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Mepolizumab for Eosinophilic Granulomatosis With Polyangiitis: A European Multicenter Observational Study

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Objective. Mepolizumab proved to be an efficacious treatment for eosinophilic granulomatosis with polyangiitis (EGPA) at a dose of 300 mg every 4 weeks in the randomized, controlled MIRRA trial. In a few recently reported studies, successful real-life experiences with the approved dose for treating severe eosinophilic asthma (100 mg every 4 weeks) were observed. We undertook this study to assess the effectiveness and safety of mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks in a large European EGPA cohort.

Methods. We included all patients with EGPA treated with mepolizumab at the recruiting centers in 2015–2020. Treatment response was evaluated from 3 months to 24 months after initiation of mepolizumab. Complete response to treatment was defined as no disease activity (Birmingham Vasculitis Activity Score [BVAS] = 0) and a prednisolone or prednisone dose (or equivalent) of ≤4 mg/day. Respiratory outcomes included asthma and ear, nose, and throat (ENT) exacerbations.

Results. Two hundred three patients, of whom 191 received a stable dose of mepolizumab (158 received 100 mg every 4 weeks and 33 received 300 mg every 4 weeks) were included. Twenty-five patients (12.3%) had a complete response to treatment at 3 months. Complete response rates increased to 30.4% and 35.7% at 12 months and 24 months, respectively, and rates were comparable between mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks. Mepolizumab led to a significant reduction in BVAS score, prednisone dose, and eosinophil counts from 3 months to 24 months, with no significant differences observed between 100 mg every 4 weeks and 300 mg every 4 weeks. Eighty-two patients (40.4%) experienced asthma exacerbations (57 of 158 [36%] who received 100 mg every 4 weeks; 17 of 33 [52%] who received 300 mg every 4 weeks), and 31 patients (15.3%) experienced ENT exacerbations. Forty-four patients (21.7%) experienced adverse events (AEs), most of which were nonserious AEs (38 of 44).

Conclusion. Mepolizumab at both 100 mg every 4 weeks and 300 mg every 4 weeks is effective for the treatment of EGPA. The 2 doses should be compared in the setting of a controlled trial.

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is an antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis characterized by asthma, ear, nose, and throat (ENT) involvement, blood and tissue eosinophilia, and systemic vasculitis manifestations (1,2). Treatment mainly relies on systemic glucocorticoids and inhaled therapies for respiratory symptoms (3). EGPA usually follows a chronic relapsing course; thus, patients are at risk of permanent tissue or organ damage, which can also be due to glucocorticoid-related toxicity. Therefore, immunosuppressive treatments are often required and are also used as glucocorticoid-sparing agents (3,4).

Among novel therapeutic options, mepolizumab is a monoclonal antibody targeting interleukin-5 (IL-5), a cytokine involved in eosinophil maturation, differentiation, and survival. Increased serum levels of IL-5 are observed in eosinophilic disorders, including EGPA (5), and a genome-wide association study identified the *IL5* region as one of the main EGPA-associated loci (6).

Mepolizumab is approved for the treatment of severe eosinophilic asthma at 100 mg every 4 weeks subcutaneously (7) and for the treatment of hypereosinophilic syndrome (HES) at 300 mg every 4 weeks (8). After encouraging results from previous studies (9,10), the phase III MIRRA trial proved the efficacy of mepolizumab 300 mg every 4 weeks subcutaneously for relapsing or refractory EGPA (11,12), leading to its approval by the US Food and Drug Administration (FDA), while in Europe it is currently used off-label.

Recent smaller studies showed the successful use of mepolizumab 100 mg every 4 weeks for the treatment of EGPA, especially for the control of respiratory manifestations (13–15). However, the benefits and side effects of mepolizumab 100 mg every 4 weeks versus 300 mg every 4 weeks for systemic and respiratory EGPA involvement have never been compared. Therefore, its optimal dose is still debated (16). This study aimed to investigate the effectiveness and safety of mepolizumab 100 mg versus 300 mg every 4 weeks in a large European cohort of patients with EGPA.

PATIENTS AND METHODS

Study design and setting. This multicenter, retrospective study was conducted on a cohort of patients with EGPA treated with mepolizumab between May 2015 and February 2020 at 38 EGPA referral centers in 8 European countries (Italy, France, Germany, the UK, Russia, Spain, Switzerland, and Sweden; see Appendix A for members of the European EGPA Study Group). The study received approval from the University of Florence Ethics Committee (reference no. 16821_OSS).

Study population and treatment. The cohort included adult patients who met the American College of Rheumatology classification criteria for EGPA (17) or the criteria proposed in the MIRRA trial (11), who received mepolizumab 100 mg every 4 weeks or 300 mg every 4 weeks, in accordance with local practice. Patients with a follow-up of <3 months after the first mepolizumab dose or those enrolled in clinical trials were excluded.

Data collection and outcome assessment. Demographic, clinical, laboratory, and treatment-related data were retrospectively collected from medical records at the time of mepolizumab initiation (time 0) and at 3 months, 6 months, 12 months, and 24 months of follow-up. The effectiveness of mepolizumab in controlling systemic disease activity was assessed using the Birmingham Vasculitis Activity Score (BVAS) (18). Complete response to treatment was defined as no disease activity (BVAS = 0) and a prednisolone or

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prednisone dose (or equivalent) of ≤4.0 mg/day, as defined by the MIRRA trial (11). Partial response to treatment was defined as no disease activity and a prednisolone or prednisone dose of >4.0 mg/day.

