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Original article

Response to mepolizumab according to disease manifestations in patients with eosinophilic granulomatosis with polyangiitis

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ABSTRACT

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a relapsing disease with frequent glucocorticoid dependence. Mepolizumab has been demonstrated to reduce flares and spare glucocorticoids (GC). However, EGPA is a heterogeneous condition and the effects of mepolizumab on specific disease manifestations has not been completely delimitated.

Objectives: To analyse the impact of mepolizumab on manifestations derived from small-vessel vasculitis, ENT (ear, nose and throat) symptoms, asthma, eosinophilic tissue infiltration and anti-neutrophil cytoplasmic antibody (ANCA) status in a single-centre cohort of EGPA patients.

Methods: Medical charts of EGPA patients treated with mepolizumab were retrospectively reviewed by the authors to describe demographics, clinical characteristics, steroid dose at the initiation of mepolizumab and during follow-up, flares, disease activity, damage accrual and laboratory results.

Results and conclusions: Among 56 patients with EGPA regularly controlled at our department, 11 patients were treated with mepolizumab because of corticodependence and unsatisfactory disease control. The mean time of treatment was 38 months (range: 3-66 months). Patients with persistent symptoms improved their asthma control, but 3 of them persisted with recurrent ENT symptoms in spite of treatment with mepolizumab. None of the patients developed vasculitic manifestations (cutaneous, neurological, gastrointestinal, renal) during treatment. All patients achieved a Birmingham Vasculitis Activity Score (BVAS) of 0 points at 12 months or earlier. In general, patients reduced the number of flares, which tended to be milder, and all related to asthma or ENT manifestations. The improvement in disease activity allowed notable glucocorticoid tapering.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis classified among anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [1]. EGPA is a rare disease with an estimated annual incidence of 1-4 cases per 1.000.000 inhabitants [2,3]. Distinctive features include asthma, often persistent and/or severe, along with peripheral blood and tissue eosinophilia. Some of its clinical manifestations are considered to be more prominently "eosinophilic--driven", such as asthma, ear, nose and throat (ENT) involvement in form of nasal polyps or sinusitis, pulmonary infiltrates, gastrointestinal infiltration or cardiomyopathy; whereas others are considered more "vasculitic", such as glomerulonephritis, digital or abdominal ischemia or purpura [4]. Although frequently not as severe as other AAV, recent studies still show an excess of mortality, with survival rates of 97% at 5

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Abbreviations and acronyms

EGPA	Eosinophilic granulomatosis with polyangiitis
ENT	Ear, nose and throat
ANCA	Anti-neutrophil cytoplasmic antibody
AAV	ANCA-associated vasculitis
IL-5	Interleukin-5
GC	Glucocorticoid/s
ACR	American College of Rheumatology
CT scan	computed tomography scan
BVAS	Birmingham Vasculitis Activity Score
VDI	Vasculitis Damage Index
FFS	Five Factor Score
SD	Standard Deviation
PDN	Prednisone
p-ANCA	perinuclear staining pattern of anti-neutrophil cytoplasmic antibodies
c-ANCA	cytoplasmic staining pattern of anti-neutrophil cytoplasmic antibodies
MPO	myeloperoxidase
Methotrexate	MTX

years [2] and 89% at 10 years [2,3]. Moreover, EGPA patients present frequent flares, which usually require glucocorticoid (GC) bursts and a medium long-term maintenance doses. Both flares and GC contribute to damage accrual, which on the long run can jeopardize the patient's quality of life and have significant impact in terms of sequelae or disability [2,5–7]. Improving these outcomes remains a challenge, for which different approaches with newer therapies are warranted. While pathogenesis of the disease remains incompletely understood, it is considered that eosinophils play a significant role and drive distinct clinical manifestations. Interleukin-5 (IL-5) is a key cytokine in promoting maturation and survival of eosinophils and, consequently, its blockade represents a logical step when considering the treatment of EGPA from a physiopathological point of view. The therapeutic effect of mepolizumab was proven with the MIRRA trial, a phase 3, double-blind, randomized, controlled trial that demonstrated efficacy of mepolizumab, an anti-IL-5 humanized monoclonal antibody, in reducing flares and sparing glucocorticoids (GC) in GC-dependent patients [8]. However, since then, there has been scarce information regarding the real-world performance of mepolizumab in EGPA patients, as well as its impact on specific disease manifestations in a highly protean and heterogeneous condition. Since mepolizumab was first tried in eosinophilic asthma, and despite the fact that in the MIRRA trial remission was based on a vasculitis activity index (Birmingham Vasculitis Activity Score, BVAS), there is some concern that mepolizumab would mainly improve manifestations derived from eosinophilic infiltration, leaving the vasculitic component of the disease uncovered. Therefore, the aim of this study was to analyze the effect to mepolizumab on the different disease manifestations or organ involvement in a single-centre cohort.

