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Efficacy and safety of mepolizumab in eosinophilic granulomatosis with polyangiitis: Insights from real-life cases and literature analysis

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Abstract. *Background and aim:* Recently, the MIRRA trial demonstrated the efficacy and safety of mepolizumab in refractory or relapsing eosinophilic granulomatosis with polyangiitis (EGPA) and the usefulness of this drug as a steroid-sparing agent. However, until now, only a few evidence is available about its effectiveness and safety in clinical practice. In this paper, we report our experience in the treatment of EGPA patients with mepolizumab in a real-world setting and review the current literature on this topic. *Methods:* We retrospectively enrolled 14 patients that underwent mepolizumab therapy for EGPA at any dose and with a follow-up of at least 3 months. For each patient, demographic and clinical manifestations of the disease, laboratory parameters, BVAS, asthma exacerbations, and therapeutic management were recorded at the beginning and at the end of mepolizumab therapy. *Results:* After a median follow-up of 16 months (3-60), all EGPA patients were in remission for both vasculitis and asthma manifestations. Mepolizumab was associated with a reduction in corticosteroids daily dose, with a significant number of patients able to discontinue corticosteroids (8/14 patients). No patients withdrew mepolizumab and no severe adverse events were recorded. *Conclusion:* Our data support the long-term effectiveness of mepolizumab and, in particular, they are suggestive for a good safety profile of this drug among patients with EGPA. In the nearest future, the possibility to obtain a sustained remission in EGPA without the use of steroids should be investigated in larger controlled studies.

Key words: mepolizumab**,** eosinophilic granulomatosis with polyangiitis, EGPA, interleukin 5-inhibitor, IL5-inhibitor, vasculitis, severe asthma, biologic therapy, mepolizumab real-life efficacy, case series, literature review

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is an antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis characterized by asthma, upper airways involvement (such as chronic rhinosinusitis with nasal polyposis), eosinophilia and systemic vasculitis manifestations (1-3). Etiopathogenesis of EGPA remains only partially understood, but eosinophils and ANCA, usually directed against myeloperoxidase (MPO) or proteinase 3 (PR3), represent the main pathophysiologic drivers of the disease (4, 5). Interleukin 5 (IL-5) is a major hematopoietin regulating the life cycle of eosinophils and represents the target of a new class of biological immunosuppressants, inducing depletion of eosinophils (6). Mepolizumab is a fully humanized

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monoclonal antibody binding free IL-5 with high specificity and affinity, thus preventing the interaction to the alpha chain of IL-5 receptor (IL-5R) on the eosinophil cell surface. Its ultimate effect is the reduction of eosinophil migration from the vasculature, thus reducing eosinophilia. The MIRRA trial demonstrated the efficacy and safety of mepolizumab in refractory or relapsing EGPA patients without organ-threatening or life-threatening disease and its utility as a steroid-sparing agent (7). The drug was firstly approved as add-on treatment of patients with severe eosinophilic asthma at the dosage of 100 mg every 4 weeks (8). EGPA management is mainly based on the treatment of both asthma and vasculitis manifestations (9). Therefore, the therapeutic management of EGPA usually includes systemic corticosteroids for the treatment of both asthmatic and vasculitic disease manifestations. Inhaled therapies for respiratory symptoms and immunosuppressants for vasculitis manifestations (e.g., cyclophosphamide, rituximab, methotrexate, azathioprine, mycophenolate mofetil) are frequently associated to oral corticosteroids (OCS) in long-term therapy. Among novel therapeutic options, mepolizumab has been recently approved for the induction and maintenance of remission of relapsing or refractory EGPA at the dose of 300 mg every 4 weeks, in addition to standard care (OCS, with or without immunosuppressive therapy) (7). However, data on the use of this drug in EGPA patients in a real-life setting are scarce and its effectiveness and safety in this population have not yet been fully elucidated. In this paper, we report our clinical experience in the treatment of EGPA patients with mepolizumab and review the current literature on this topic.

Materials and methods

We retrospectively analyzed all patients with EGPA treated with mepolizumab from two Italian outpatient's clinics, namely "Policlinico" of Modena and hospital "Santa Maria delle Croci" of Ravenna. In these two centers, a multidisciplinary team for the diagnosis and treatment of EGPA are available, including both rheumatologist and pulmonologist, and both respiratory and systemic manifestations of the disease are routinely collected. Our cohort included adult patients who met the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for EGPA (10) that underwent mepolizumab therapy at any dose (100 or 300 mg every 4 weeks), in accordance with local clinical practice, and with a follow-up of at least 3 months. For each patient, demographic and clinical data of the disease, other than laboratory parameters and therapeutic management were recorded before and after mepolizumab use. Birmingham Vasculitis Activity Score version 3 (BVAS v3) (11) was also recorded to assess systemic disease activity. With regard to respiratory outcomes, we collected asthma exacerbations, defined as asthma attacks needing an increase in OCS dose and/or asthma-related emergency department admission. Additional outcome included glucocorticoid-sparing effect of mepolizumab. During follow-up, variations in monthly mepolizumab dose, adverse events, vasculitis or asthma relapses and variations of the OCS dose were also recorded.