Relapse was assessed only in patients in whom complete response to treatment had been achieved and was defined, as in the MIRRA trial, by at least 1 of the following criteria: 1) active vasculitis (defined as BVAS >0) and/or 2) worsening asthma and/or ENT manifestations leading to an increase in prednisolone or prednisone dose to >4.0 mg/day, initiation of a new immunosuppressive therapy, or hospitalization (11).

With regard to respiratory outcomes, we assessed asthma exacerbations, defined as any of the following events: asthma attack needing an increase in oral prednisone dose, asthma-related emergency department admission, and/or use of acute oral glucocorticoids, antibiotics, or short-acting beta agonists. In addition, the effect of mepolizumab on lung function was monitored by the variation in pre-bronchodilator forced expiratory volume in 1 second (FEV_1). ENT relapse was defined as the reappearance of ENT symptoms, following symptoms having been under complete control at the previous time point.

Additional outcomes assessed included changes in organ manifestations (assessed separately from BVAS items), glucocorticoid-sparing and disease-modifying antirheumatic drug (DMARD)–sparing effect, variation in the proportion of ANCA-positive patients, and reduction in eosinophil count.

During follow-up, variations in monthly mepolizumab dose or treatment discontinuation were recorded. All adverse events (AEs) occurring during treatment were also recorded, and their seriousness was assessed in accordance with the World Health Organization criteria (19). All study outcome measures were analyzed in the entire cohort and compared between patients receiving stable treatment with mepolizumab 100 mg every 4 weeks and those treated with 300 mg every 4 weeks. Stable treatment was defined as no change in the monthly mepolizumab dose during the entire follow-up period.

Statistical analysis. Data are presented as the median and interquartile range (IQR) for continuous variables, and as the absolute number and percentage for qualitative variables. Continuous end points at 3–24 months were compared with time 0 (baseline) using the Wilcoxon signed rank test, whereas qualitative variables were compared using McNemar's test. Nonparametric tests were used since the distribution of the data was not normal. Complete response and partial response rates and AE rates were compared between patients receiving stable treatment with mepolizumab 100 mg every 4 weeks and those receiving 300 mg every 4 weeks using Fisher's exact test. Cox proportional hazards regression models were fitted to derive Kaplan–Meier curves and to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the occurrence of asthma and ENT exacerbations over time.

If a patient was still receiving mepolizumab treatment at a given follow-up time point but had missing data regarding EGPA manifestations, BVAS score, and/or daily glucocorticoid dose, the data were imputed using the last observation carried forward method, as these parameters were necessary to assess the primary outcome measure of this study. For all other clinical and laboratory parameters, the analyses were conducted only on subjects with available data at the given time point.

Statistical analyses were performed using Stata, version 14. *P* values less than 0.05 were considered significant.

Data availability. Deidentified individual participant data will be made available upon reasonable request to the corresponding author.

RESULTS

We included 203 patients, of whom 57.1% were women (Table 1). The median age at the time of mepolizumab initiation was 55.1 years (IQR 46.7–62.5), and the median disease duration was 4.8 years (IQR 4.9–9.2). At the time of EGPA diagnosis, 70 patients (34.5%) were positive for ANCAs, most of whom had either perinuclear ANCAs or myeloperoxidase ANCAs (84.3%). Before mepolizumab treatment was initiated, 150 of 203 patients (73.9%) had received traditional DMARDs, 51 (25.1%) received biologic DMARDs, and 18 (9.0%) received intravenous immunoglobulin. Disease remission, according to clinical judgment, was achieved in 120 patients after induction therapy. At the time of mepolizumab initiation (baseline), 92.1% of the patients had active disease, with a median BVAS score of 4 (IQR 2–8). The most common manifestations were pulmonary (89.7%), ENT (71.4%), constitutional (27.6%), and peripheral neurologic (22.7%). Ten patients had cardiac involvement at baseline, including 1 case of pericarditis, 1 case of myocarditis, and 8 cases of cardiomyopathy with cardiac failure. Of 190 patients with available ANCA test results, 38 (20.0%) were ANCA positive at the time mepolizumab was initiated, most of whom had perinuclear ANCAs or myeloperoxidase-ANCAs (89.5%). At baseline, almost all patients (95.6%) had received stable glucocorticoid treatment in the previous 3 months, at a median prednisone dose of 10 mg/day (IQR 5–20). Additional therapies included conventional DMARDs, mostly methotrexate (18.7%), azathioprine (11.3%), rituximab (11.3%), or intravenous immunoglobulin (5.9%). One hundred ninety-two patients (95%) were receiving inhaled therapy for asthma.

One hundred sixty-eight patients initially received mepolizumab at 100 mg every 4 weeks, and 35 at 300 mg every 4 weeks. During follow-up, 10 patients switched from 100 mg to 300 mg every 4 weeks due to inefficacy. Another 2 patients switched from 300 mg to 100 mg every 4 weeks due to personal reasons (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.