2. Material and methods

2.1. Patients

We performed a retrospective review of the medical charts of EGPA patients followed in a referral unit of a tertiary hospital to identify all patients who, over the course of their disease, had received at least 3 months of mepolizumab treatment. EGPA was defined according to the American College of Rheumatology (ACR) 1990 classification criteria [9] or inclusion criteria in the MIRRA trial [8], and the diagnosis was reassessed by the investigators (RRG, GEF, MCC) to ensure that only EGPA and not other eosinophilic disorders were included. Patients were followed regularly according to clinical practice: every three to four months, unless the clinical situation of the patient at a given visit advised for a closer follow-up. The investigation was approved by the ethical committee in our centre (HCB/2020/1149). Written informed consent was obtained from all the patients.

2.2. Baseline measurements

Demographical data, as well as clinical, biological and radiological data, both at diagnosis, and at every follow-up visit were retrieved. The following clinical variables were included: presence of asthma (defined by historical diagnosis, wheezing, use of inhaled bronchodilators and/or compatible pulmonary function tests when available), fever (defined as temperature >37.0°C), weight loss (defined as a loss >5% of bodyweight in 6 months or less), presence of pulmonary infiltrates or pleural effusion (as defined by CT scan or chest X-rays), alveolar haemorrhage, skin involvement (either as a palpable purpura, rash, ischemic ulcers, erythematous papules or urticaria), rhinitis, nasal polyps, paranasal sinus involvement (clinical signs and symptoms supported by image techniques, usually CT scan and nasal endoscopy), peripheral nervous system involvement (mononeuritis multiplex or polyneuropathy), central nervous system involvement (ischemic or hemorrhagic stroke, eosinophilic meningitis), gastrointestinal involvement (demonstration of intestinal vasculitis, eosinophilic esophagitis or gastroenteritis), cardiac involvement (myocarditis, pericardial effusion, myopericarditis, ischemic heart disease due to vasculitis), renal involvement (proteinuria >500 mg/24h, haematuria > 5-10 red blood cells/high power field, a supportive biopsy or renal failure attributed to renal vasculitis) or musculoskeletal involvement (arthralgia, arthritis, myalgia or myositis). Concomitant medications were registered, particularly immunosuppressants and corticosteroids, both at baseline and during follow-up, including mepolizumab dose.

2.3. Disease activity, damage and other scores

Disease activity was assessed by the BVAS, version 3 [10] and damage was evaluated by Vasculitis Damage Index (VDI) [11]. Both scores were calculated retrospectively: BVAS at diagnosis, at the initiation of mepolizumab and every six months thereafter, and VDI at mepolizumab initiation, and subsequently on a yearly basis or last follow-up. Also, the revised Five Factor Score (FFS) was calculated at diagnosis [12].

2.4. Outcomes

The outcomes assessed in this study comprised the number of relapses, the effect of mepolizumab on clinical and laboratory findings (eosinophil counts and ANCA testing) and its effect on the dose and use of concomitant immunosuppressive drugs.

A relapse was defined as worsening in the clinical status of the patient attributed to disease activity, with BVAS>0 (considering active asthma symptoms included in the BVAS term *wheezing*, or signs or active nasal or sinus disease) which required an escalation in the dose of glucocorticoids, in the immunosuppressive treatment or hospitalization, similarly as the definition used in the MIRRA trial [8]. To standardise and compare the effect of the administration of mepolizumab, the total of patient-years exposed to a flare prior and post-administration of mepolizumab was calculated and the incidence of flare was reported as annualized rate.

