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Factors Associated with Successful Immunosuppressant Discontinuation After Mepolizumab Initiation in Eosinophilic Granulomatosis with Polyangiitis

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Abstract

Background. To identify clinical factors associated with successful discontinuation of conventional immunosuppressants after initiation of mepolizumab in patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Methods. We retrospectively recruited 80 EGPA patients treated at the National Hospital Organization Yokohama Medical Center (April 2022 to March 2026). Patients were categorized into the IS-continuation group (immunosuppressant + corticosteroid + mepolizumab) and the IS-discontinuation group (corticosteroid + mepolizumab) on the basis of immunosuppressant use at mepolizumab initiation. Peripheral blood eosinophil counts, Birmingham Vasculitis Activity Score (BVAS), systemic corticosteroid dosage, remission induction rates, and duration of relapse-free period following the introduction of mepolizumab were compared. Multivariable logistic regression identified predictors of continued immunosuppressant use.

Results. Compared with the IS-continuation group, the IS-discontinuation group was older at EGPA onset (P = 0.027), had a shorter period from diagnosis to initiation of mepolizumab (P = 0.03), had less myocardial involvement (P = 0.03), and had lower BVAS before treatment with mepolizumab (P = 0.03). In multivariable logistic regression analysis, myocardial involvement was independently associated with continued immunosuppressant use (OR 4.85, 95% CI 1.17–20.15, P = 0.030). The non-IS group achieved remission faster (P = 0.04), had a higher cumulative remission rate (P = 0.004), and had a higher relapse-free rate (P = 0.033).

Conclusion. Patients with less cardiac involvement and lower disease activity were more likely to successfully discontinue conventional immunosuppressants after initiation of mepolizumab while maintaining long-term remission. These findings may help identify patients in whom immunosuppressant withdrawal can be considered in clinical practice.

Background

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small-vessel vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCAs). It differs from other ANCA-associated vasculitides, including microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), by its frequent association with asthma, eosinophilia, and peripheral nerve involvement (1, 2) and, lower prevalence of ANCA-positivity. Although corticosteroids are effective for inducing remission in ANCA-associated vasculitides, EGPA relapses more frequently than MPA or GPA, even in patients without poor-prognosis factors (3). In EGPA patients with a Five-Factor Score (FFS) (4) of 0, glucocorticoid monotherapy has historically been considered sufficient, yet relapse occurs in approximately 35% (5). Peripheral neuropathy is a strong predictor of relapse, highlighting the limitations of FFS alone as a guide to initial therapy (6). Although an FFS of 0 may indicate that there will be no adverse effect on overall survival, relapse contributes to irreversible damage, as reflected by higher Vasculitis Damage Index scores (7).

These findings support the early introduction of immunosuppressive therapy, even in patients without poor-prognosis factors.

Cyclophosphamide (CYC) remains the standard remission-induction therapy for severe EGPA and reduces relapse in a dose-dependent manner (8). Although toxicity limits its use, modified low-dose regimens have demonstrated comparable efficacy with fewer adverse events (9). These findings indicate that immunosuppressive therapy should not be withheld solely because of age and suggest the importance of proactive immunosuppressive strategies in EGPA, regardless of initial FFS, to reduce relapse risk and minimize long-term organ damage. Combination therapy with systemic corticosteroids plus IVCY is often recommended for EGPA with life-threatening or major organ involvement. However, both corticosteroids and cytotoxic immunosuppressants carry substantial risks, including infection, malignancy, and long-term organ toxicity (10, 11).

Mepolizumab, an anti–IL-5 monoclonal antibody, reduces blood eosinophil counts and has proven effective in severe asthma (12, 13). In EGPA, a 2010 pilot study demonstrated that intravenous mepolizumab (750 mg every 4 weeks) safely reduced peripheral eosinophils (14). The 2017 MIRRA trial—the first randomized, double-blind, placebo-controlled study of subcutaneous mepolizumab (300 mg monthly) in relapsing or refractory EGPA—showed significantly longer remission, with 53% of patients achieving remission versus 19% with placebo (15). However, current guidelines leave the role of mepolizumab in the treatment of EGPA incompletely defined. European Alliance of Associations for Rheumatology (EULAR) recommends mepolizumab for relapsing or refractory non–organ-threatening EGPA, whereas CYC or rituximab (RTX) remains the preferred treatment for organ- or life-threatening disease (16). The timing of mepolizumab initiation is not addressed. The guidelines also suggest switching from CYC to maintenance agents (azathioprine [AZA], methotrexate [MTX], RTX, or mepolizumab) after remission induction, but they do not specify a preferred sequence.

Other proposed treatment algorithms vary. Raffray and Guillevin (17) recommend corticosteroids as initial therapy for patients with an FFS of 0, with mepolizumab added if induction of remission fails or asthma persists; for patients with FFS ≥ 1, CYC is used for induction, and following remission, maintenance therapy with AZA, MTX, or RTX is initiated, with mepolizumab added if needed. This algorithm implies that mepolizumab should be considered in nearly all patients except those achieving remission with corticosteroids alone. However, the criteria for selecting mepolizumab over other agents remain undefined. Emmi et al. (18) recommend combining mepolizumab with maintenance therapy after induction in newly diagnosed EGPA, regardless of severity. In relapsing disease, they suggest corticosteroids alone or with mepolizumab for non-severe cases, whereas severe relapses require high-dose corticosteroids in combination with CYC or RTX. Mepolizumab is not mentioned in the context of severe relapses. Notably, neither approach defines how mepolizumab compares with conventional immunosuppressants in severe disease, leaving its optimal timing and integration uncertain.

We previously investigated mepolizumab in EGPA, assessing remission induction, corticosteroid-sparing effects, and its effectiveness across a broad spectrum of vasculitic manifestations. In one study, we also

confirmed potential synergy between mepolizumab and intravenous immunoglobulin (IVIG) (19). In another, we found that long-term administration of mepolizumab (> 3 years on average) significantly suppressed relapse rates, particularly in patients classified as super-responders (20). Across those studies, serious adverse events typically associated with conventional immunosuppressants—such as bone marrow suppression, infection, hepatotoxicity, nephrotoxicity, or increased risk of malignancy—were not observed during treatment with mepolizumab. However, it remains unclear whether long-term remission can be sustained with corticosteroids plus mepolizumab alone, without AZA or MTX, following initial remission induction.

In Japan, mepolizumab has been approved for clinical use since 2018. Patients diagnosed before its approval were typically treated with corticosteroids plus conventional immunosuppressants before subsequent addition of mepolizumab. In contrast, after 2018, mepolizumab has increasingly been introduced earlier in the disease course, sometimes without concomitant immunosuppressants.

The primary aim of this study was to identify baseline clinical factors associated with successful discontinuation of conventional immunosuppressants after mepolizumab initiation. We additionally compared disease activity, remission induction, relapse-free survival, eosinophil counts, and corticosteroid requirements between the groups.