Table 1. Characteristics of the patients with EGPA at the time of mepolizumab initiation*

	Overall (n = 203)	Mepolizumab 100 mg/4 weeks (n = 158)	Mepolizumab 300 mg/4 weeks (n = 33)	*P*
Female	116 (57.1)	88 (55.7)	22 (66.7)	0.333
Smoking status				
Former	44 (21.7)	36 (22.8)	5 (15.2)	0.640
Current	3 (1.5)	3 (1.9)	0	
Age at diagnosis, median (IQR) years	49.1 (37.7–57.1)	48.7 (37.9–57.5)	49.2 (39.8–53.4)	0.380
Age at mepolizumab initiation, median (IQR) years	55.1 (46.7–62.5)	55.1 (46.7–62.8)	53.0 (47.3–59.3)	0.426
Disease duration at mepolizumab initiation, median (IQR) years	4.8 (4.9–9.2)	4.9 (1.6–8.9)	3.9 (1.1–14.1)	0.921
Active organ involvement at mepolizumab initiation				
Constitutional	56 (27.6)	50 (31.7)	3 (9.1)	0.009
Purpura	15 (7.4)	11 (7.0)	2 (6.1)	1.000
ENT	145 (71.4)	121 (76.6)	17 (51.5)	0.005
Pulmonary	182 (89.7)	141 (89.2)	29 (87.9)	0.765
Cardiac	10 (4.9)	8 (5.1)	1 (3.0)	1.000
Gastrointestinal	9 (4.4)	8 (5.1)	1 (3.0)	1.000
Renal	5 (2.5)	5 (3.2)	0	NA
Peripheral neurologic	46 (22.7)	36 (22.8)	6 (18.2)	0.650
Active disease at mepolizumab initiation (BVAS >0)	187 (92.1)	144 (91.1)	31 (93.9)	0.792
BVAS score at mepolizumab initiation, median (IQR)	4 (2–8)	4 (2–8)	4 (2–7)	0.163
Laboratory parameters at mepolizumab initiation†				
ANCA positive	38 (20.0)	28 (18.9)	9 (27.3)	0.339
Perinuclear ANCA	34 (17.9)	26 (17.6)	8 (24.2)	
Cytoplasmic ANCA	4 (2.1)	2 (1.4)	1 (3.0)	
MPO ANCA	34 (17.9)	27 (18.2)	8 (24.2)	
PR3 ANCA	4 (2.1)	2 (1.4)	1 (3.0)	
Eosinophil count, median (IQR)‡	610 (200–1,040)	700 (200–1,080)	440 (200–910)	0.328
Pharmacologic therapies administered before mepolizumab initiation				
Oral glucocorticoids	201 (99.0)	156 (98.7)	33 (100.0)	NA
Azathioprine	91 (44.8)	69 (43.7)	17 (51.5)	0.446
Methotrexate	78 (38.4)	56 (35.4)	18 (54.6)	0.050
Cyclophosphamide	57 (28.1)	44 (27.9)	11 (33.3)	0.531
Mycophenolate	39 (19.2)	29 (18.4)	6 (18.2)	1.000
Cyclosporine	21 (10.3)	18 (11.4)	1 (3.0)	0.206
Rituximab	39 (19.2)	36 (22.8)	3 (9.1)	0.097
IV immunoglobulin	18 (8.9)	17 (10.8)	1 (3.0)	0.321
Omalizumab	17 (8.4)	13 (8.2)	2 (6.1)	1.000
Other immunosuppressants	16 (7.9)	13 (8.2)	1 (3.0)	0.471
Pharmacologic therapies at mepolizumab initiation				
Prednisone equivalent daily dose in the previous 3 months, median (IQR)§	10 (5–20)	10 (IQR 5-20)	10 (IQR 5-22.5)	0.854
Oral glucocorticoids	194 (95.6)	149 (94.3)	33 (100.0)	NA
Prednisone equivalent daily dose, median (IQR)	10 (5–20)	10 (5–20)	10 (5–25)	0.511
Methotrexate	38 (18.7)	29 (18.4)	9 (27.3)	0.240
Azathioprine	23 (11.3)	19 (12.0)	3 (9.1)	0.772
Mycophenolate	18 (8.9)	12 (7.6)	4 (12.1)	0.486
Cyclosporine	2 (1.0)	1 (0.6)	0	NA
Rituximab	23 (11.3)	20 (12.7)	3 (9.1)	0.771
IV immunoglobulin	12 (5.9)	11 (7.0)	1 (3.0)	0.695
Other immunosuppressants	5 (2.5)	3 (1.9)	1 (3.0)	0.535
Inhaled therapy for asthma	192 (95.0)	150 (94.9)	30 (90.9)	0.407

* Except where indicated otherwise, values are the number (%). EGPA = eosinophilic granulomatosis with polyangiitis; IQR = interquartile range; ENT = ear, nose, and throat; NA = not applicable; BVAS = Birmingham Vasculitis Activity Score; ANCA = antineutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3; IV = intravenous.
† Data were available for 190 patients overall, 148 patients receiving mepolizumab 100 mg/4 weeks, and 33 patients receiving mepolizumab 300 mg/4 weeks.
‡ Data were available for 194 patients overall, 152 patients receiving mepolizumab 100 mg/4 weeks, and 32 patients receiving mepolizumab 300 mg/4 weeks.
§ Data were available for 195 patients overall, 151 patients receiving mepolizumab 100 mg/4 weeks, and 32 patients receiving mepolizumab 300 mg/4 weeks.

41943). Conversely, in 158 patients (77.8%) and 33 patients (16.3%), stable treatment with mepolizumab of 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, was maintained over the entire follow-up period.

Baseline demographic and clinical characteristics were comparable between these 2 groups, with the exception of constitutional and ENT manifestations, which were more frequent among patients receiving mepolizumab 100 mg every 4 weeks than those receiving 300 mg every 4 weeks (31.7% versus 9.1% [$P = 0.009$] and 76.6% versus 51.5% [$P = 0.005$], respectively) (Table 1).