2.5. Statistical analysis

Patient characteristics are reported as the number and percentage for categorical variables and as the mean ± SD for continuous variables. This is a descriptive series and no statistical analysis was performed.

3. Results

Among the cohort of 56 EGPA patients followed on a regular basis at our department, 11 patients were treated with mepolizumab. The main demographics and clinical characteristics are summarized in Table 1.

The mean age ± SD at diagnosis was 48.6 ± 14.7 years, without clear sex predominance (6 males, 5 females). Nine of them were Caucasian (from Spain), 1 was Hispanic (from Dominican Republic) and 1 was Asian (from Pakistan). All of them fulfilled both the ACR 1990 classification criteria [9] and the MIRRA trial classification criteria [8].

The mean time between the beginning of symptoms attributable to EGPA and the diagnosis of EGPA was 3.1 ± 1.9 years, and at the time of diagnosis, the mean BVAS was 10 ± 6.4. Only 1 patient presented with a modified FFS of 1, whereas in the rest it was 0. At diagnosis, 5 patients were already on glucocorticoids due to persistent asthma or ENT symptoms, with a mean dose of 16 mg/d of prednisone (PDN).

At diagnosis, all patients had asthma, with a mean duration prior the diagnosis of EGPA of 4.9 ± 4 years. Other organ involvement, ordered by frequency, were paranasal sinus involvement (8/11, 72.7%), nasal polyps (6/11, 54.5%), pulmonary infiltrates (6/11, 54.5%), rhinitis (5/11, 45.5%), mononeuritis multiplex (4/11, 36.4%), skin involvement (2 patients with palpable purpura, 2 with urticaria), weight loss (3/11, 27.3%), alveolar haemorrhage, eosinophilic myositis, fever, arthralgia, myalgia (1 patient each).

For remission induction, PDN at 1 mg/kg of body weight was used in 11 patients. Additionally, methylprednisolone pulses were administered to 1 patient (at a dose of 500 mg daily for 3 days), cyclophosphamide monthly pulses to 4 patients (the dose ranged from 500 mg to 1000 mg per pulse, and the number of pulses from 8 to 12, according to the severity of the initial manifestations) and methotrexate (MTX) to 2 patients (1 patient received 20 mg weekly during a year and could be discontinued 1 year and a half later; in 1 patient the initial dose is unknown, and maintained methotrexate during 5 years). Subsequently, in 2 out of the 4 patients who received cyclophosphamide, azathioprine (AZA) was used for maintenance of the remission; whereas only corticosteroids in the other 2 patients.

As shown in Table 1, in all but 2 patients, there was >10% eosinophils among the total white blood cell count (in 1 patient this data was missing), with a mean eosinophil count of 4979 ± 3614 cells per cubic millilitre. ANCA positivity, assessed by indirect immunofluorescence was present in 9 patients (1 was negative; in 1 this information was not available) with p-ANCA specificity in 7 of them and c-ANCA in 2 of them. The myeloperoxidase (MPO) titters, when available, had a mean of 229 (range 3.2-740; negative below 19.9).

Mepolizumab was prescribed when a) patients required PDN at ≥ 7.5 mg/d to maintain stability (8 patients), b) when maintained with < 7.5mg/d, presented at least 4 exacerbations/year requiring an increase in PDN dose (2 patients), or c) when vasculitic manifestations appeared, especially in the context of the two later options (1 patient).

