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Mepolizumab *versus* benralizumab for eosinophilic granulomatosis with polyangiitis (EGPA): A European real-life retrospective comparative study

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ABSTRACT

Background: Following the results of the MANDARA trial, this real-life study aimed at comparing the effectiveness and safety profile of mepolizumab *versus* benralizumab in a European EGPA cohort.
Methods: We conducted a retrospective observational comparative study including EGPA patients, who received mepolizumab or benralizumab at the asthma dose. Patients were matched 1:1 by sex, age, BVAS and oral corticosteroid (OCS) dosage at the treatment initiation (T0). Complete response (CR) and partial response (PR), disease activity, OCS, pulmonary parameters, eosinophil count, relapses, and safety outcomes were also compared at 3, 6 and 12 months.
Results: Patients treated with mepolizumab or benralizumab (n = 88 each) were matched: 57 % were females, median age was 54 years (IQR 45–60), median OCS dose 10 (7.5–12.5) and 10 (7–13) mg/day, median BVAS 4 (2–7) and 3 (2–8), respectively. 45.4 % of patients in the mepolizumab group and 51.1 % in the benralizumab group achieved CR or PR at T3, with CR steadily increasing during follow-up for both treatments. At T12, a higher CR rate was found in the benralizumab group (48.1 % vs 32.4 %, $p = 0.005$). No differences in BVAS, OCS, and respiratory parameters were observed between groups at the different timepoints. Throughout the follow-up, both treatments reduced eosinophil count, although a deeper reduction was found in the benralizumab group at all timepoints ($p < 0.0001$). Safety profile was comparable between patient groups.
Conclusion: Mepolizumab and benralizumab showed comparable overall effectiveness and safety in EGPA. However, benralizumab achieved a higher CR rate at T12, and a deeper peripheral eosinophil reduction.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is an Anti-Neutrophil Cytoplasmatic Antibody (ANCA)-associated vasculitides, alongside granulomatosis with polyangiitis and microscopic polyangiitis [1,2]. EGPA mainly affects small vessels and is mostly characterised by asthma, ear-nose-throat (ENT) involvement and blood hyper-eosinophilia, and eosinophils play a major role in its pathophysiology. Consistently, monoclonal antibodies targeting interleukin 5 (IL-5), a cytokine involved in eosinophil maturation, differentiation, and survival [3], have changed the management of patients with EGPA [4,5]. Among anti-IL5 therapies, mepolizumab is currently licensed for EGPA, at the

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dosage of 300 mg subcutaneously/4 weeks, following the positive results of the MIRRA trial [6]. Real-world studies have also been published, confirming the effectiveness and safety of mepolizumab both for respiratory and systemic manifestations of EGPA, also at a lower dosage (100mg/4 weeks, as approved for severe eosinophilic asthma) [7–9].

Based on these results, other agents targeting the IL-5 axis have been investigated for the treatment of EGPA. Among them, benralizumab is a humanised antibody against the IL-5 receptor α (IL-5Rα), inducing eosinophil depletion not only by competing with IL-5 for its receptor, but also by inducing antibody-dependent cellular cytotoxicity [10]. Benralizumab is currently approved for severe eosinophilic asthma at the dosage of 30 mg subcutaneously/4 weeks for 3 administrations, then every 8 weeks, and proved effective and safe in a prospective pilot study of 10 patients with EGPA treated with a higher benralizumab dosage (30mg/4 weeks) [11]. Concomitantly, real-world multicentre studies have also indicated the effectiveness and safety of benralizumab for the control of overall disease activity and respiratory manifestations in large independent cohorts of EGPA patients [12–15].

The randomised, double-blind phase 3 MANDARA trial, formally comparing the efficacy and safety of benralizumab versus mepolizumab in patients with relapsing or refractory EGPA [16], suggested non-inferior rates of remission with benralizumab as compared to mepolizumab in patients receiving oral corticosteroids (OCS) with or without stable immunosuppressive therapy [17]. However, data matching the two drugs in a real-world setting are lacking. Based on these considerations, this study was undertaken to compare the effectiveness and safety profile of mepolizumab *versus* benralizumab at the asthma dose in a large European retrospective cohort of patients with EGPA.

2. Patients and methods

2.1. Study design and setting

A retrospective observational comparative study was conducted on a cohort of patients with EGPA treated with mepolizumab or benralizumab, followed at 41 reference centers belonging to the European EGPA Study Group (EESG) in 9 countries (Italy, France, UK, Spain, Switzerland, Germany, Sweden, Netherlands, Russia). The study received ethical approval (University of Florence Ethics Committee, IRB approval n. 22336_oss, November 29, 2022).