Materials and methods

Patients

We retrospectively enrolled 80 patients with EGPA who were treated at the Department of Respirology, National Hospital Organization Yokohama Medical Center, Kanagawa, Japan between April 2022 and March 2026. EGPA was diagnosed according to the criteria for allergic granulomatosis angiitis (known as Churg–Strauss syndrome) (21) and classified by using both the 1990 (22) and 2022 (23) American College of Rheumatology criteria. Inclusion required at least four of the following six features: asthma, eosinophilia, polyneuropathy, pulmonary infiltrate, paranasal sinus abnormality, and extravascular eosinophils.

Study Design

Of 80 patients with EGPA seen at the National Hospital Organization Yokohama Medical Center (April 2022 to March 2026), 66 who did not achieve remission with conventional therapy (e.g., corticosteroids, CYC, AZA, or MTX) received mepolizumab. Among the 66 patients who received mepolizumab, 61 were included in the analysis after excluding 5 patients who achieved remission with corticosteroids alone and therefore never required immunosuppressants were excluded. All 61 patients received combination therapy with corticosteroids and immunosuppressive agents as initial treatment. Prior to the initiation of mepolizumab, immunosuppressive agents were discontinued in patients whose Birmingham Vasculitis Activity Score (BVAS) (version 3)(24) reduction by ≥50% from baseline or decreased to BVAS <10 (the IS-discontinuation group (CS+mepolizumab)). In contrast, in patients with <50% improvement in BVAS,

mepolizumab was initiated while continuing combination therapy with corticosteroids and immunosuppressive agents (the IS-continuation group (CS+IS+mepolizumab)) (Figure 1). At our institution, discontinuation of conventional immunosuppressants before mepolizumab initiation was determined by the treating physicians according to disease activity, primarily based on improvement in BVAS and overall clinical assessment.

Definitions

A state of remission was defined as a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) (24) and receipt of a prednisolone (PSL) dose 5.0 mg or less per day according to a modified definition based on the MIRRA study (15). A state of relapse was defined as the recurrence, after remission, of vasculitis symptoms and signs, including exacerbation of asthma or sinusitis that required the resumption of immunosuppressive therapy or an increased dose of immunosuppressants or prednisolone or additional intravenous immunoglobulin (IVIG). We excluded peripheral blood eosinophilia without accompanying worsening of vasculitic manifestations from the definition of relapse. Although a large increase in tissue eosinophilia might have been correlated with an increase in the severity of vasculitis signs and symptoms, this criterion was not considered in our definition of relapse.

Frequent relapse was defined as ≥1 relapse every 2 years after a period of initial remission; infrequent relapse was defined as <1 relapse every 2 years (25).

Assessment of organ involvement

Multiple mononeuritis, a measure of motor nerve dysfunction, was evaluated by using manual muscle testing (0 to 5, on the Medical Research Council scale), as well as by electromyographic examination. Sensory nerve dysfunction was evaluated subjectively on the basis of symptoms and physical examination.

Lung involvement was considered in cases with ground glass opacity, nodules within the ground glass opacity, interlobular septal thickening (26, 27), bronchial wall thickening, lymphadenopathy (28, 29), pleural effusion (identified by high-resolution computed tomography) (26, 30), or infiltration by eosinophils (identified by lung biopsy).

Cardiac involvement was defined by compatible symptoms together with abnormalities on echocardiography, Holter electrocardiogram, and myocardial imaging using ^{123}I-metaiodobenzylguanidine (31); or elevated plasma B-type natriuretic peptide levels.

Gastrointestinal involvement was defined as symptoms of epigastralgia, abdominal pain, diarrhea, constipation, positive endoscopy signs, and gastrointestinal eosinophil infiltration or colonic submucosal edematous change detected by biopsy (32).

Skin involvement was defined as the presence of purpura, erythema, livedo, ulceration, acrocyanosis, nodule formation, or eosinophilic infiltration as detected by biopsy.

Central nervous system involvement was defined as the presence of headache, visual disturbance, abnormal visual sensation, cerebral infarction or bleeding, or cranial nerve dysfunction.

Renal involvement was defined by any one of the following: presence of eosinophiluria, glomerulonephritis, nephrosis (proteinuria > 3.5 g/day), renal dysfunction (i.e., elevation of creatinine level to >20% of baseline), or proteinuria (>0.5 g/day or 50 mg/dL).

Otitis media was diagnosed by an otorhinolaryngologist.

In all patients with EGPA, disease severity was scored by using FFS 1996 (4) or FFS 2009 (33). When the total number of organs involved was counted, those that were compromised by asthma or sinusitis were not included. We evaluated the disease activity at onset and at first relapse by using the BVAS, which examines symptoms and signs within nine categories (systemic; cutaneous; mucous membranes and eyes; ear, nose, and throat; chest; heart and vessels; gastrointestinal tract; renal system; and nervous system) (24). The maximum number of points is 7 in each category, with a maximum total score of 63.

Data collection

We investigated white blood cell count, eosinophil count, MPO-ANCA (myeloperoxidase-antineutrophil cytoplasmic autoantibody), PR3-ANCA (proteinase 3-ANCA), and rheumatoid factor (RF) levels in the serum at EGPA onset. Treatments were extracted from the patients' medical records, including methylprednisolone (mPSL) pulse therapy (1000 mg/day for 3 consecutive days), initial doses of PSL, immunosuppressants (CYC, AZA, MTX, cyclosporine, and RTX) during induction or maintenance, and IVIG (400 mg/kg daily for 5 days; Venilon, Teijin, Tokyo, Japan).

Endpoints

The primary endpoint was remission rate, and secondary endpoints was relapse-free survival after induction of mepolizumab. We evaluated eosinophil count in the peripheral blood, daily dose of PSL, and BVAS, and we recorded survival status, cause of death, remission or relapse status, and ongoing treatment at last examination.

Human Ethics and Consent to Participate declarations:

This study was performed in accordance with the principles of the Declaration of Helsinki. All patient data were collected retrospectively from medical records. The study was approved by the Ethics Committee of the National Hospital Organization Yokohama Medical Center (approval no. 2022-06). All patients were fully informed about the study, and written informed consent was obtained from all patients or their legal representatives.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Statistical analysis

Continuous variables are expressed as means ± SD and medians (range), unless otherwise specified. Differences among groups were compared statistically by using the paired t-test. Multivariable logistic regression analysis was performed to identify independent predictors of continued immunosuppressant use. Cox proportional hazards regression was used to estimate hazard ratios. Correlations were evaluated with Spearman's rank correlation coefficient. Survival analyses were performed by using Kaplan–Meier analysis with log-rank test and Wilcoxon tests. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed by using SPSS for Windows, version 29 (SPSS, Inc., Chicago, IL, USA).

Results

Comparison of baseline characteristics at diagnosis between the IS-comtinuation group and the IS-discomtinuation group

Characteristics of the 61 EGPA patients treated with mepolizumab are summarized in Table 1. Baseline demographic and laboratory characteristics were comparable between groups, including sex, peripheral eosinophil count, MPO-ANCA, PR3-ANCA, RF, BNP, serum IgE, and IgG levels. In contrast, age at EGPA onset ($P = 0.027$) was higher in the IS-discontinuation group, and the interval from diagnosis to mepolizumab initiation was shorter ($P = 0.002$).