Effectiveness of mepolizumab on systemic disease activity. At 3 months, complete response to treatment had already been achieved in 25 of 203 patients (12.3%), whereas partial response to treatment had been achieved in 64 patients (31.5%) (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Complete response rates increased to 23.6% at 6 months, 30.4% at 12 months, and 35.7% at 24 months. Response rates were similar between patients receiving mepolizumab 100 mg every 4 weeks and those receiving 300 mg every 4 weeks (Figure 1). In particular, complete response to treatment had been achieved in 12.0% and 18.2% of patients receiving 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, at 3 months, whereas partial response to treatment had been achieved in 32.9% and 36.4% of patients receiving 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, at 3 months ($P = 0.474$). Complete response rates further increased during follow-up for both treatment groups ($P = 0.204$ and $P = 0.809$ for mepolizumab 100 mg versus 300 mg every 4 weeks at 6 months and 12 months, respectively). At 24 months, only 39 patients receiving mepolizumab 100 mg every 4 weeks and 12 patients receiving 300 mg every 4 weeks had available follow-up data. A greater proportion of patients receiving mepolizumab 300 mg every 4 weeks had complete response to treatment (58.3% versus 33.3%) or partial response to treatment

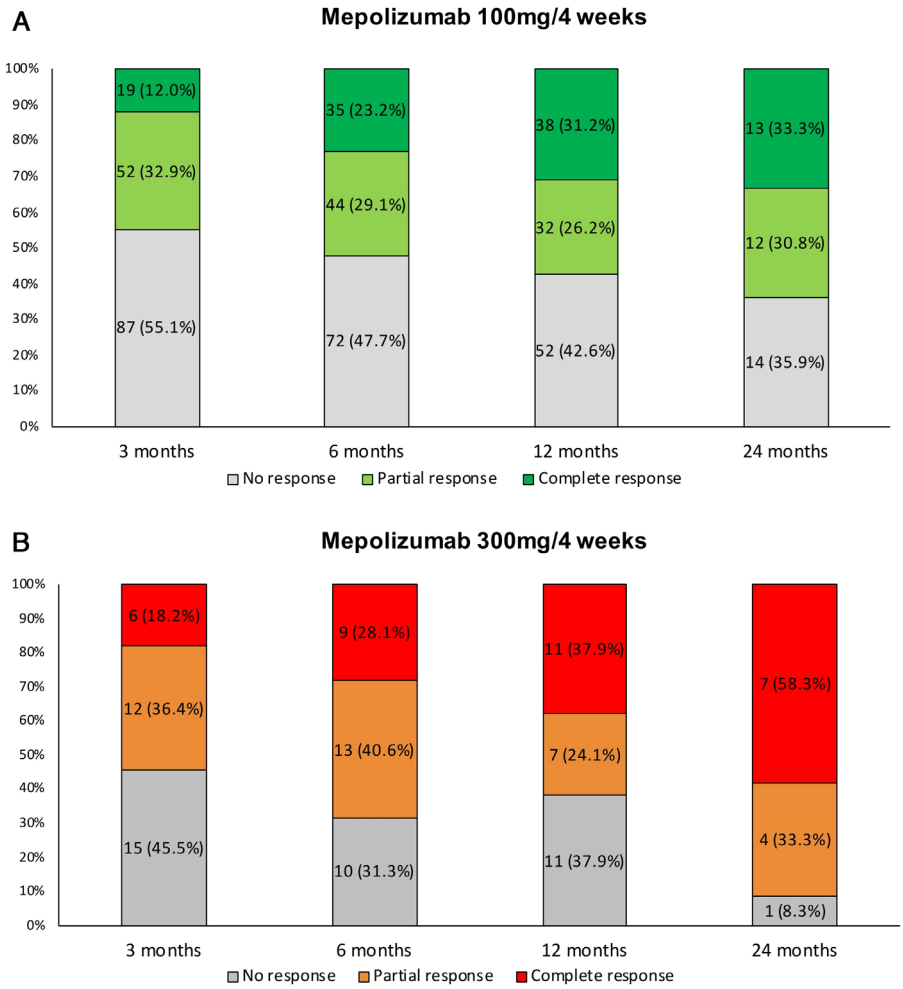
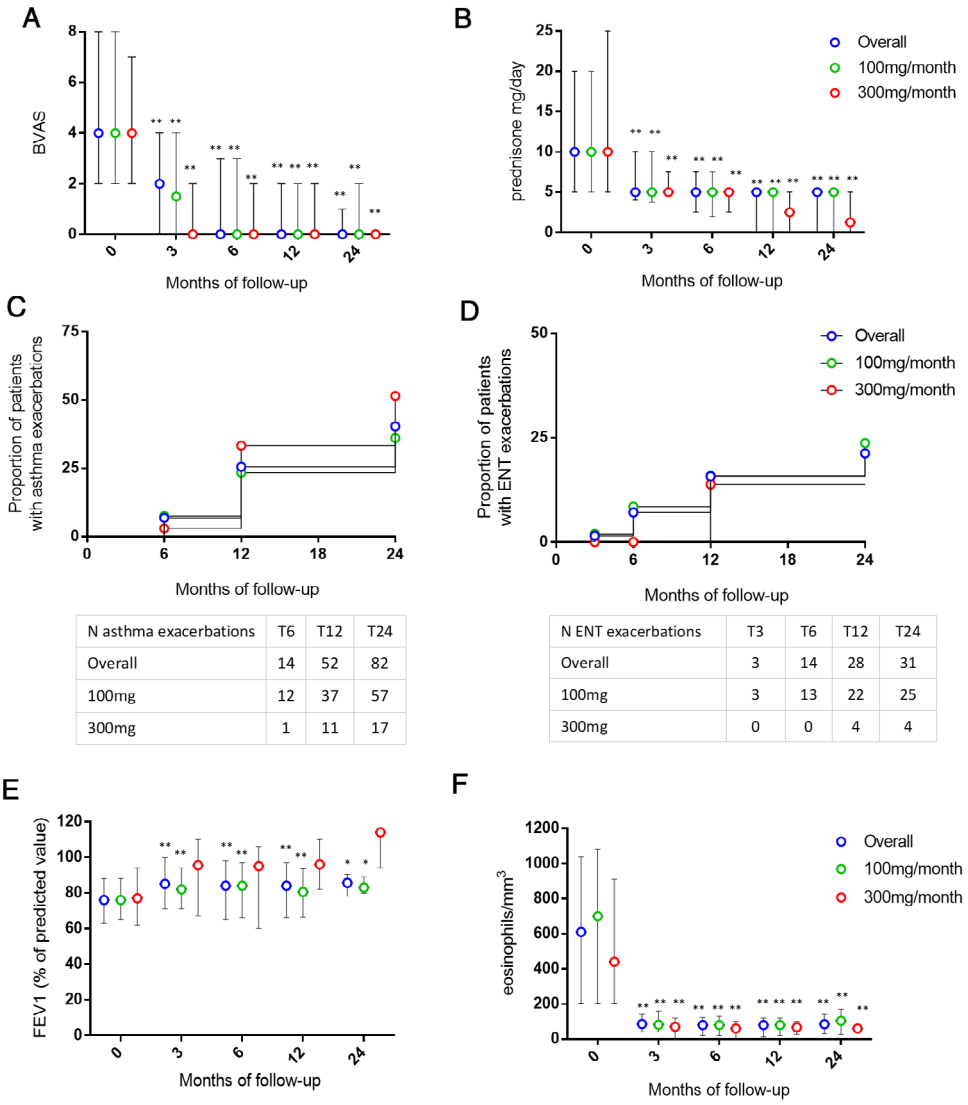