2.2. Study population and treatment

The cohort included adult patients diagnosed with EGPA who met the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for EGPA [18] or the criteria proposed in the MIRRA trial [6], who gave written informed consent and were included in two previous studies published by the EESG [7](13). Only patients who received mepolizumab 100 mg every 4 weeks or benralizumab 30mg/4 weeks for the first three injections and then every 8 weeks (i.e., the dosages approved for severe eosinophilic asthma) were included. Patients previously treated with mepolizumab before benralizumab and patients with a follow-up shorter than three months after mepolizumab or benralizumab initiation were excluded (Fig. 1) (Supplementary Table 1)

2.3. Data collection and outcome analysis

Demographic, clinical and laboratory data were retrospectively collected from medical records at the time of treatment beginning (T0) and after 3, 6 and 12 months (T3-T12).

To ensure homogeneity between the two treatment groups, EGPA patients in the benralizumab group were matched 1:1 with those in the mepolizumab one, by sex, age (±5 years), disease activity assessed by the Birmingham Vasculitis Activity Score (BVAS) (±2) and OCS dosage (±2.5 mg/day) at the time of treatment initiation. The comparison between the two groups was performed in terms of control of systemic disease activity, OCS tapering, respiratory function, relapse and discontinuation rate, and safety profile.

Systemic disease activity was assessed using the BVAS version 3. Complete response (CR) was defined, according to the MIRRA trial [6,7], as no disease activity (BVAS = 0) and OCS dose or prednisone equivalent ≤4.0 mg/day. Partial response (PR) was defined as the absence of disease activity (BVAS = 0) and a dose of OCS or prednisone equivalent >4.0 mg/day, while no response was defined as active disease (i.e., BVAS >0), as previously reported [7](13).

OCS tapering was evaluated considering the ongoing OCS dosage in mg/day at each timepoint, and OCS discontinuation was defined as the absolute number and percentage of patients who managed to completely stop OCS therapy at a defined follow-up timepoint in each group of treatment.

Pulmonary function was assessed by the pre-bronchodilator forced expiratory volume in 1 s (FEV1), reported as percentage of the predicted

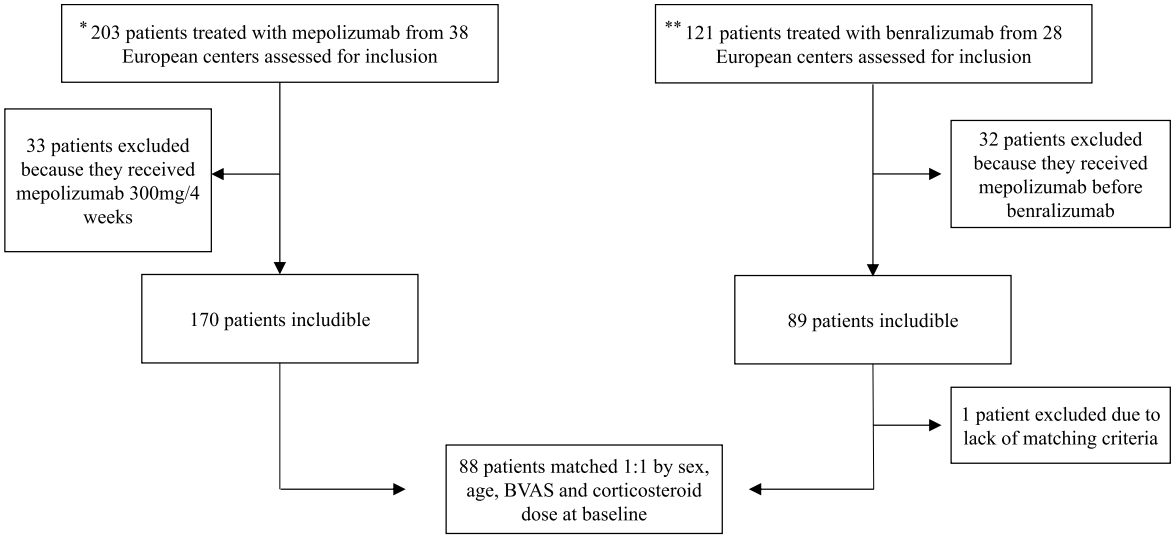

Fig. 1. Study flow chart.

value. The effect of mepolizumab and benralizumab was reported in terms of FEV1 values at a given follow-up timepoint and as ΔFEV1, calculated as the percentage difference between the FEV1 at a given follow-up timepoint and the FEV1 at T0.

The variation in absolute eosinophil count at the different timepoints was also assessed. Normal eosinophil count was defined, according to previous clinical trial on eosinophilic asthma and the summaries of Product Characteristics (SPCs), as $<150/mm^3$ [19–23].

Relapses were assessed only in patients in whom CR to treatment had been obtained and was defined, as in the MIRRA trial, by at least one of the following criteria: 1) active disease (defined as BVAS >0); and/or 2) worsening asthma and/or ENT manifestations leading to an increase in OCS dose to >4.0 mg/day; 3) initiation of a new immunosuppressive therapy; or 4) hospitalization [6,7].

Also, treatment persistence was assessed by considering the proportion of patients who fully discontinued the drugs for any reason; when available, data on the reason for discontinuation were also collected.