Clinical manifestations at diagnosis were similar between groups, except for myocardial involvement, which was significantly more prevalent in the IS-continuation group ($P = 0.03$). BVAS before treatment with mepolizumab was also higher in the IS-continuation group ($P = 0.03$). Scores based on the ACR 1990 criteria, ACR/EULAR 2022 criteria, FFS 1996, and FFS 2009 did not differ between the two groups.

There was no significant difference between the two groups in the proportion of patients who received mPSL pulse therapy or in the initial dose of PSL. All patients in both groups received immunosuppressants during initial treatment. Cyclophosphamide was used more frequently in the IS-discontinuation group (85.0%, P = 0.046).

Maintenance PSL dose before mepolizumab initiation did not differ significantly. However, at the final examination, dose of PSL was significantly less in the IS-discontinuation group than those in the IS-continuation group ($P = 0.024$) and by the final follow-up, 19 of 41 patients (46.3%) in the IS-continuation group had successfully discontinued immunosuppressants.

The interval from EGPA diagnosis to mepolizumab initiation was significantly longer in the IS-continuation group ($P = 0.03$). The duration of mepolizumab treatment was significantly longer in the IS-

continuation group ($P = 0.015$), and the time to remission was significantly longer in the IS-continuation group ($P = 0.04$).

Multivariable logistic regression analysis identified myocardial involvement as an independent predictor of continued immunosuppressant use (OR 4.85, 95% CI 1.17–20.15; P = 0.030) (Table 2).

Changes in eosinophil count, PSL dose, BVAS, and relapse rate

In both the IS-continuation group and the IS-discontinuation group, peripheral blood eosinophil counts had already decreased significantly before the initiation of mepolizumab ($P < 0.01$). A further significant reduction was observed 1 month after mepolizumab initiation, and counts remained low throughout follow-up the final follow-up visit (Figure 2).

The daily dose of PSL decreased in both groups following conventional therapy. A further significant reduction was observed at 1 year after mepolizumab initiation and at the final visit ($P < 0.01$). There was no significant difference in the degree of reduction between groups (Figure 3, Table 1).

At diagnosis, BVAS did not differ significantly between the two groups ($P = 0.40$) (Table 1**)**. However, BVAS was significantly higher in the IS-continuation group before mepolizumab initiation (P = 0.03), whereas BVAS at the final follow-up did not differ between groups (P = 0.48) (Figure 4**)**.

In the IS-discontinuation group, relapse rates (times/year) decreased after 1 year of mepolizumab ($P < 0.01$) and at the final visit ($P < 0.01$). In contrast, the IS-continuation group did not show a significant decrease in relapse rate at 1 year after mepolizumab initiation; however, a significant reduction was observed by the time of the final visit ($P < 0.01$) (Figure 5**)**.

Cumulative remission rate and relapse-free rate

Cumulative remission after mepolizumab initiation was analyzed using the Kaplan–Meier method (Figure 6). Furthermore, the cumulative remission rate was significantly higher in the IS-discontinuation group (log-rank $P = 0.004$). Moreover, remission was achieved in a significantly shorter period following mepolizumab initiation in the IS-discontinuation group than in the IS-continuation group (5.1 ± 5.7 months vs. 11.8 ± 14.9 months; $P = 0.04$).

Relapse-free survival after the initiation of mepolizumab was also analyzed by using the Kaplan–Meier method (Figure 7). The IS-discontinuation group had a significantly higher relapse-free rate than the IS-continuation group (log-rank $P = 0.033$). Approximately half of the patients in the IS-discontinuation group remained relapse-free throughout the observation period, whereas relapse occurred more frequently in the IS-continuation group.

Discussion

In this study, we identified clinical characteristics associated with successful discontinuation of conventional immunosuppressants after mepolizumab initiation in patients with EGPA. To our knowledge, this is among the few studies to directly compare outcomes—including peripheral eosinophil counts, BVAS, corticosteroid dose, relapse rates, remission induction, and remission maintenance—between these two therapeutic strategies. Remission was defined according to a modified MIRRA definition because tapering PSL below 5 mg/day was associated with frequent relapse in our clinical practice before the introduction of mepolizumab. Thus, remission in this study was defined as PSL ≤5 mg/day, adapted from the MIRRA trial definition (PSL ≤4 mg/day) (15).

We used frequent relapse was defined as ≥1 relapse every 2 years or infrequent relapse was defined as <1 relapse every 2 years (25). Patients with frequent relapses exhibit upregulated expression of CD80 and CD86 on B cells, which has been found to induce Apo-1, leading to a reduction in B cell numbers and suggesting a functional abnormality that may contribute to the mechanism underlying frequent relapses (25).

The IS-discontinuation group was characterized by an older age at diagnosis, lower frequency of cardiac involvement, with 85.0% of them treated with CYC in initial treatment. Nearly half (40%) had an FFS 1998 score of 0; nevertheless, the early administration of adequate immunosuppressive therapy may have contributed to the successful induction and long-term maintenance of remission in this cohort. Multivariable logistic regression identified myocardial involvement as the only independent predictor of continued immunosuppressant use. Notably, myocardial involvement was the only independent predictor of continued immunosuppressant use, underscoring the importance of cardiac disease burden when considering immunosuppressant withdrawal.

Although the IS-discontinuation group had fewer patients with cardiac involvement and thus fewer poor prognostic factors than the IS-continuation group, the significantly shorter time from diagnosis to mepolizumab initiation suggests that earlier use of mepolizumab contributed to successful remission induction and maintenance.

Additionally, patients in the IS-continuation group had higher BVAS scores before mepolizumab initiation compared with the IS-discontinuation group, suggesting a more treatment-refractory disease course. Although while the IS-continuation group did not show reduced relapse rates within the first year of mepolizumab therapy, a decrease was observed at the final follow-up, implying that prolonged treatment may be necessary in this subgroup. In contrast, the non-IS group demonstrated a significant reduction in relapse rates as early as 1 year after mepolizumab initiation, suggesting a more favorable and rapid therapeutic response. These findings suggest that, in non-severe EGPA with less frequent cardiac involvement, early remission induction and sustained remission may be achievable through mepolizumab, potentially reflecting improved long-term prognosis.

Our results are consistent with prior data. In a previous report (20), we demonstrated that, in the super-responder group, relapse rates were significantly lower in the third year of mepolizumab and at the last visit (mean ± SD, 4.3 ± 1.0 years after initiation) than in the first year, suggesting that long-term

administration promotes sustained remission. Similarly, in the present IS-continuation group, immunosuppressants were successfully discontinued in 46.3% of patients, suggesting that prolonged mepolizumab treatment may facilitate subsequent discontinuation of conventional immunosuppressants.

Conventional immunosuppressants are associated with cumulative toxicities, including infection, hepatotoxicity, bone marrow suppression, infertility, and malignancy risk (11, 34). In a retrospective study of 57 patients with EGPA, both AZA and MTX were effective for induction and maintenance of remission. MTX was associated with earlier remission and greater steroid-sparing effects in some clinical settings, but it also resulted in a higher incidence of adverse events. The most common MTX toxicities were gastrointestinal disturbance (37%) and elevated transaminase levels (26%) (35).