Results

Fourteen EGPA patients (females/males 11/3) ongoing mepolizumab were enrolled, with a median age of 54 year (49-64).

The main clinical features of our patients are described in Table 1.

All patients except one received mepolizumab 300 mg every 4 weeks, and in all cases the drug was prescribed to control asthma or ENT symptoms and/or as steroid-sparing therapy. The median dose of OCS at beginning of mepolizumab was 5 (range 0-25); only one patient, already in therapy with omalizumab, didn't take OCS. Nine patients underwent concurrent therapy with immunosuppressants, namely methotrexate in one, azathioprine in five, and mycophenolate mofetil in three patients. Five out of 14 patients didn't receive any immunosuppressants other than mepolizumab. No patients changed immunosuppressants during the follow-up. Four patients initially received mepolizumab 100 mg every 4 weeks, but during follow-up, 3 of them switched to 300 mg every 4 weeks for the relapse of asthmatic symptoms. The median duration of mepolizumab therapy was 16 months (range from 3 to 60 months). At baseline, all patients except one received OCS for the previous 3 months at medium/low dose (median prednisone dose of 5.625 mg daily (range 5-25), and they were all steroid-dependent patients with asthmatic phenotype, while vasculitis symptoms were mild or

Table 1. Clinical features of EGPA patients

	Gender	Age	ANCA	Vasculitis clinical manifestations	OCS at baseline	BVAS before MEPO	MEPO dose (mg)	Duration MEPO therapy (months)	Immunosuppressive therapy*	OCS last clinical evaluation	BVAS last clinical evaluation	Asthma relapses
Pt 1	F	50	Neg	PNS (PN), CRSwNP, oral aphthosis	6.25	2	300	12	0	2.5	0	0
Pt 2	F	68	Neg	CRSwNP, recurrent mastoiditis	5	1	300	20	AZA	5	0	0
Pt 3	M	55	Pos	PNS (MNM)	20	3	300	6	MTX	0	0	0
Pt 4	F	38	Pos	PNS (MNM), skin vasculitis, proteinuria	5	1	300	50	0	0	0	0
Pt 5	M	47	Neg	CRSwNP, pulmonary involvement	25	1	300	32	MMF	0	0	0
Pt 6	F	40	Neg	PNS (PN), skin vasculitis, arthritis	15	1	300	6	AZA	7.5	0	0
Pt 7	F	58	Neg	CRSwNP, hearing loss	0	1	100	27	AZA	0	0	0
Pt 8	F	47	Neg	skin vasculitis	5	2	300	22	0	0	0	0
Pt 10	F	60	Neg	CRSwNP, pulmonary involvement, skin vasculitis, PNS (PN), microhematuria	5	2	300	60	AZA	0	2	0
Pt 11	F	54	Pos	CRSwNP, PNS (MNM), pulmonary involvement	10	5	300	24	MMF	1.25	3	0
Pt 12	F	48	Pos	CRSwNP, PNS (MNM), pulmonary involvement	12.5	21	300	3	0	0	0	0
Pt 13	M	51	neg	CRSwNP, skin vasculitis, pulmonary involvement	7.5	9	300	8	MMF	1.25	0	0
Pt 14	F	54	Neg	PNS (PN), skin vasculitis	2.5	1	300	3	AZA	0	0	0
Pt 15	F	64	Neg	CRSwNP, PNS (MNM)	5	3	300	4	0	2.5	3	1

Abbreviations: neg=negative; pos=positive; PNS=peripheral nervous system; PN=polyneuropathy; MNM=mononeuritis multiplex; CRSwNP=chronic rhinosinusitis with nasal polyps; ANCA=anti-neutrophil cytoplasmic antibodies; OCS=oral corticosteroids; MTX=methotrexate; AZA=azathioprine; MMF=mycophenolate mofetil.
*During mepolizumab treatment.