All adverse events (AEs) that occurred during therapy were recorded. In compliance with the European Medicines Agency (EMA) statement, AEs resulting in death, life-threatening, necessitating hospitalization or the prolongation of existing hospitalization, or resulting in persistent or significant disability or incapacity were considered serious (SAEs).

2.4. Statistical analysis

Data are presented as median and interquartile range (IQR) for continuous variables, and as absolute number and percentage for qualitative variables. Baseline characteristics (beside matching variables) were compared between the two groups (i.e., mepolizumab versus benralizumab) using the Mann–Whitney *U* test for unpaired data or the Chi-squared test for continuous and categorical variables, respectively. Continuous endpoints were compared between the two groups at T3, T6, T12 using the Mann–Whitney *U* test for unpaired data. Non-parametric tests were used as the distribution of the data was not normal.

Proportions of patients achieving CR at the different timepoints or discontinuing treatment were reported together with their 95 % Confidence Intervals (CI) and were compared between the two treatments using the Chi-squared test. All analyses were conducted only on subjects with available data at the given time point. Statistical analyses were performed using the software GraphPad Prism 9, version 14. According to the Bonferroni correction for multiple comparisons (three follow-up timepoints), p-values <0.017 were considered statistically significant.

3. Results

3.1. Patients' characteristics

Eighty-eight patients with EGPA treated with mepolizumab and 88 treated with benralizumab were matched according to the predefined set of baseline variables (sex, age, BVAS and OCS dosage) collected at the time of treatment beginning (T0). Fifty patients in each group (57.0 %) were female, with a median age at T0 of 54 years (IQR 45–60 in the mepolizumab and IQR 44–60 in the benralizumab groups). The median BVAS was 4 (IQR 2–8) in the mepolizumab and 3 (IQR 2–8) in the benralizumab groups and the median OCS dose was 10 (IQR 7.5–12.5) and 10 [IQR 7–13] mg/day, respectively (matching variables). Considering lung function, the median FEV1 was 75 % (62–83 %) in the mepolizumab and 81 % (65–91 %) in the benralizumab groups (p = 0.106). The median age at diagnosis was 48 years (IQR 39–55) in the mepolizumab and 45 years (IQR 36–53) in the benralizumab groups, and the median disease duration of 5 years (IQR 2–11) for mepolizumab and 5 (IQR 2–12) for benralizumab were also comparable between the two groups (p = 0.235 and p = 0.222, respectively) (Table 1).

At T0, 14/86 patients (16 %) in the mepolizumab and 17/78 patients (22 %) in the benralizumab groups were positive for ANCA (p = 0.186), and all had perinuclear (p-ANCA) and/or anti-myeloperoxidase (MPO) specificity. The median eosinophil count was 700/mm3 (IQR 280–1037.5) in the mepolizumab and 540/mm3 (207.5–1080) in the benralizumab groups (p = 0.498) (Table 1).

In terms of clinical features at T0, 80 patients (91 %) in the mepolizumab and 84 (95.5 %) in the benralizumab groups had asthma and 66 (75 %) and 65 (73.9 %) patients had ENT involvement, respectively. Other disease manifestations included constitutional symptoms (28.4 % vs 40.9 %), neurological (22.7 % vs 18.2 %), cutaneous (7.9 % vs 11.4 %), cardiac (3.4 % vs 10.3 %), gastrointestinal (4.5 % vs 5.7 %) and renal (2.3 % vs 6.9 %) involvement (Table 1).

At T0, 83/88 (94.3 %) and 84/88 (95.5 %) patients in the mepolizumab and benralizumab groups were receiving OCS at a median dosage of 10 mg/day (IQR 7.5–12.5) and 10 mg/day (IQR 7–13), respectively (matching variable) (Table 1).

Overall, the Five Factor Score (FFS) at diagnosis, and the disease manifestations and systemic treatments recorded between EGPA diagnosis and anti-IL-5/IL-5Ra treatment beginning, are reported in the Supplementary Table 2.

Table 1
Baseline characteristics at the time of treatment initiation.

	Patients treated with mepolizumab (n = 88)	Patients treated with benralizumab (n = 88)	p-value
General features			
Female sex	50 (57.0 %)	50 (57.0 %)	Matching variable
Age at therapy beginning, years (IQR)	54 (45–60)	54 (44–60)	Matching variable
BVAS, median (IQR)	4 (2–7)	3 (2–8)	Matching variable
Daily OCS dose, median (IQR)	10 (7.5–12.5)	10 (7–13)	Matching variable
FEV 1, median (IQR)	75 (62–83)	81 (65–91)	0.106
Age at diagnosis, (IQR) years	48 (39–55)	45 (36.53)	0.235
Disease duration, median (IQR) years	5 (2–11)	5 (2–12)	0.222
ANCA positivity	14/86 (16 %)	17/78 (22 %)	0.186
Eosinophil count (IQR)	700 (280–1037.5)	540 (207.5–1080)	0.498
Organ involvement or clinical manifestations, n (%)			
Asthma	80 (91.0)	84 (95.5)	
ENT	66 (75)	65 (73.9)	
Constitutional	25 (28.4)	36 (40.9)	
Neurological symptoms	20 (22.7)	16 (18.2)	
Cutaneous	7 (7.9)	10 (11.4)	
Cardiac	3 (3.4)	9 (10.3)	
Gastrointestinal	4 (4.5)	5 (5.7)	
Renal	2 (2.3)	6 (6.9)	
Systemic treatment			
Oral glucocorticoids, n (%)	83 (94.3)	84 (95.5)	
DMARDs, n (%)			
Azathioprine	8 (9.1)	14 (15.9)	
Methotrexate	20 (22.7)	11 (12.5)	
Mycophenolate	10 (11.4)	3 (3.4)	
Cyclosporine	1 (1.1)	1 (1.1)	
Rituximab	9 (10.2)	3 (3.4)	
IvIg	4 (4.6)	1 (1.1)	
Other immunosuppressants	2 (2.3)	6 (6.8)	