These adverse effects are especially relevant in older patients and during long-term administration, necessitating careful monitoring and individualized risk–benefit assessment. Safer alternatives such as mepolizumab, with more favorable side-effect profiles, are increasingly important for long-term disease control, particularly in older patients or those at high risk of treatment-related complications.

Long-term extension of the MIRRA trial confirmed sustained disease control and a favorable safety profile with prolonged mepolizumab use, highlighting its role in remission maintenance and glucocorticoid tapering (36). Adding to this body of evidence, a recent meta-analysis of eight retrospective studies confirmed the overall efficacy and safety of mepolizumab 300 mg in EGPA, including in patients with varied severity and treatment histories. The pooled data demonstrated consistent reductions in disease activity, relapse rates, and corticosteroid use, further supporting this drug's incorporation into EGPA treatment algorithms (37, 38).

Alternative biologics are also emerging. Benralizumab, an anti–IL-5Rα monoclonal antibody, was introduced in 2024, and it demonstrated non-inferiority to mepolizumab in the head-to-head MANDARA trial (39). A Japanese study suggested differential response patterns between mepolizumab and benralizumab, possibly reflecting mechanistic differences that may guide therapeutic choice by disease phenotype or immunological profile (40). A large European real-world study reported comparable efficacy between the two agents, although further prospective head-to-head comparisons are needed (41). In addition to anti–IL-5 agents, other biologics, including omalizumab (anti-IgE) (42) and dupilumab (anti–IL-4/IL-13) (43, 44), have also been investigated in EGPA, particularly in patients with overlapping eosinophilic or atopic features.

Potential biomarkers may further guide therapy. In a previous study, we found that super responders to mepolizumab were characterized by elevated peripheral eosinophil counts at diagnosis (before corticosteroid exposure) and marked reduction in BVAS in response to conventional treatment (19). We also reported that, in EGPA, levels of ILC2 and IL-33 levels were high during disease onset and relapse and low during remission (45). These findings suggest that eosinophil counts and immunologic signatures may help identify patients most likely to benefit from anti–IL-5 therapy.

Several limitations should be acknowledged. This was a retrospective study, subject to inherent bias and confounding. Subgroup sizes were small, reducing statistical power, and the findings may not be generalizable outside our setting. Group allocation reflected clinical decision-making based on treatment response rather than randomization, introducing the possibility of confounding by indication.

Conclusion

In summary, our study provides real-world evidence that mepolizumab is effective in both non-severe and refractory EGPA. Patients in the IS-discontinuation group group—many with non-severe disease with less cardiac involvement and high eosinophil counts at diagnosis—achieved early remission induction and reduced relapse rates within one year. The interval from diagnosis to mepolizumab initiation was significantly shorter in the non-IS group, suggesting that early introduction of mepolizumab may have contributed to successful remission induction and maintenance.

Importantly, multivariable logistic regression identified myocardial involvement as the only independent predictor of continued immunosuppressant use. This finding suggests that patients without cardiac involvement may be the best candidates for immunosuppressant withdrawal after mepolizumab initiation.

These patients also demonstrated favorable responses to conventional therapy, and their high eosinophil counts in the steroid-naïve state may serve as a predictive biomarker for robust response to mepolizumab. Patients in the IS-continuation group, who had more refractory disease, required longer treatment to achieve similar control, but 46.3% of patients (IS-continuation group) were able to discontinue immunosuppressants. Taken together, these findings underscore the importance of early and individualized treatment strategies. Mepolizumab remains a key therapeutic option, not only for relapsing or refractory disease but also for eosinophil-driven, non-severe phenotypes. Prospective studies are warranted to validate biomarkers of treatment response and to optimize the integration of biologics into personalized EGPA management.

Abbreviations

ANCA, antineutrophil cytoplasmic autoantibody; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; FFS, Five-Factor Score; GPA, granulomatosis with polyangiitis；IVIG, intravenous immunoglobulin; MIRRA, Mepolizumab in Relapsing or Refractory EGPA; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; PSL, prednisolone; EULAR, European Alliance of Associations for Rheumatology

Declarations

Ethics Approval and Consent to Participate

This study was performed in accordance with the principles of the Declaration of Helsinki. All patient data were collected retrospectively from medical records. The study was approved by the Ethics Committee of the National Hospital Organization Yokohama Medical Center (approval no. 2022-06). All patients were fully informed about the study, and written informed consent was obtained from all patients or their legal representatives.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

The data presented in this paper was not published elsewhere and the article has not been submitted to any other journal. We give our consent for the publication of this manuscript.

Availability of data and materials

The data are available from the corresponding author upon reasonable request.

Competing interests

N. Masumoto, Y. Yamashita, S. Takaoka, T. Nakashima, K. Matsunaga, Y. Kodama, K. Terada, H. Masumitsu, A. Miyasaka, T. Muraoka, T. Kaneko have no conflicts of interest to disclose regarding this study. N. Tsurikisawa has received lecture fees from GlaxoSmithKline Co., Ltd. and Teijin Healthcare Co., Ltd.

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Authors' contributions

N.M: examination of patients, analysis of data, construction of figures and tables, and writing of main document

Y.Y: examination of patients, analysis of data, and contributions to the discussion

S.T, K.M, T.N, Y.K, K.T, H.M, A.M, and T.M: examination of patients, and contributions to the discussion

T.K: contributions to the discussion

N.T: examination of patients, analysis of data, construction of figures and tables, discussion and summary of paper