Figure 1. Complete and partial response rates in patients with eosinophilic granulomatosis with polyangiitis who received stable treatment with mepolizumab 100 mg every 4 weeks (**A**) and 300 mg every 4 weeks (**B**). Complete response was defined as no disease activity (Birmingham Vasculitis Activity Score [BVAS] = 0) and daily prednisone dose ≤4 mg/day. Partial response was defined as no disease activity (BVAS = 0) and daily prednisone dose >4 mg/day. No response was defined as active disease (BVAS >0).

Table 2. Organ involvement among the patients with EGPA receiving stable treatment with mepolizumab 100 mg or 300 mg every 4 weeks*

	Mepolizumab initiation (baseline) (n = 158/33)	3 months (n = 158/33)	*P*, 3 months vs. baseline	6 months (n = 151/32)	*P*, 6 months vs. baseline	12 months (n = 122/29)	*P*, 12 months vs. baseline	24 months (n = 39/12)	*P*, 24 months vs. baseline
Constitutional symptoms									
100 mg/4 weeks	50 (31.7)	25 (15.8)	<0.001	23 (15.2)	<0.001	15 (12.3)	<0.001	6 (15.4)	0.035
300 mg/4 weeks	3 (9.1)	0	NA	2 (6.3)	0.564	2 (6.9)	1.564	0	NA
Purpura									
100 mg/4 weeks	11 (7.0)	6 (3.8)	0.025	4 (2.7)	0.014	3 (2.5)	0.008	0	NA
300 mg/4 weeks	2 (6.1)	1 (3.0)	0.317	1 (3.1)	0.317	2 (6.9)	1.000	0	NA
ENT									
100 mg/4 weeks	121 (76.6)	64 (40.5)	<0.001	55 (36.4)	<0.001	34 (27.9)	<0.001	8 (20.5)	<0.001
300 mg/4 weeks	17 (51.5)	12 (36.4)	0.025	7 (21.9)	0.003	8 (27.6)	0.034	0	NA
Pulmonary									
100 mg/4 weeks	141 (89.2)	61 (38.6)	<0.001	46 (30.5)	<0.001	37 (30.3)	<0.001	7 (18.0)	<0.001
300 mg/4 weeks	29 (87.9)	10 (30.3)	<0.001	5 (15.6)	<0.001	9 (31.0)	<0.001	1 (8.3)	0.005
Cardiac									
100 mg/4 weeks	8 (5.1)	4 (2.5)	0.046	4 (2.7)	0.046	3 (2.5)	0.046	1 (2.6)	0.317
300 mg/4 weeks	1 (3.0)	0	NA	0	NA	0	NA	0	NA
Gastrointestinal									
100 mg/4 weeks	8 (5.1)	0	0.005	5 (3.3)	0.257	4 (3.3)	0.257	0	0.083
300 mg/4 weeks	1 (3.0)	1 (3.0)	NA	0	NA	0	NA	0	NA
Renal									
100 mg/4 weeks	5 (3.2)	1 (0.6)	0.046	0	NA	1 (0.8)	0.180	0	0.317
300 mg/4 weeks	0	2 (6.1)	0.157	0	NA	1 (3.5)	0.317	0	NA
Peripheral neurologic									
100 mg/4 weeks	36 (22.8)	23 (14.6)	0.005	21 (13.9)	0.001	15 (12.3)	0.001	2 (5.1)	0.005
300 mg/4 weeks	6 (18.2)	6 (18.2)	NA	3 (9.4)	0.157	2 (6.9)	0.157	0	NA

* Except where indicated otherwise, values are the number (%); n values are the number of patients receiving mepolizumab 100 mg every 4 weeks/number of patients receiving mepolizumab 300 mg every 4 weeks. EGPA = eosinophilic granulomatosis with polyangiitis; NA = not applicable; ENT = ears, nose, and throat.