Abbreviations used in the table. ANCA: anti-neutrophil cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; DMARDs: disease-modifying antirheumatic drugs; ENT: ear-nose-throat; FEV1: forced expiratory volume in the first second; IQR: interquartile range; IvIg: intravenous immunoglobulins.
[a] Continuous variables are reported as median value and interquartile range (in brackets); all the other rows refer to nominal data reported as absolute frequencies and percentages (in brackets).

3.2. Treatment efficacy

The proportion of patients achieving CR remarkably increased during follow-up for both treatments. At T3, CR was reported in 12 out of 88 patients (13.6 %, 95 % CI 7.2–22.6 %) in the mepolizumab and nine out of 88 patients (10.2 %, CI 4.8–18.5 %) in the benralizumab groups ($p = 0.485$). At T6, the CR rates increased to 18/83 patients (21.7 %, CI 13.4–32.1 %) in the mepolizumab and 21/66 (31.8 %, CI 20.1–44.4 %) in the benralizumab groups ($p = 0.128$), further increasing to 22/68 (32.4 %, CI 21.5–44.8 %) and 25/52 (48.1 %, CI 34.0–62.4 %) at month 12, with a significantly higher CR for benralizumab as compared to mepolizumab ($p = 0.005$).

PR was observed at T3 in 28/88 patients (31.8 %, CI 22.2–42.6 %) treated with mepolizumab and in 36/88 (40.9 %, CI 30.5–51.9 %) treated with benralizumab, and at T6 in 24/83 patients (28.9 %, CI 19.5–39.9 %) and in 19/66 patients (41.3 %, CI 18.3–41.3 %) in the two groups, respectively. At T12, PR was reported in 14/68 patients (20.6 %, CI 11.7–32.1 %) on mepolizumab and in 12/52 patients (23.1 %, CI 12.5–36.8 %) on benralizumab (Fig. 2A).

A reduction in BVAS was observed in both groups and no differences emerged when comparing the median BVAS at the different timepoints in the two groups: namely, the BVAS dropped from 4 (IQR 2–8) at T0 to 1 (IQR 0–4) at T3, 0 (IQR 0–3) at T6 and 0 (IQR 0–2.5) at T12 in the mepolizumab group; similarly, it decreased from 3 (IQR 2–8) at T0 to 0 (IQR 0–2.5) at T3, 0 (IQR 0–2) at T6 and 0 (IQR 0–1) at T12 in the benralizumab group (Fig. 2B).

Regarding the OCS-sparing effect, both mepolizumab and benralizumab were associated with a reduction in daily OCS dosage, from 10 mg/day (IQR 5–12.5) at T0 to 5 mg/day (IQR 3–7.5) at T3, 5 mg/day (IQR 1.3–5) at T6, and 4 mg/day (IQR 0–4.5) at T12 in the mepolizumab cohort, and from 10 mg/day (IQR 7–13) at T0 to 5 mg/day (IQR 5–8) at T3, 5 mg/day (IQR 2–5) at T6, and 2.5 mg/day (IQR 0–5) at T12 in the benralizumab cohort. No differences were observed when comparing the daily OCS dosage between the two groups at T3 ($p = 0.467$), T6 ($p = 0.823$) and T12 ($p = 0.115$) (Fig. 2C).

Accordingly, patients treated with mepolizumab who managed to completely withdraw OCS therapy were 12/85 (14.1 %) at T3, 19/86 (22.1 %) at T6, and 18/67 (26.9 %) at T12, whereas patients treated with benralizumab who discontinued OCS were 14/88 (15.9 %) at T3, 18/74 (24.3 %) at T6, and 24/64 (37.5 %) at T12. No differences were found when comparing the two groups at T3 ($p = 0.671$), 6 ($p = 0.738$), and 12 ($p = 0.192$).