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Figures

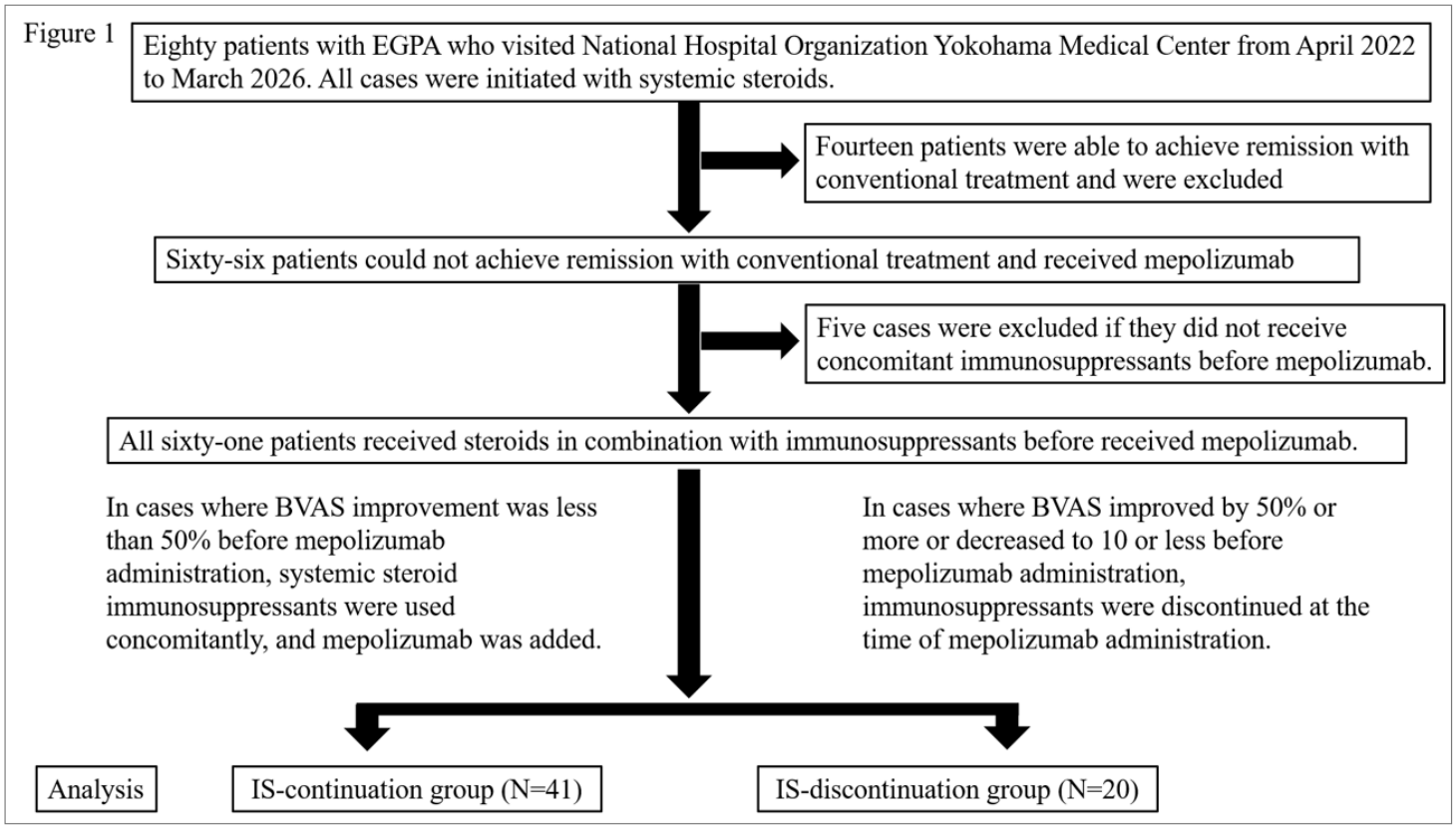


Figure 1

Study protocol. Of 80 patients with EGPA seen at the National Hospital Organization Yokohama Medical Center (April 2022 to March 2026), 66 who did not achieve remission with conventional therapy received mepolizumab.

Among the 66 patients who received mepolizumab, 61 were included in the analysis after excluding 5 patients who did not require concomitant immunosuppressive therapy during initial treatment. All 61 patients received combination therapy with corticosteroids and immunosuppressive agents as initial treatment.

Prior to the initiation of mepolizumab, immunosuppressive agents were discontinued in patients whose Birmingham Vasculitis Activity Score (BVAS) improved by ≥50% from baseline at diagnosis or decreased to <10 (IS-continuation group). In contrast, in patients with <50% improvement in BVAS, mepolizumab was initiated while continuing combination therapy with corticosteroids and immunosuppressive agents (IS-discontinuation group).

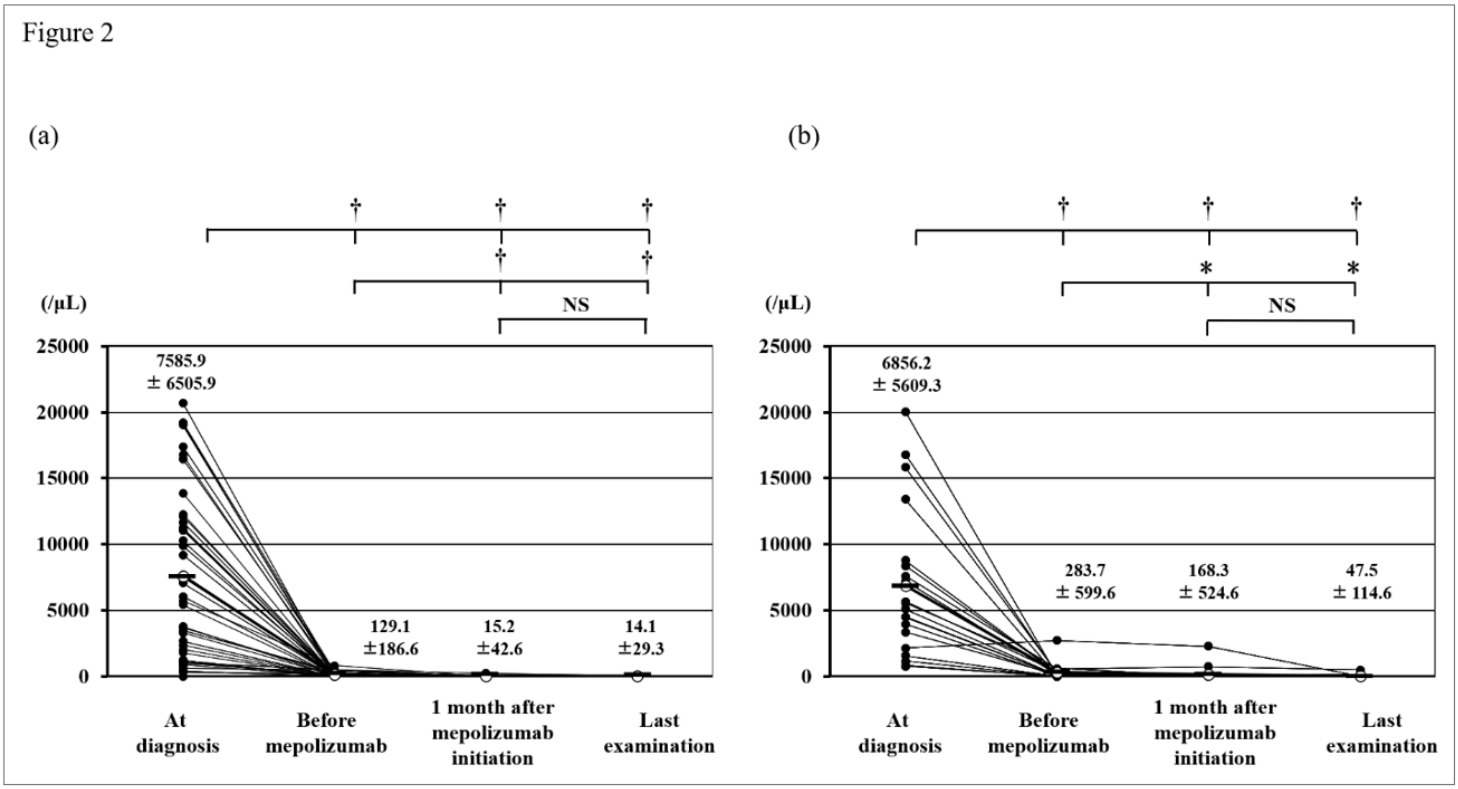


Figure 2

Changes in peripheral blood eosinophil counts. Eosinophil counts are shown throughout the course of treatment in EGPA patients in (**a**) the IS-continuation groupand (**b**) the IS-discontinuation group. The short horizontal line represents the mean count at each measurement point (value above each set of measurements is mean ± SD). Mean values were compared by using the Wilcoxon matched-pairs *t*-test. * $P < 0.05$; † $P < 0.01$; NS, not significant. Upper brackets above each set of measurements indicate the significance of differences between time at diagnosis and subsequent time points (before mepolizumab,

1 month after initiation, and last examination). Medium and lower brackets indicate differences between before mepolizumab and later time points (1 month and last examination).