At the time of mepolizumab initiation, there were 62.4 patient-years of follow-up and 109 flares were registered, all of them related to asthma or ENT manifestations, except 1 patient who in addition had exacerbation of the peripheral neuropathy, with an annual flare rate of 1.75 per patient-year. A summary of clinical characteristics, laboratory findings, disease-related scores and concomitant treatments is presented in Table 1. Compared with the clinical picture at diagnosis, the disease was less active at the initiation of mepolizumab, with a mean BVAS of 3.33 ± 1.6 in patients with active disease. Five patients at that time had BVAS of 0 related to previous glucocorticoid increase. Three patients were still presenting with uncontrolled asthma, 2 with pulmonary infiltrates, 4 with nasal polyps and 3 with rhinitis and paranasal sinus involvement. There were no other pulmonary involvement (pleural effusion, alveolar haemorrhage), constitutional symptoms (fever or weight loss), musculoskeletal, cutaneous, cardiovascular, gastrointestinal or central nervous system involvement at this moment. Damage accrual assessed by VDI had a mean of 1.73, being 0 in only 3 patients.

Table 1
Clinical characteristics, lab results, treatment and evolution of mepolizumab-treated EGPA patients

	At diagnosis	At mepolizumab initiation	At last follow-up
Age at diagnosis, mean (range) years	48.6 (22.9-66.6)	54.3 (34.7-68.8)	57.5 (36.1-71.9)
Male, n (%)	6 (54.5%)	-	-
Female, n (%)	5 (45.5%)	-	-
BVAS, median (range, SD)	10 (2-20, 6.36)	3.33 (0-6, 1.63)	0 (0-0, 0)
FFS at diagnosis, value (n,%)	1 (1, 9.1%)	-	-
Yearly rate of flares	-	1.75	0.51
VDI, mean (range)	-	1.9 (0-5)	2.1 (0-5)
Time under treatment with Mepolizumab, mean(range) months	-	-	38 (3-66)
Clinical manifestations			
Asthma	11 (100%)	3 (27.3%)	0 (0%)
Years of asthma prior EGPA diagnosis, median (range, SD) years	4.8 (1.3-14.9, 4.0)	-	-
Fever, n (%)	1 (9.1%)	0 (0%)	0 (0%)
Weight Loss, n (%)	3 (27.3%)	0 (0%)	0 (0%)
Pulmonary Infiltrates, n (%)	7 (63.6%)	2 (18.2%)	0 (0%)
Pleural Effusion, n (%)	0 (0%)	0 (0%)	0 (0%)
Alveolar Hemorrhage, n (%)	1 (9.1%)	0 (0%)	0 (0%)
Skin Involvement, n (%)	4 (36.4%)	0 (0%)	0 (0%)
Nasal Polyps, n (%)	6 (54.5%)	4 (36.4%)	2 (18.2%)
Rhinitis, n (%)	5 (45.5%)	3 (27.3%)	2 (18.2%)
Paranasal Sinuses Involvement, n (%)	8 (72.7%)	3 (27.3%)	2 (18.2%)
Peripheral Nervous System Involvement, n (%)	4 (36.4%)	1 (9.1%)	0 (0%)
Central Nervous System Involvement, n (%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal Involvement, n (%)	1 (9.1%)	0 (0%)	0 (0%)
Cardiomiopaty, n (%)	0 (0%)	0 (0%)	0 (0%)
Renal Involvement, n (%)	0 (0%)	0 (0%)	0 (0%)
Ocular Involvement, n (%)	1 (9.1%)	0 (0%)	0 (0%)
Arthralgias, n (%)	1 (9.1%)	0 (0%)	0 (0%)
Arthritis, n (%)	0 (0%)	0 (0%)	0 (0%)
Myalgias, n (%)	1 (9.1%)	0 (0%)	0 (0%)
Myositis, n (%)	1 (9.1%)	0 (0%)	0 (0%)
Lab tests			
Eosinophils, mean (range, SD) cells x10^9	4979 (600-8850, 3614)	240 (0-600, 254.7)	55 (0-200, 68.8)
Eosinophil count> 10%, n (%)	8 (72.7%)	0 (0%)	0 (0%)
ANCA positivity (IIF)	9 (81.8%)	3 (27.3%)	2 (18.2%)
pANCA (IIF)	7 (63.6%)	3 (27.3%)	2 (18.2%)
cANCA (IIF)	2 (18.2%)	0 (0%)	0 (0%)
Anti-MPO titters, mean (range)	229 (3.2-740)	88.3 (3.2-739.8)	7.7 (3.2-37.2)
Remission induction treatment			
Methylprednisolone pulses	1 (9.1%)	-	-
Prednisone at 1 mg/kg	9 (81.8%)	-	-
Cyclophosphamide pulses	4(36.4%)	-	-
Methotrexate	2 (18.2%)	-	-
Remissionmaintenancetreatment			
Prednisone dose, mg/d (range)	-	11.4 (5-22.5)	5.125 (0-10)
Immunosuppressive drugs, n*	-	3	1
Omalizumab	0	2	2
Montelukast	0	1	1