Concerning lung-function, both treatments were associated with improvement in FEV1. When analysing the median FEV1 value at the different follow-up timepoints, a higher FEV1 was observed in the benralizumab cohort at T3 [92 % (80–98 %) vs 79 % (71–89 %) for benralizumab and mepolizumab, respectively; $p = 0.002$)] and T12 [95 % (82–99 %) vs 84 % (71–91 %); $p = 0.005$] (Fig. 3A). Conversely, no differences in FEV1 increase towards baseline were observed between the groups [from T0 to T3: +6.6 % (IQR 2–17.5) for mepolizumab vs. +13.7 % (4.4–22.1) for benralizumab ($p = 0.069$); from T0 to T6: +12.0 % (2.1–16.5) vs +14.7 % (7.73–29.3) ($p = 0.669$); from T0 to T12: +10.6 % (4.7–25.9) vs +13.2 % (0.1–43.9) ($p = 0.267$)] (Fig. 3B). Moreover, Supplementary Table 3 shows surrogate asthma-related outcomes at different time points. The eosinophil counts dropped in both cohorts, from a median of 700 cells/mm^3 (IQR 280–1040) at T0 to a median of 90/mm^3 (40–140) at T3, 100/mm^3 (IQR 40–130) at T6 and 75/mm^3 (IQR 0–108) at T12 in the mepolizumab group and from a median of 540 cells/mm^3 (IQR 215–1070) at T0 to a median of 0/mm^3 (IQR 0–8) at T3, which persisted at 0/mm^3 (0-0) at T6 and T12 in the benralizumab group. The median eosinophil count was lower in the benralizumab group at all follow-up timepoints ($p < 0.0001$) (Fig. 3C).

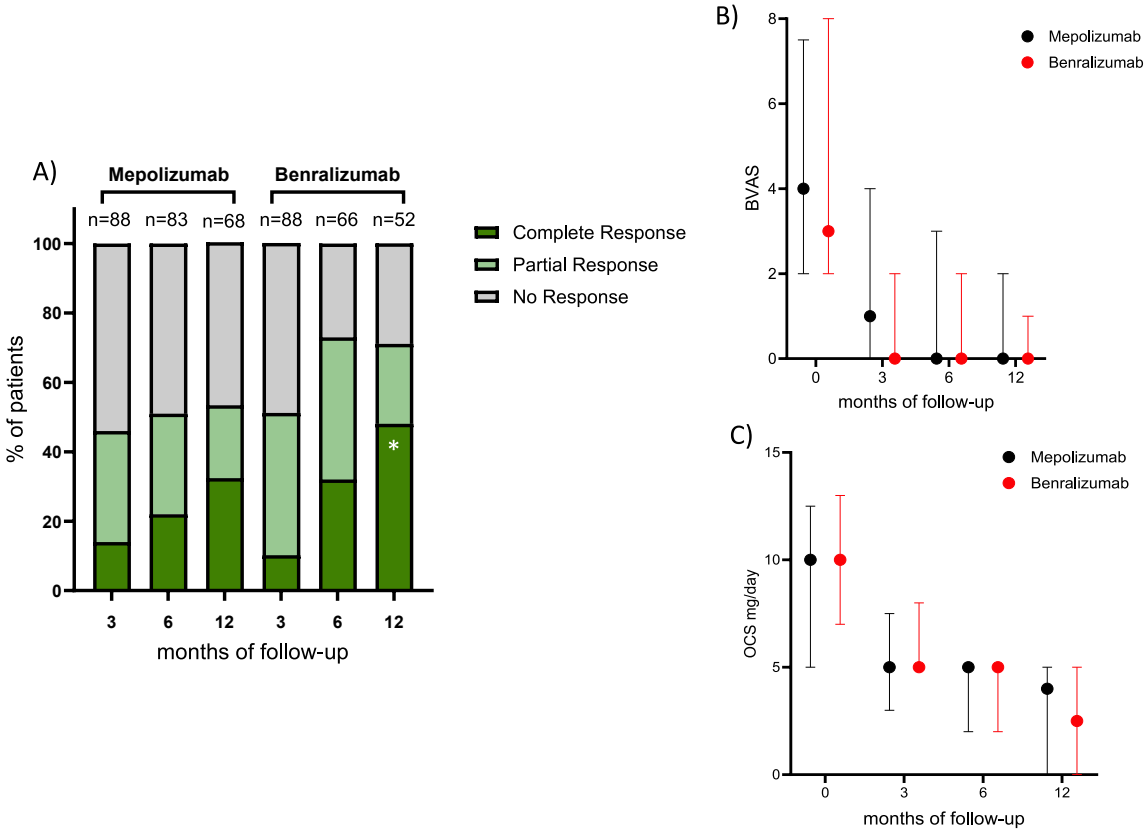

Fig. 2. (A) Clinical response rates following anti IL-5 treatment. Complete Response: BVAS = 0 and daily prednisone dose ≤4 mg. Partial response: BVAS = 0 and daily prednisone dose >4 mg. No response: active disease (i.e., BVAS > 0). (B) Variation in disease activity using the Birmingham Vasculitis Activity Score (BVAS) (C) Daily dose of oral corticosteroids (OCS).