N asthma exacerbations	T6	T12	T24
Overall	14	52	82
100mg	12	37	57
300mg	1	11	17

N ENT exacerbations	T3	T6	T12	T24
Overall	3	14	28	31
100mg	3	13	22	25
300mg	0	0	4	4

Figure 2. **A** and **B,** Variation in disease activity using the Birmingham Vasculitis Activity Score (BVAS) (**A**) and daily dose of prednisone equivalents (**B**) among patients with eosinophilic granulomatosis with polyangiitis receiving mepolizumab 100 mg every 4 weeks and those receiving mepolizumab 300 mg every 4 weeks. **C** and **D,** Respiratory outcomes in patients during mepolizumab treatment. Kaplan–Meier curves show the occurrence of asthma exacerbations (**C**) and ear, nose, and throat (ENT) exacerbations (**D**). **E** and **F**, Variation in the forced expiratory volume in 1 second (FEV_1) (**E**) and eosinophil count (**F**). Values in **A**, **B**, **E**, and **F** are the median and interquartile range.* = $P < 0.05$; ** = $P < 0.01$, versus baseline.

(33.3% versus 30.8%), but these differences were not statistically significant ($P = 0.168$). Notably, the small number of patients at the different follow-up time points, particularly those receiving mepolizumab 300 mg every 4 weeks, did not allow sufficient power to detect significant differences in the proportion of complete responses between the 2 doses at the different time points (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943).

Of 71 patients in whom complete response to treatment had been achieved, 22 (31.0%) experienced a relapse after a median time of 6 months (IQR 6–9). At all time points, relapse rates were comparable between both treatment groups ($P = 1.000$ at 6 months and 12 months; $P = 0.642$ at 24 months), the overall relapse rates being 32.1% (17 of 53) and 25.0% (4 of 16) for mepolizumab 100 versus 300 mg every 4 weeks, respectively. The median time to relapse was 6 months (IQR 3–9) and 10 months (IQR 9–12) in the mepolizumab 100 mg every 4 weeks group compared to the 300 mg every 4 weeks group, respectively ($P = 0.081$). Response rates were higher among ANCA-negative patients, especially at 24 months, but the differences were not statistically significant (Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943).

The efficacy outcomes in the 10 patients who switched from mepolizumab 100 mg every 4 weeks to 300 mg every 4 weeks are summarized in Supplementary Figure 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Follow-up data suggested

Table 3. AEs in the patients with EGPA during mepolizumab treatment*

	0–3 months	4–6 months	7–12 months	13–24 months
At least 1 AE experienced, no. of patients/total no. of patients (%)	21/203 (10.3)	20/195 (10.3)	16/161 (9.9)	9/56 (16.1)
Receiving stable treatment with mepolizumab 100 mg/4 weeks	10/158 (6.3)	13/151 (8.6)	6/122 (4.9)	3/39 (7.7)
Receiving stable treatment with mepolizumab 300 mg/4 weeks	9/33 (27.3)	5/32 (15.6)	10/29 (34.5)	6/12 (50.5)
P	<0.001	0.322	<0.001	0.003
No. of patients with AEs requiring hospitalization	0	2	2	2
Receiving stable treatment with mepolizumab 100 mg/4 weeks	0	1	2	1
Receiving stable treatment with mepolizumab 300 mg/4 weeks	0	1	0	1
AEs requiring treatment discontinuation	2	3	1	0
Receiving stable treatment with mepolizumab 100 mg/4 weeks	2	3	1	0
Receiving stable treatment with mepolizumab 300 mg/4 weeks	0	0	0	0
Type of AE and no. of cases				
Infections and infestations				
Lower respiratory tract infections	4	3†	7†	2
Upper respiratory tract infections	2	–	–	1
Other infections	–	2†	1	1
Musculoskeletal and connective tissue disorders				
Myalgia/arthralgia	3	1	1	–
Osteoporosis/fractures	1	1	1	1
Epicondylitis	–	1	–	–
Nervous system disorders				
Dizziness	1	–	1	–
Headache	2	1	–	–
Transient color vision disorder	–	1	–	–
Skin and subcutaneous tissue disorders				
Eczema/urticaria	2	1	–	–
Papillary edema	–	–	1	–
General disorders and administration site conditions				
Malaise	2	–	–	–
Swelling at injection site	1	–	–	–
Endocrine disorders				
Secondary adrenal insufficiency	–	–	–	1†
Blood and lymphatic system disorders				
Sialoadenitis	–	1	–	–
Cardiac disorders				
Myocarditis	–	–	–	1†
Hepatobiliary disorders				
Acute hepatitis	–	–	1	–
Renal and urinary disorders				
Renal colic	–	1	–	–
Respiratory, thoracic, and mediastinal disorders				
Lung consolidation	–	–	1	–
Vascular disorders				
TIA	–	–	1†	–

* AEs = adverse events; EGPA = eosinophilic granulomatosis with polyangiitis; TIA = transient ischemic attack.
† Hospitalization required in 1 patient.

no clear benefit in terms of EGPA control following the increase in monthly mepolizumab dose.