moderate (median BVAS at baseline 0 (range 0-3). At the time of EGPA diagnosis, 4 patients were positive for anti-MPO ANCA. Other than severe/uncontrolled asthma, the most common clinical manifestations was related to ENT involvements (in 10/14 cases), mainly chronic rhinosinusitis with nasal polyposis (CRSwNP) (in 9/14) except one patient with chronic mastoiditis, and peripheral system nervous (in 8/14), including mononeuritis multiplex in 5 cases and sensory-motor polyneuropathy in the remaining 3 cases. Six patients had mucocutaneous involvement, mainly skin vasculitis (in 6/14). Finally, pulmonary involvement was recorded in 5 out of 14 patients, while renal involvement in other 2 (microhematuria in one case and low-grade proteinuria in the other). Only one patient had arthritis. After 6 months of treatment, all EGPA patients were in remission for both vasculitis and asthma manifestations, with a median BVAS score of 0 (range 0-3). During the follow-up, no patients experienced vasculitis relapse, while asthma exacerbation was recorded only in one case, one month after starting mepolizumab. In particular, patient-reported symptoms related to peripheral nervous system improved in all cases. Mepolizumab was associated with a reduction in OCS daily dose, with a significant number of patients able to discontinue glucocorticoid use. The median prednisone dose at the end of follow-up was 0 mg daily (range 0-7.5), with 8/14 patients discontinuing OCS therapy during the follow-up. In five cases, prednisone dose was ≤ 5 mg per day at the last visit, and in only one the prednisone dose was 7.5 mg daily, even if with a short follow-up lower than 6 months. Among the 6 subjects with ongoing OCS treatment, two didn't take any immunosuppressant for previous intolerance and side effects. In our study, mepolizumab was generally well-tolerated. No patients discontinued mepolizumab and no severe adverse events were recorded. However, under-reporting of mild and transitory adverse events cannot be excluded due to the retrospective design of this study.

Discussion

Mepolizumab recently demonstrated its efficacy and safety in refractory or relapsing EGPA patients with an encouraging safety profile (9), but until now, only a few papers have aimed to describe its role in clinical practice (Table 2) (12-22).

However, most of these studies concern the use of mepolizumab 100 mg and confirmed its efficacy mostly in patients with severe asthma and nasal symptoms rather than in EGPA (12, 13, 16, 17, 20, 21). Only one Japanese study described the real-world use of mepolizumab 300 mg in a large cohort of patients (MARS study) (18), confirming its favorable effectiveness and safety profile among patients with EGPA. In our paper, we describe the real-life experience with mepolizumab 300 mg every 4 weeks in a small cohort of Italian EGPA patients over a long follow-up period. In our population, mepolizumab allowed an effective control of both respiratory/ENT and systemic vasculitis manifestations of EGPA and also allowed a glucocorticoid-sparing effect without significant adverse events. Moreover, effectiveness of mepolizumab in maintaining disease remission was observed over a long follow-up period, up to 5 years (from 3 to 60 months) and, at the end of the follow-up, all patients were still in sustained remission. For each patient, a close monitoring, by both pulmonologist and rheumatologist, of clinical (asthma episodes, signs and symptoms of vasculitis), laboratory parameters (complement fractions, anti-MPO antibodies), other than BVAS, allowed a progressive reduction of OCS dose. Patients that didn't need OCS intake or with a daily OCS intake ≤5 mg of prednisone were 6/14 and 8/14, respectively, while only one patient was treated with prednisone 7.5 mg daily. Thus, our data strongly reinforce the usefulness of mepolizumab as OCS sparing, allowing in the meantime a good effectiveness on the disease also without concurrent OCS, confirming previous data from randomized clinical trials and other real-life experiences (7, 14, 15, 18, 19). Some case-reports have suggested the use of mepolizumab 100 mg in EGPA in selected cases with limited vasculitic symptoms (12, 13, 20, 21). Moreover, in a recent European multicentre observational study of 191 patients, comparing the two doses of mepolizumab (158 and 33 patients treated with 100 or 300 mg, respectively), the drug seemed to be effective in patients with low disease activity regardless the dosage. However, the small number of patients at the different follow-up time points did not allow sufficient power to detect a significant difference in the proportion of complete responses between the 2 doses at the different time points (15). These observations have not been confirmed in patients from our cohort. In fact, asthma was only partially controlled

Table 2. Real-life use of Mepolizumab in EGPA patients: review of the literature.