Anti-MPO titers: negative if <19.9.
*Azathioprine or methotrexate.
EGPA Eosinophilic granulomatosis with polyangiitis; ANCA: Antineutrophil cytoplasmic antibodies; pANCA: perinuclear staining pattern of ANCA; cANCA: cytoplasmic staining pattern of ANCA; IIF: indirect immunofluorescence; Anti-MPO titters: anti-myeloperoxidase titters; SD: Standard Deviation; BVAS: Birmingham Vasculitis Activity Score;FFS: Five Factor Score; VDI: Vasculitis Damage Index

Regarding treatment, 6 patients received mepolizumab at 300 mg/month, 1 patient received 4 doses of 100 mg which was later escalated to 300 mg/month, 1 patient received a first dose of 300 mg and subsequently continued with 100 mg/month and 3 patients received 100 mg monthly. Additionally, all received prednisone at a mean dose of 11.36 ± 6.7 mg/day, and 3 of them an additional immunosuppressive agent (2 AZA, 1 MTX).

At mepolizumab initiation, none of the patients had >10% of eosinophils among the total white blood cell count (in 1 patient this data was missing), with a mean eosinophil count of 240 ± 254 cells per cubic millilitre, probably reduced by previous GC treatment. ANCA, assessed by indirect immunofluorescence remained positive in three of the patients (negative in the other eight patients) with p-ANCA specificity in all three. MPO titters were also lower, with a mean of 88.3 (range 3.2-740; negative below 19.9). There was a total of 35.3 patient-years of follow-up (median follow-up 3.19 years, IQR: 3.84 years, range 3 months to 5.6 years) after the initiation of mepolizumab treatment and, during this time, a total of 18 flares were registered, resulting in a yearly flare rate of 0.51. All flares registered during this period were asthma or ENT related. Interestingly, 5 patients had no flares during follow-up. All the patients but 1 who were active at the initiation of mepolizumab achieved a BVAS of 0 in 12 months or earlier. Regarding clinical manifestations, persistent asthma was controlled within less than 3 months in 2 of the patients, although the third remained insufficiently controlled up to 12 months. Pulmonary infiltrates resolved in both 2 patients in less than 3 months. ENT manifestations responded more poorly, with nasal polyps still present in 2 patients at the end of their follow-up in the study and present for more than a year and with recurrences in a third one. Paranasal sinuses involvement and rhinitis was also commonly persistent, with 2 patients still presenting them at the end of the study. No additional organ involvement occurred during the treatment with Mepolizumab. At the end of follow-up, the mean VDI was 2.1.

During the follow-up, all patients but 2 were able to tapper the PDN dose, achieving a mean dose at the end of the study of 5.125 ± 2.8 mg/day, with 1 patient being able to discontinue it completely. Two patients remained with the same PDN dose as at the beginning of mepolizumab treatment but with clearly fewer exacerbations. In 1 patient, tapering was not possible due to persistence of ENT manifestations, although disease control was better. In the other, due to short follow-up (3 months) since Mepolizumab initiation tapering was not attempted. Moreover, 2 of the 3 patients who were taking other immunosuppressive agents were able to discontinue them (1 AZA, 1 MTX). None of them had to stop the administration of mepolizumab due to side effects or lack of efficacy. The most frequent side effects reported were upper respiratory tract infections and reactions in the site of injection. In 1 patient, who had excellent disease control, mepolizumab was discontinued 11 months after achieving remission, but a subsequent exacerbation when she was 5 months mepolizumab-free prompted mepolizumab re-administration, with excellent response, being able to discontinue PDN during follow-up.