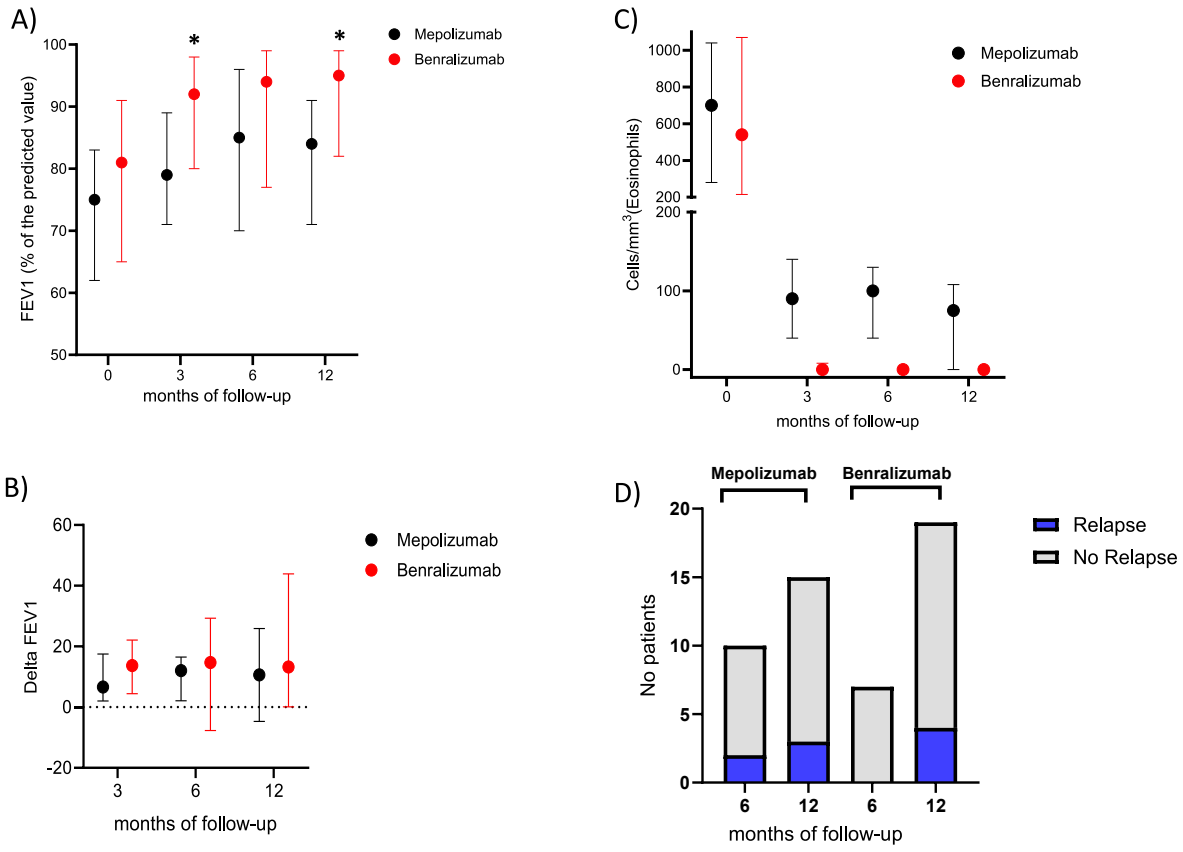

Fig. 3. **A** and **B**, Variation in the forced expiratory volume in 1 s (FEV1) as (A) absolute number and (B) delta FEV1. Eosinophil count (**C**) and number of relapse (**D**). Values in **A**, **B**, **C**, and **D** are the median and interquartile ange.* = $P < 0{,}017$.

Among mepolizumab-treated patients, five relapsed after achieving CR (2 relapses occurred at T6 and 3 at T12), while among those receiving benralizumab, four relapsed after achieving CR, all at T12 (Fig. 3D). In the mepolizumab group all relapses were related to asthma exacerbations, and two out of five patients, were ANCA-positive (p-ANCA/MPO); conversely in the benralizumab group, all relapses occurred in ANCA-negative patients, and were characterised by ENT involvement exacerbation in three patients and by asthma and ENT involvement in one (Supplementary Table 4).

Finally, Supplementary Table 5 shows the prevalence of organ involvement throughout the follow-up, n (%).

3.3. *Treatment persistence and safety*

Nine of 88 patients (10 %) discontinued mepolizumab and 16/88 (18 %) discontinued benralizumab during follow-up (p = 0.130). In the mepolizumab group, six discontinued before T6 due to malaise (n = 2), erythema at the site of injection (n = 1), unknown reasons (n = 2) and one for lack of efficacy, while three discontinued before T12 due to erythema at the site of injection in one case, malaise in the other case, and unknown reason for another case. In the benralizumab group, eight discontinued before T6, five due to treatment inefficacy, one for erythema at the site of injection and two for unknown reasons and 8 between T6-T12, seven due to treatment inefficacy and one for pregnancy (Table 2). Regarding safety, 11 (12.5 %) patients reported AEs during mepolizumab treatment, including five in the first trimester of treatment, four in the second trimester and two in the second semester. Most AEs (n = 10) were non-serious and related to lower respiratory tract infections (n = 4), headache, urticaria, syncope, or arthralgia; one patient had reactivation of Herpes Zoster. Only one patient experienced a SAE requiring hospitalization for respiratory syncytial virus infection.