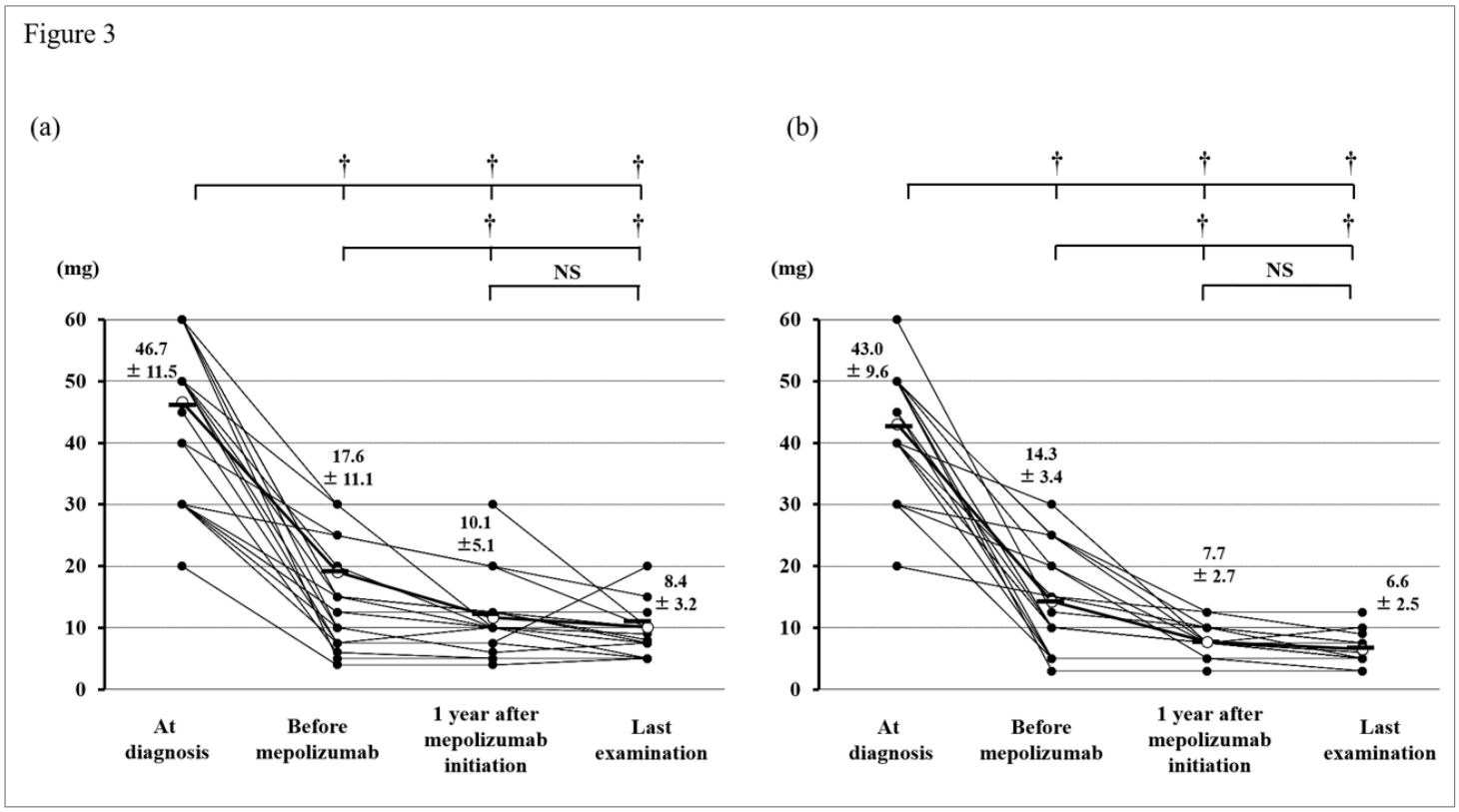


Figure 3

Changes in daily prednisolone dose. Prednisolone dose is shown from diagnosis to before mepolizumab, after mepolizumab initiation, and last examination in patients with EGPA in (**a**) the IS-continuation group and (**b**) the IS-discontinuation group. The short horizontal line represents the mean dose of prednisolone (value above each set of measurements is mean ± SD). Mean values were compared by using the Wilcoxon matched-pairs *t*-test. † $P < 0.01$; NS, not significant.

