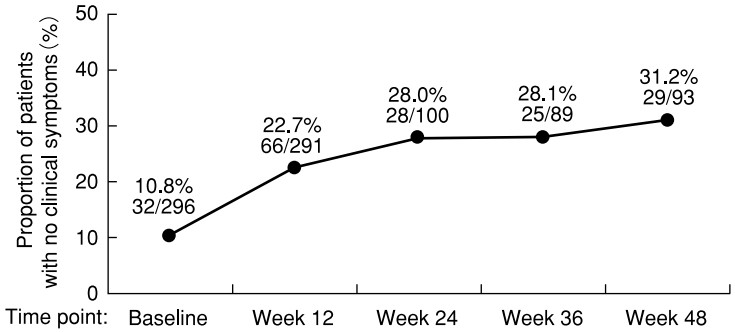
The baseline period was defined as the 4 weeks before the start of mepolizumab treatment.
ADR：adverse drug reaction, AE：adverse event, SD：standard deviation



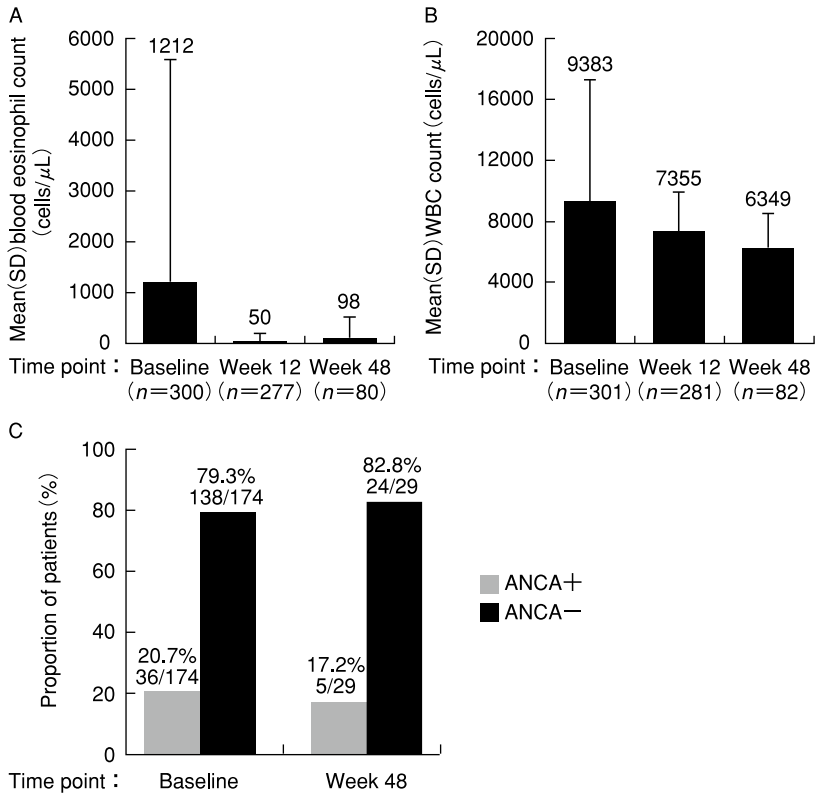
e-Fig. 1 Proportion of patients with clinical symptoms* before and during mepolizumab treatment, by ANCA status†

These secondary analyses include patients in the clinical symptom analysis population with relevant clinical symptoms and ANCA status data available at each given time point. 'Baseline' values represent the 4 weeks before the start of mepolizumab treatment. ANCA status was unknown for 136 patients at baseline, 132 patients at Week 12 and 37 patients at Week 48. *Clinical vasculitis symptoms were selected based on the symptoms used for calculating the Birmingham Vasculitis Activity Score (a clinical index of vasculitis[28]); †ANCA-positive status includes patients who were positive for MPO and/or PR3; ‡general symptoms include myalgia, arthralgia/arthritis, fever and weight loss.

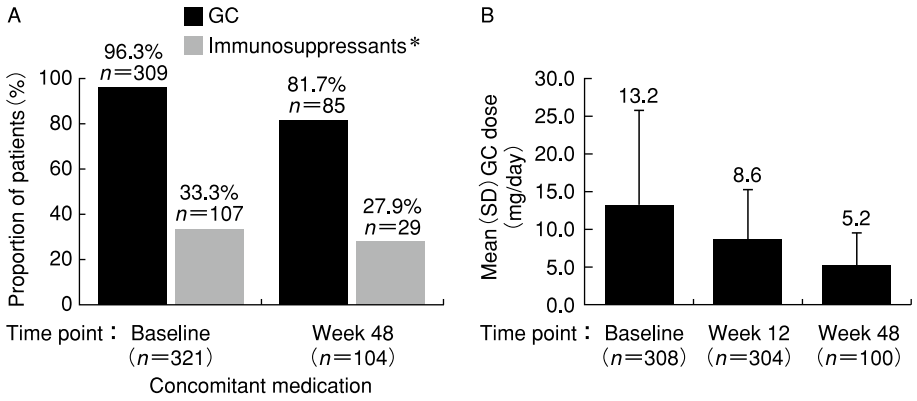
ANCA: anti-neutrophil cytoplasmic antibodies, MPO: myeloperoxidase, PR3: proteinase 3



e-Fig. 2 Proportion of patients with no clinical symptoms* before and during mepolizumab treatment
Analyses include patients in the clinical symptom analysis population who had clinical symptom data available at each given time point. 'Baseline' values represent the 4 weeks before the start of mepolizumab treatment. *Clinical vasculitis symptoms were categorized based on the Birmingham Vasculitis Activity Score (Refer to e-Table 1[28]).



e-Fig. 3 Laboratory findings before and during mepolizumab treatment
Mean blood eosinophil count (A), mean WBC count (B), and proportion of patients with ANCA status (C). Analyses included patients in the safety population who had blood eosinophil count, WBC count, or ANCA status data available at each given time point. 'Baseline' values represent the 4 weeks before the start of mepolizumab treatment.
ANCA: anti-neutrophil cytoplasmic antibodies, SD: standard deviation, WBC: white blood cell



e–Fig. 4　Concomitant medication use before and during mepolizumab treatment

Proportion of patients receiving GC or immunosuppressants at baseline and Week 48 (A); mean GC dose (prednisolone equivalent) at baseline and Week 12 and Week 48 (B). 'Baseline' values represent the 4 weeks before the start of mepolizumab treatment. Concomitant medication data were assessed for patients in the safety population with data available at each given time point.

*Immunosuppressants included azathioprine, cyclophosphamide, methotrexate, cyclosporin, tacrolimus and mycophenolate mofetil.

GC: glucocorticoid, SD: standard deviation