Table 2
Adverse events and discontinuation rates in the two cohorts of patients with EGPA treated with mepolizumab and benralizumab.

	T3	T6	T12	Overall
N patients experiencing at least one adverse event (AE)				
Mepolizumab	5/86 (5.8 %)	4/82 (4.9 %)	2/66 (3.0 %)	11
Benralizumab	7/82 (8.5 %)	5/76 (6.6 %)	4/64 (6.25 %)	16
AE requiring hospitalization				
Mepolizumab	0	0	1	1
Benralizumab	2	0	0	2
N patients discontinuing therapy				
Mepolizumab	3/84 (3.6 %)	3/76 (3.9 %)	3/68 (4.4 %)	9
Benralizumab	3/87 (3.4 %)	5/83 (6 %)	8/72 (11.1 %)	16

[a]Data not available for all patients at each time point.

Sixteen patients treated with benralizumab (18 %) experienced AEs, including seven in the first trimester, five in the second trimester, and four in the second semester. Most AEs (n = 14) were non-serious and included headache (n = 4), fever (n = 3), myalgia (n = 3), pulmonary infection (n = 1), sinusitis (n = 1), rash (n = 1) and local reaction at the site of injection (n = 1). Conversely, two patients experienced SAEs requiring hospitalization, including one case of asthma relapse and one of bone fracture (Table 2).

4. Discussion

To date, the efficacy and safety profile of benralizumab was compared to mepolizumab in the randomised, double-blind phase 3 MANDARA study in patients with EGPA [17]. Benralizumab was non-inferior to mepolizumab in inducing remission in patients with relapsing or refractory EGPA receiving OCS with or without stable

immunosuppressive therapy, suggesting benralizumab is an alternative treatment for EGPA [16].

Our real-life study compared the effectiveness and safety of mepolizumab and benralizumab at the dose approved for severe eosinophilic asthma over a follow-up of 12 months in a large European cohort, confirming that both treatments are effective in controlling systemic and respiratory manifestations of EGPA while also allowing for OCS sparing with a good safety profile. Notably, in the present study, more than 45 % of patients in the mepolizumab and over 50 % in the benralizumab groups achieved CR and/or PR within T3 of treatment, with CR rates increasing during follow-up; nevertheless, benralizumab achieved a higher rate of CR at T12 ($p = 0.005$). The importance and clinical relevance of this result needs to be interpreted cautiously; indeed, even though the two cohorts were matched for key variables, patients in the mepolizumab group seemed to have a more "severe" profile, being previously treated more aggressively (higher percentage of traditional immunosuppressants and rituximab), starting with a slightly higher eosinophil count, and a trend to lower FEV1.

Moreover, this result might be partly driven by the higher percentage of patients in the benralizumab group who discontinued OCS by T12 (although, non-statistically significant), as OCS dosage is included in the definition of CR. In this regard, although the initial dose of 10 mg/day observed in both groups is lower than the doses typically used for remission induction in severe EGPA(5),our results confirmed the OCS sparing effect of both drugs [11,24–26]. Specifically, our findings indicate that a remarkable percentage of patients treated with both drugs were able to discontinue OCS therapy within T6 (24 % in mepolizumab and 22 % in benralizumab), with more patients discontinuing OCS within T12 on benralizumab (37.5 % vs 26.9 %, p = ns).

The effectiveness of both treatments was also confirmed by a reduction in the BVAS, which dropped to 0 within T3/T6 in both groups. These results confirm previous findings [7,8,27] and are consistent with the data deriving from a recent study assessing the effectiveness and safety of mepolizumab and benralizumab in nine Italian specialized centers [14].

Pulmonary function improved in both cohorts, confirming the efficacy of anti-IL-5/IL-5Ra therapies on respiratory outcomes [6,7,12,13,27]. Interestingly, in this study, improvements in lung function were slightly more pronounced with benralizumab, in contrast to a study by Nolasco et al. [15] However, it is worth considering that, in our cohorts, patients treated with mepolizumab started with a lower median FEV1 (median value of 75 %, IQR 62–83) than those treated with benralizumab (81 %, IQR 65–91), thus showing a greater severity of respiratory manifestations at baseline. Indeed, when assessing the median percentage variation in lung function as compared to the baseline value in the two treatment groups, no significant difference emerged between the two treatments.

Additionally, we found a reduced eosinophil count after three months of treatment with both drugs, in line with the accumulating literature supporting the eosinophil depletion effect of both IL-5 inhibitors [28]. Particularly, a depletion to a median value of 0 was observed in the benralizumab group already after 3 months of therapy. This is well explained by the mechanism of action of benralizumab which, acting as an IL- 5Rα antagonist, is known to prevent signal transduction while triggering antibody-dependent cell-mediated cytotoxicity, resulting in almost complete eosinophil depletion [29,30]. However, both drugs confirmed their ability to normalise eosinophil count, according with previously published studies [14,28].