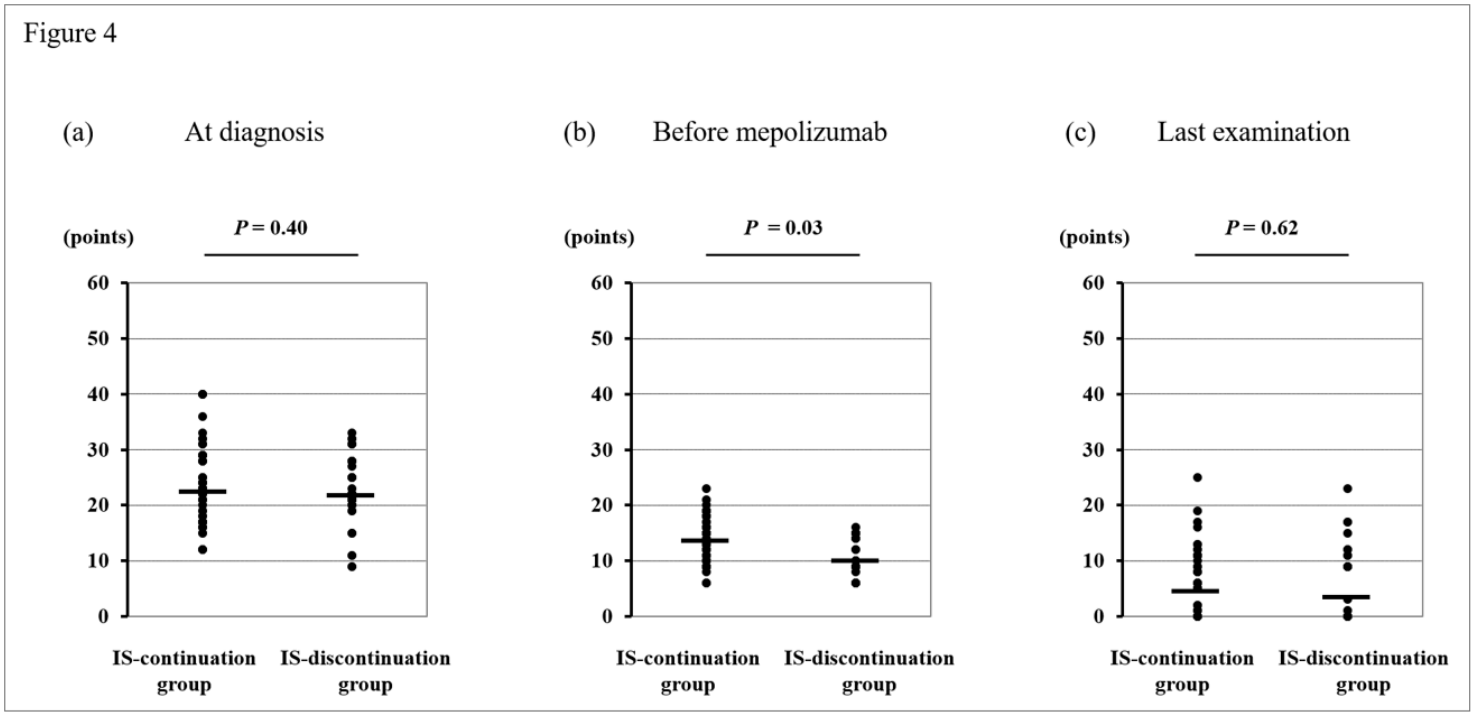


Figure 4

Changes in Birmingham Vasculitis Activity Scores (BVAS) (version 3).BVAS is shown (**a**) at diagnosis, (**b**) before mepolizumab, and (**c**) at last examination in EGPA patients in the IS-continuation group and the IS-discontinuation group. Mean values were compared by using the Mann–Whitney U test. $P < 0.05$ was considered statistically significant.

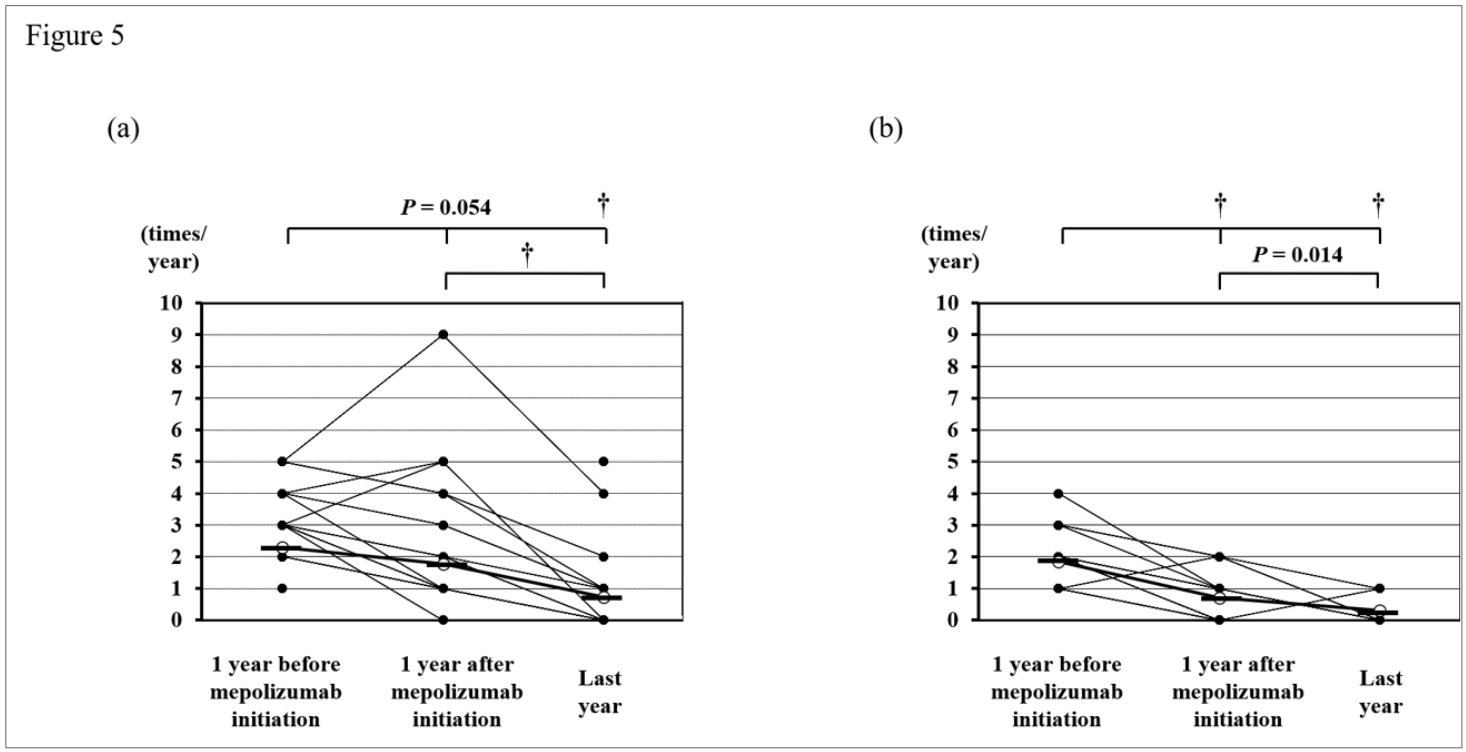


Figure 5

Changes in relapse frequency. Relapse rates (times/year) are shown for at the one year before mepolizumab, the one year after mepolizumab, and the final year of follow-up in EGPA patients in (**a**) the IS-continuation group and (**b**) the IS-discontinuation group. Mean values for each patient group were compared by using the Wilcoxon matched-pairs *t*-test. $P < 0.05$ was considered statistically significant. † < 0.01; NS, not