The impact of mepolizumab on the different disease manifestations is summarized in Table 2 and in Supplementary Table 4 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943). A significant reduction in all active manifestations was already observed at 3 months in patients receiving stable mepolizumab 100 mg every 4 weeks. Control of constitutional, pulmonary, ENT, and peripheral neurologic manifestations was maintained during follow-up. With mepolizumab 300 mg every 4 weeks, a significant reduction in the proportion of patients with pulmonary and ENT manifestations was observed at all time points, whereas no clear effect was observed on nonrespiratory manifestations.

Systemic disease activity also decreased during follow-up for both treatment groups, with the median BVAS score of the entire

cohort decreasing from 4 (IQR 2–8) at baseline to 2 (IQR 0–4) at 3 months ($P < 0.001$). The median BVAS score decreased further to 0 at the subsequent time points ($P < 0.001$ for both treatment groups at 6 months, 12 months, and 24 months) (Figure 2A). Similarly, both mepolizumab doses were associated with a significant reduction in the daily glucocorticoid dose (Figure 2B), with a significant proportion of patients able to discontinue glucocorticoid use (29.2% and 41.7% at 24 months in the 100 mg mepolizumab group and the 300 mg mepolizumab group, respectively) (Supplementary Table 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Concomitantly, a DMARD-sparing effect was observed in both treatment groups, though statistical significance was only achieved for mepolizumab 100 mg every 4 weeks (Supplementary Table 5).

Effectiveness of mepolizumab on respiratory outcomes. Respiratory outcomes are reported in Figures 2C–F and in Supplementary Table 6 (http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Overall, 82 patients (40.4%) experienced asthma exacerbations after a median time of 12 months (IQR 12–24). Asthma exacerbations occurred in 36.1% of patients receiving stable mepolizumab 100 mg every 4 weeks and in 51.5% receiving mepolizumab 300 mg every 4 weeks ($P = 0.139$) (Figure 2C). ENT relapses occurred after a median time of 12 months (IQR 6–12) in 25 patients receiving mepolizumab 100 mg every 4 weeks (15.8%), 4 receiving 300 mg every 4 weeks (12.2%), and 2 who switched mepolizumab dose (unadjusted HR 0.67 [95% CI 0.23–1.91] for mepolizumab 300 mg every 4 weeks versus 100 mg every 4 weeks, $P = 0.450$) (Figure 2D).

With regard to lung function, a significant improvement in FEV_1 was already observed 3 months after the initiation of mepolizumab 100 mg every 4 weeks (Figure 2E). FEV_1 also improved in patients receiving mepolizumab 300 mg every 4 weeks, though statistical significance was not reached.

Additional outcomes. Both mepolizumab regimens were already associated with a dramatic reduction in eosinophil count at 3 months. This was maintained during the entire follow-up period (Figure 2F). Although ANCA testing was available for only a small subgroup of patients during follow-up, a significant reduction in the proportion of ANCA-positive patients was observed among those receiving stable mepolizumab 100 mg every 4 weeks and those receiving 300 mg every 4 weeks (Supplementary Figure 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943).

Treatment persistence and safety. Twenty-three patients discontinued mepolizumab. Sixteen of these patients were receiving mepolizumab 100 mg every 4 weeks; reasons for discontinuation were AEs in 6 cases (malaise in 2 patients, arthralgia in 1, reactivation of herpes zoster in 1, and not reported in 2) and inefficacy in 3 cases. In the remaining 7 patients, the reason for treatment discontinuation was unknown. Seven patients discontinued mepolizumab 300 mg every 4 weeks due to inefficacy (4 patients) and unknown reasons (3 patients).

Forty-four patients (21.7%) experienced AEs, mostly related to lower respiratory tract infections or to myalgias or arthralgias. At all time points, AEs were more frequent among patients receiving mepolizumab 300 mg every 4 weeks (Table 3). Overall, 6 AEs required hospitalization, of which 4 occurred in patients receiving mepolizumab 100 mg every 4 weeks (lower respiratory tract infection, secondary adrenal insufficiency, transient ischemic attack, and infection of the central venous catheter). The other 2 AEs occurred in patients receiving mepolizumab 300 mg every 4 weeks (lower respiratory tract infection and myocarditis).

DISCUSSION

In this study, conducted on the largest series of mepolizumab-treated patients with EGPA reported so far to our knowledge, we observed that mepolizumab at either 100 mg every 4 weeks or 300 mg every 4 weeks is effective and safe in controlling systemic and respiratory disease manifestations. The use of mepolizumab in EGPA has solid evidence. Indeed, the randomized controlled MIRRA trial proved the superiority of mepolizumab 300 mg every 4 weeks compared to placebo for relapsing and/or refractory EGPA (11,12), leading to the FDA approval of mepolizumab 300 mg every 4 weeks.

Despite this, our data show that, in real practice, most patients with EGPA received mepolizumab 100 mg every 4 weeks, the dose approved for severe eosinophilic asthma, rather than 300 mg every 4 weeks. This prescription was probably based on the rationale that mepolizumab 100 mg every 4 weeks effectively controls severe eosinophilic asthma, which is an invariable feature of EGPA, and was also driven by regulatory reasons, since mepolizumab 300 mg every 4 weeks is not currently approved in Europe.

In the MIRRA trial, the dose choice was based on the phase IIb/III dose range–finding study of mepolizumab in severe eosinophilic asthma (7), and in a trial of HES (20,21). This choice was also supported by the concept that EGPA, similarly to HES, is a more aggressive condition compared to eosinophilic asthma (14). After the FDA approval of mepolizumab 300 mg every 4 weeks for EGPA, a growing body of literature from real clinical practice suggested that mepolizumab 100 mg every 4 weeks might also be used for EGPA (13–15,22). Notably, in all patients included in these studies, disease was in remission (13,15) or disease activity was low (14) at treatment initiation, with mepolizumab being initiated mainly for the control of asthma.