As previously reported [6,7,12,13,27], our findings confirm that both treatments were well-tolerated. Eleven patients reported AEs during mepolizumab treatment, and 14 during benralizumab therapy; most AEs (n = 10 e n = 12, respectively) were non-serious. Only one patient in the mepolizumab cohort and two in the benralizumab cohort experienced a SAE requiring hospitalization. However, underreporting of AEs cannot be ruled out, and causality assessment was not carried out at the time of the AE occurrence, an inherent limitation of retrospective studies.

Interestingly, in our cohorts, patients treated with mepolizumab showed a higher, although not significant, treatment persistence as compared to those treated with benralizumab, with treatment discontinuation occurring in nine patients in the mepolizumab and 16 in the benralizumab groups. This finding should be interpreted cautiously, since data on patients treated with mepolizumab were collected when it was the only drug available for treating EGPA patients, even if off-label; conversely, patients on benralizumab started this treatment later, and the availability of a different anti-IL5 agent (i.e., mepolizumab) might have facilitated the medical choice of changing treatment in case of suboptimal response or intolerance.

Interestingly, the introduction of these biologic therapies has also raised important questions regarding associated costs. Although there are few studies evaluating the economic impact of these drugs on the healthcare system, total costs per patient have been reported to be lower for benralizumab than for mepolizumab in patients with severe asthma [31,32]. Future pharmacoeconomic analyses are advocated also in the setting of rare diseases such as EGPA.

Finally, patients included in our study had similar baseline characteristics to those in the MANDARA trial, particularly with regard to gender (in our study, mepolizumab vs. benralizumab: 57 % vs. 57 %; in MANDARA: 56 % vs. 64 %), median age (in our study: mepolizumab vs. benralizumab: 54 vs. 54 years; MANDARA: mepolizumab vs. benralizumab: 55 vs. 55 years), disease duration (our study: mepolizumab vs. benralizumab: 5.0 vs. 5.0 years; MANDARA: mepolizumab vs. benralizumab: 5.4 vs. 4.9 years), and the median OCS dosage (our study: mepolizumab vs. benralizumab: 10 mg/day vs. 10 mg/day; MANDARA: mepolizumab vs. benralizumab: 10 mg/day vs. 10 mg/day).

However, the BVAS was higher in our study (mepolizumab 4 vs. benralizumab 3) and the eosinophil count ($700/mm^3$ vs. $540/mm^3$) exceeded that of patients in the MANDARA study (1.9 vs. 2.3 and 225 vs. 240, respectively). Interestingly, despite these differences the patients were treated with the approved dosages for eosinophilic asthma and both therapies proved effective in controlling the disease.

Some limitations of this study must be acknowledged: although patients were matched for key variables, there were differences between groups in terms of previous therapies. Indeed, patients treated with mepolizumab had a more severe history of disease than those treated with benralizumab (26.1 % vs 12.5 % treated with rituximab; 11.4 % vs 6.8 % treated with IvIg and generally a higher percentage of patients in the mepolizumab group had received traditional immunosuppressants). These differences might be attributed to the different time frame of data collection of the two historical cohorts (from May 2015 to February 2020 for the mepolizumab group, and from January 2019 to September 2022 for the benralizumab one). Also, our study compared the two drugs at the dosage approved for the eosinophilic asthma and it is not possible to exclude whether using the approved doses for EGPA could yield different results. Additionally, another limitation is related to the sourcing of data, that mainly derives from rheumatology and immunology centers, where routine use of asthma-specific tests, such as ACT (Asthma Control Test), or ACQ (Asthma Control Questionnaire) scores, and ENT-specific scales, like SNOT (Sino-Nasal Outcome Test), is uncommon, thus limiting the availability of comprehensive information. Finally, data regarding body surface area and body mass index were not collected, so we could not assess whether this aspect influences the efficacy of drug response.

However, our study also presents several strengths. First, our patient cohorts were treated at European centers with expertise in the management of EGPA, which ensures the accuracy of the data. Second, the cohort of patients included were quite large. We employed an accurate matching, which yielded reliable results thanks in part to the cooperation of 41 reference centers that allowed us to obtain data otherwise difficult to reach in single-center studies. Third, coming from centers belonging to the EESG, these data could be generalised at the European level.

In conclusion, these findings show a comparable therapeutic effectiveness on systemic and respiratory manifestations, OCS tapering effect and safety profile of mepolizumab and benralizumab in patients with EGPA. The cumulative response rates steadily increased during the follow-up for both treatments, with more patients on benralizumab achieving CR at 12 months; additionally, a deeper peripheral eosinophil reduction was shown in patients on benralizumab.

CRediT authorship contribution statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2025.103398.

Data availability

Data will be made available on request.

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