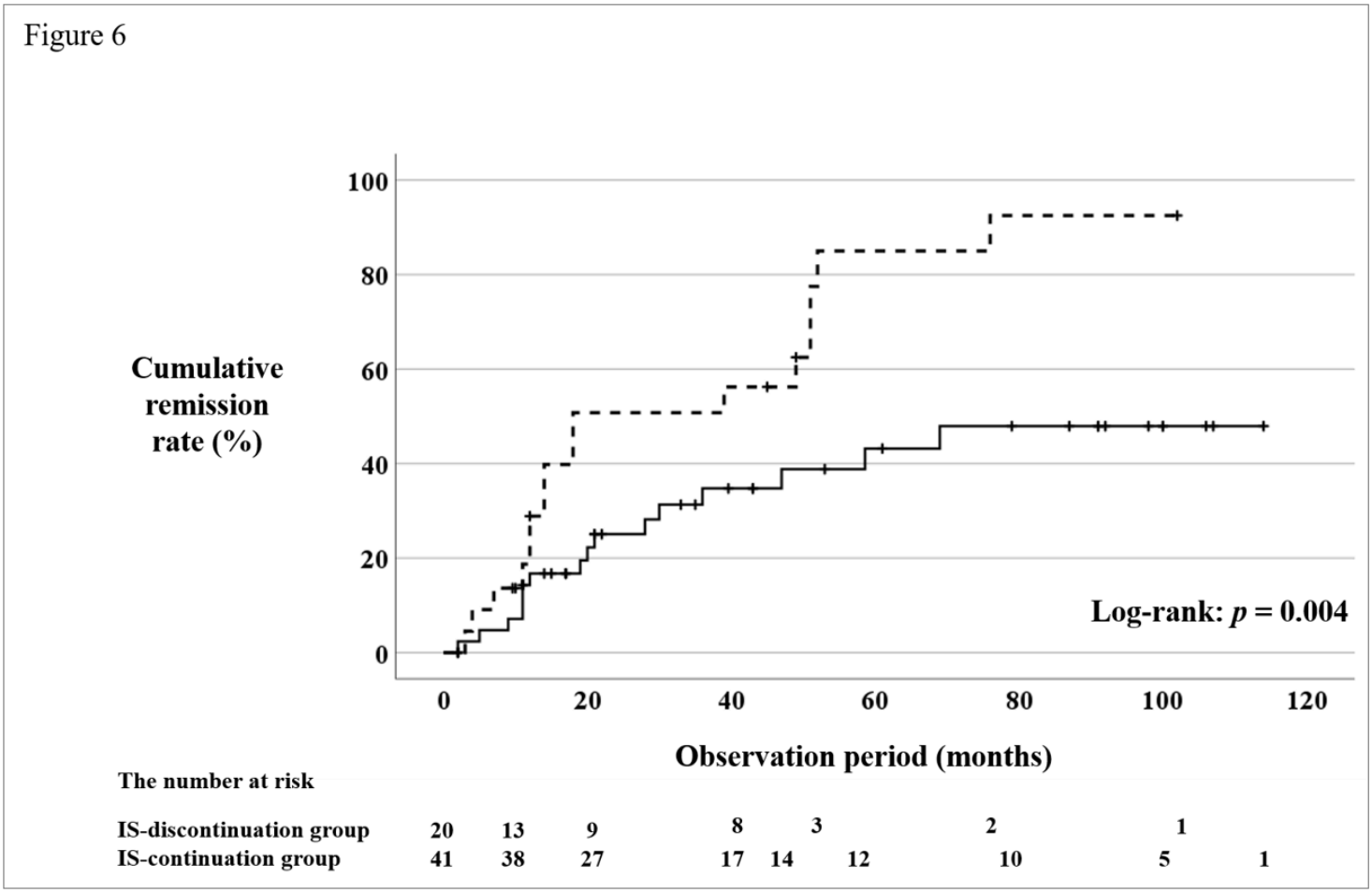


Figure 6

Cumulative remission rate after mepolizumab initiation. Kaplan–Meier curves show cumulative remission in EGPA patients in the IS-discontinuation group(dotted line) and the IS-continuation group (solid line). Remission rate was defined as BVAS 0 and less than 5mg of PSL. Data were censored after a maximum of 114 months of follow-up. *P*-values were determined by log-rank test. $P < 0.05$ was considered statistically significant. Cumulative remission rate in the IS-discontinuation groupshowed a significantly higher than those in the IS-continuation group(log-rank p = 0.004). The hazard ratio for events in the IS-discontinuation groupwas 8.0 (95% CI, 3.1-12.9). The hazard ratio was estimated using a Cox proportional hazards model.

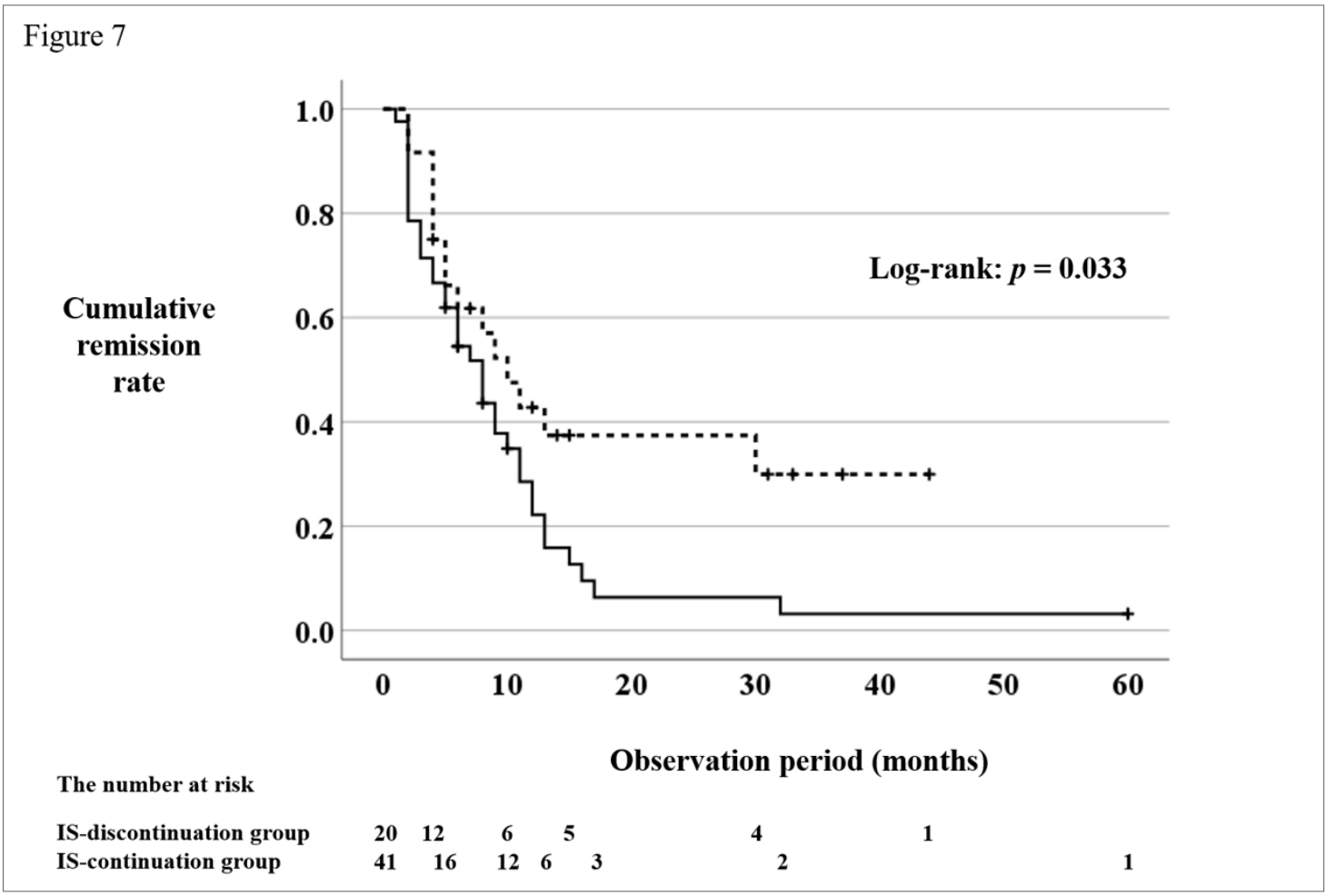


Figure 7

Relapse-free rate after mepolizumab initiation. Kaplan–Meier curves show relapse-free survival in EGPA patients in the IS-discontinuation group (dotted line) and the IS-continuation group (solid line). Data were censored after a maximum of 60 months of follow-up. *P*-value were determined by log-rank test. $P < 0.05$ was considered statistically significant. Relapse-free rate in the IS-discontinuation groupshowed a significantly higher than those in the IS-continuation group(log-rank p = 0.033). The hazard ratio for events in the IS-discontinuation groupwas 11.0 (95% CI, 6.2-15.8). The hazard ratio was estimated using a Cox proportional hazards model.