Our results indicate that mepolizumab at both 100 mg every 4 weeks and 300 mg every 4 weeks was associated with effective control of respiratory EGPA manifestations and an improvement in systemic disease activity. Both also allowed glucocorticoid-sparing.

Also, the proportion of ANCA-positive patients significantly decreased unexpectedly; nevertheless, given the small number of patients with ANCA (re)testing, this finding should be interpreted with caution. Though the exact mechanisms of ANCA positivity-to-negativity switch are unknown, this may be accounted for by anti–IL-5–mediated eosinophil depletion. Eosinophils have been shown to promote B cell survival, T-independent and T-dependent B cell activation and proliferation, and immunoglobulin secretion (23). B cells and their progeny produce and release ANCAs; thus, eosinophil depletion following mepolizumab treatment may account for the reduction in antigen presentation and plasma cell survival, with a consequent reduction in ANCA titers.

The proportion of complete responses steadily increased throughout follow-up, reaching 31.2% and 37.9% at 12 months and 33.3% and 58.3% at 24 months for mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, with only a small proportion of patients experiencing disease relapse. However, response rates at 24 months must be interpreted with caution, as only 39 patients receiving mepolizumab 100 mg every 4 weeks and 12 patients receiving 300 mg every 4 weeks had available follow-up data. Notably, complete response rates observed with both doses were similar to that reported in the MIRRA trial for mepolizumab 300 mg every 4 weeks, where complete response to treatment was achieved in 32% of patients at both weeks 36 and 48 (11). The response rates in our study were lower than those in the observational study by Canzian et al (14) in a small EGPA cohort (76% and 82% complete responses at 12 months for mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, as defined by BVAS = 0 and a prednisone dose ≤5 mg/day) (14).

In our study, complete response rates appeared to be higher among ANCA-negative patients, though the subgroups were too small to draw conclusions. We speculate that these findings reflect the different nature of ANCA-positive EGPA and ANCA-negative EGPA, the latter being traditionally associated with a more prominent eosinophilic phenotype (24–26).

Control of systemic disease activity was paralleled by the improvement in asthma and lung function with both mepolizumab regimens. Interestingly, the lower mepolizumab dose was not associated with an increased risk of asthma re-exacerbation during follow-up. Additionally, both mepolizumab doses were associated with good control of ENT manifestations, according to recent data (27). Moreover, we also observed a remarkable reduction in peripheral neuropathy during treatment with mepolizumab. In EGPA, neuropathy seems to have not only a vasculitic etiology but also a neurotoxic etiology, mainly due to eosinophil products (28,29). Thus, eosinophil depletion via mepolizumab could effectively counteract this pathogenetic mechanism. To date, the possible role of mepolizumab in the control of EGPA neurologic manifestations was reported only in a retrospective study of 6 patients (30). Our results, however, must be taken with caution, as other factors may contribute to the improvement of neuropathy, including progressive nerve function recovery or delayed effects of previous and concomitant therapies.

In our study, mepolizumab was generally well-tolerated. Approximately one-fifth of patients experienced AEs, and the 100 mg every 4 weeks dose appeared to be associated with a lower rate of AEs. Most AEs were related to infections or to myalgias/arthralgias, as observed in the MIRRA trial (11). Only a few AEs required treatment discontinuation or hospitalization. However, as is the case in all retrospective studies, underreporting of AEs cannot be excluded.

Our study has other limitations, mostly related to its retrospective nature. First, as data were retrospectively captured from medical records, some data were missing, and the assessment of clinical parameters was not systematic. Second, heterogeneity in clinical management among centers cannot be excluded. Third, consistent with the MIRRA trial, the BVAS calculation was used to retrospectively assess disease activity and treatment outcomes, as no standard assessment tool is validated specifically for EGPA. Nevertheless, it cannot be excluded that items related to chronic or persistent damage were erroneously counted in the BVAS score. Fourth, the disparity in sample size between the 100 mg every 4 weeks group and 300 mg every 4 weeks group did not allow us to draw definite conclusions. Finally, given the small sample size, the effect of mepolizumab dose escalation in patients with inappropriate response to 100 mg every 4 weeks could not be ascertained. Despite these limitations, this study also had several strengths, including a long follow-up period, large sample size representative of the European clinical setting, and availability of detailed longitudinal clinical data.

In conclusion, this large European real-world study shows that mepolizumab is associated with effective control of respiratory EGPA manifestations, with a good safety profile. Our results further suggest a role of mepolizumab in the treatment of systemic manifestations, though the retrospective assessment of systemic disease activity requires cautious interpretation of these findings.

Our data also suggest that mepolizumab 100 mg every 4 weeks could be an acceptable dose for patients with EGPA and a valid alternative to the dose approved for this therapeutic indication (300 mg every 4 weeks). Nevertheless, caution is needed, as some reports suggest a risk of systemic disease flare in patients receiving anti–IL-5 treatments at the dose for asthma control (31,32). Randomized clinical trials are advocated to compare the efficacy and safety of these 2 EGPA treatment regimens and assess whether dose escalation from 100 mg to 300 mg every 4 weeks can be effective in case of unsatisfactory clinical responses, as well as to compare the efficacy of mepolizumab as an alternative to or sequential treatment with other biologic therapies for EGPA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bettiol had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX A: EUROPEAN EGPA STUDY GROUP

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