The eosinophil count remained within normal ranges during treatment and at the end of the study, with a mean eosinophil count of 55 ± 69 cells per cubic millilitre. ANCA by indirect immunofluorescence remained positive in 2 of the patients with MPO-ANCA specificity.

4. Discussion

In this study we describe the performance of Mepolizumab in a real-world cohort of EGPA patients, followed regularly in a tertiary hospital with expertise in the vasculitis field. Mepolizumab was approved by FDA in 2017 for its use in EGPA after the publication of the positive results of the phase 3 MIRRA trial [8]. Since then, no real-world data that explore the effect of IL-5 blockage with Mepolizumab on EGPA have been reported. In addition, some uncertainties regarding mepolizumab efficacy on distinct clinical manifestations still exist. There is some concern that mepolizumab may control asthma and ENT manifestations with a lower impact on the vasculitic component of the disease. Our study provides information about the longest follow-up period of all reported series/cohorts published to date [8,13–16] and during this time we did observe a heterogeneous response according to different organs and systems.

Previous uncontrolled-trials published before the MIRRA trial enrolled 10 and 7 patients respectively [13–15], with generally shorter follow-up periods. In these studies, the dose of mepolizumab was IV 750 mg monthly, in contrast with the SC 300 mg in the MIRRA trial [8] and the present series, where almost one third of patients received even lower maintenance doses. These previous studies were focused on demonstrating the preliminary efficacy of blocking the IL-5 pathway, using notably higher doses than currently used, proving the safety of Mepolizumab and highlighting the plausibility of relapse when withdrawing the treatment. The different methodology and endpoints of the studies, along with the differences in duration of active treatment, hamper the comparison between studies and advocate for caution when interpreting the results.

In general, our series confirmed the reduction in the number and rate of flares and the GC-sparing ability of mepolizumab previously reported [8,13–16]. The annualized relapse rate after mepolizumab in our series was 0.51, with a predominance of asthmatic flares, followed by ENT, and notably with no vasculitic flares. On the other hand, the MIRRA trial showed an annualized relapse rate of 1.14, higher than that of our study. Similarly to our findings, asthma and ENT were common causes of flares. By contrast, vasculitis was present as the second cause of exacerbation in patients enrolled in the MIRRA trial and we did not observe vasculitic flares in our patients. Some of these differences, particularly those related to our lower annualized rate, may be explained by a more heterogeneous management within the multicentric clinical trial where concomitant GC dose was not standardized, in contrast to a more homogeneous and tailored management in our patients, since the definition of flare used in both studies was the same. Also, differences in number of patients included in both studies may account for such disparities. Regarding the GC-sparing ability, in our study, the mean dose of prednisone could be tapered from 11.4 mg/d of PDN to 5.125 mg/d throughout the study (mean of 38 months), representing a 45% decrease. In other series and cohorts, similar results were obtained, with tapering ranging from 12.9 mg/d to 4.6 mg/d in 3 months [15], from 19 mg/d to 4 mg/d in 9 months [13] or from 12 mg/d to 5 mg/d in 13 months [8].

In our study, 7 patients were maintained on the long term on 300 mg monthly and 4 patients on 100 mg monthly, suggesting that even lower doses than currently accepted for EGPA could be beneficial in terms of reducing flares and sparing GC. The evidence supporting the use of 300 mg monthly is more solid, while that of using 100 mg monthly is weaker and not free from bias (i.e., giving lower doses to patients with a less severe disease) [17]. In our study, those patients who were maintained with 100 mg, the clinical indication was mainly severe asthma, either with persistent symptoms at initiation of Mepolizumab (2 patients), with frequent flares (1 patient) or with requirements of high doses of PDN (2 patients) and the dose was adjusted to the severity of the clinical picture, according to the treating physician. The response in this subset of patients was excellent, with no exacerbations after the initiation of mepolizumab.

The VDI in our series increased from 1.9 to 2.1 during the follow-up. Out of the 11 patients, the VDI remained stable in 9, increasing 1 point in 2 patients (1 bone fracture in a previously osteoporotic patient; 1 development of radiologic evidence of ENT bone destruction). Previous GC load and previous insufficient disease control may have also accounted for an increase in the damage. These data are similar to those observed in the MIRRA trial, with only 54 week follow-up. The longer follow-up of our study suggests that mepolizumab may be able to avoid damage accrual in the long term. The MIRRA trial was probably not long enough to detect a decrease in damage accrual rate in patients with long-lasting disease and previous treatments.

When examining in detail individual clinical manifestations in our study, persistent and recurrent asthma ceased in 3 patients under mepolizumab treatment. However, asthma exacerbations, although clearly less frequent, were still present in 6 (54.5%) of the patients despite mepolizumab. Persistent ENT involvement at initiation was as prevalent as asthma, in the form of nasal polyps, paranasal sinus abnormalities and rhinitis. The benefit of ENT manifestations observed under treatment was not as satisfactory as the benefit on asthma. Two out of 3 patients remained with ENT persistent symptoms, being ENT flares the second most common type of flare after asthma. Notably, no vasculitic manifestations were registered during all the follow-up, despite being ANCA positive 9 out of 11 patients at diagnosis (not available in 1 of the patients), and 6 out of 11 having histopathologically proven vasculitis (2 of the patients had vasculitis proven in biopsy of paranasal sinuses; 1 in a cutaneous biopsy and 3 in nerve biopsy. Additionally, at diagnosis, other findings suggesting vasculitis, but not proven by histology, were: 1 alveolar haemorrhage, 1 intestinal ischaemia, and 2 polyneuropathy shown by EMG).

Prior studies focused on general aspects and did not report details on specific organ manifestations. In the initial study by Moosig et al.[13] 8 out of 10 patients maintained remission during 8 months, and during this period, no relapses were observed, which indeed occurred during a longer follow-up of 22 months, after switching to MTX [14], with a clear predominance of ENT flares. No annualized rate flare was shown to allow the comparison with our study. By contrast, Kim et al.[15] described few flares during 3 months of active treatment, which increased sharply when Mepolizumab was withdraw (4 flares during 2-month washout period, 14 flares during 5-month safety monitoring period), reporting asthma as a frequent cause of flare, without specifying numbers in detail [15]. The MIRRA trial also reported the clinical improvement in form of percentage of patients who achieved remission (BVAS 0 and PDN $<$ 7.5 mg/day), accrued duration of remission or reduction in relapse rate, but did not report results on clinical manifestations in those patients considered as not responders.

This study has some limitations. It is a retrospective study and may not be exempt of certain biases proper of its nature. Additionally, none of the patients had severe vasculitic manifestations at the time of mepolizumab onset so the response to these manifestations could not be properly assessed.

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5. Conclusions

In our study, mepolizumab treatment produced a substantial improvement in all patients but complete response of all clinical manifestations was not achieved in all patients. A heterogeneous response of distinct clinical manifestations was also observed. The number of flares was greatly reduced but not disappeared, being asthma and ENT flares the main types of exacerbations. Pulmonary symptoms, in the form of persistent asthma, showed better clinical response than ENT persistent manifestations. In spite of the GC tapering, no vasculitic manifestations appeared during the follow-up. The clinical improvement achieved by mepolizumab allowed for remarkable GC tapering, which in the long-term may contribute to diminish damage accrual. Mepolizumab has been a major achievement in the treatment of EGPA but incomplete response in some clinical manifestations underlines the need for additional therapies.

Author's contributions

RRG, GEF and MCC designed the research. RRG, SPG, JHR, EA, IA, and AEP collected reviewed and analysed the data. RRG drafted the manuscript, which was critically reviewed by all co-authors.

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Declaration of competing interest

Maria C Cid has received consulting fees from GSK, Abbvie and Janssen, a research grant from Kiniksa Pharmaceuticals and lecturing fees from Vifor and GSK.

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Isam Alobid: Consultant for Menarini, Sanofi, Mylan, GSK, Novartis.

The rest of authors declare no conflict of interests.

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