Author	Country	N. pts. (F/M)	Mepo dose	Median follow up (months)	Aim of the study	Results
Vultaggio A., 2020 (12)	Italy	18 (12/6)	100 mg	12	effectiveness on asthma symptoms, OCS and/or immunosuppressors spearing and maintainance of clinical remission without relapses.	effectiveness in EGPA patients with severe asthma and nasal symptoms; significant OCS- and immunosuppressor-sparing effect; no relapses
Detoraki A., 2021 (13)	Italy	8 (2/6)	100 mg	12	effects of low-dose MEPO in EGPA patients in terms of disease control, sinonasal and asthma control	MEPO improve BVAS score, sinonasal and asthma outcomes and reduce OCS intake
Ueno M., 2021 (14)	Japan	16 (9/7)	300 mg	12	effectiveness and safety of MEPO for relapsing/ refractory EGPA resistant to corticosteroids	12-month remission rate after the initiation of MPZ was 75%; significant decrease of BVAS, eosinophil count, or concomitant CS
Bettiol A., 2022 (15)	Europe	203 (116/87)	100 mg (158 pts); 300 mg (33 pts)	24	effectiveness and safety of mepolizumab 100 mg and 300 mg in a large European EGPA cohort	MEPO is effective for the treatment of EGPA
Özdel Öztürk, 2022 (16)	Turkey	25 (18/7)	100 mg	12	effectiveness on asthma, rhinitis control, and quality of life scores	Low-dose mepolizumab improved sinonasal and asthma outcomes and decreased daily dose of OCS
Can Bostan O., 2023 (17)	Turkey	11 (NA)	100 mg	12	sinonasal and respiratory outcomes in EGPA	significant decrease in sinonasal outcome test values, especially in nasal and sleep domains, eosinophil counts and OCS dose in the 6th month
Ishii T., 2023 (18)	Japan	118 (65/53)	300 mg	12	real-world safety/ effectiveness of MEPO in Japan EGPA	no adverse events realted to MEPO use; effectiveness and safety in EGPA patients
Masumoto N., 2023 (19)	Japan	25 (15/10)	300 mg	NA	efficacy/safety of MEPO long-term treatment (3 years) in EGPA	MEPO treatment of super-responders sustainably reduced the relapse rate
Pena T., 2023 (20)	Colombia	2 (1/1)	100 mg	NA	efficacy/safety of MEPO in EGPA	effectiveness in EGPA patients
Portacci A., 2023 (21)	Italy	39 (25/14)	100 mg	12	to assess super-responder features in real-life patients with SEA and EGPA treated with mepolizumab	>70% of the enrolled patients could be classified as super-responders; MEPO is safe and effective in patients with EGPA
Yamane T., 2023 (22)	Japan	27 (12/15)	NA	31	efficacy of MEPO in EGPA and factors contributing to OCS discontinuation	After 3 years of treatment 48% of patients with EGPA achieved GC-free status

Abbreviations: F: female; M: male; OCS=oral corticosteroids, NA=not available, MEPO=mepolizumab, EGPA=Eosinophilic Granulomatosis with Polyangiitis.

with the initial dose of mepolizumab 100 mg every 4 weeks in our patients, and the increasing of the dose to 300 mg allowed to control respiratory symptoms, thus confirming the need for higher dosage in EGPA patients. Regarding the different clinical phenotypes of EGPA, a recent post-hoc analysis of the MIRRA trial demonstrated the benefit of mepolizumab across varying baseline clinical features and irrespectively of the use of immunosuppressants or disease duration (23). In our cohort, approximately 1/3 of patients obtained a sustained remission without immunosuppressive therapy. Moreover, 3 of these 5 patients were also OCS free, suggesting the possible use of mepolizumab as monotherapy in maintaining remission. OCS discontinuation was one of the aims of mepolizumab treatment. In patients treated with a combination therapy including OCS and immunosuppressant, discontinuation of OCS was proposed whenever possible, while immunosuppressant was maintained in combination with mepolizumab. Discontinuation of immunosuppressant might be evaluated in case of long-term disease remission. However, we need future research to speculate about additional DMARDs-sparing effect of mepolizumab in larger cohort of EGPA patients. Clinical behaviour of EGPA is generally divided into predominantly vasculitic or eosinophilic phenotypes based on clusters of often overlapping clinical features (24-26). Common features of the vasculitic phenotype include palpable purpura, peripheral neuropathy, and glomerulonephritis. In contrast, the eosinophilic phenotype is more frequently characterized by lung infiltrates and cardiomyopathy and is often associated with elevated blood and tissue eosinophil counts (25, 26). Terrier et al. recently evaluated efficacy of mepolizumab according to EGPA phenotype, demonstrating that the time in remission was higher for mepolizumab than placebo regardless the baseline features of disease (27). In our patients, we collected a predominant vasculitic clinical behaviour. Despite the low number of subjects, we reported a high rate of disease remission independently by the features of disease requiring mepolizumab. A consistent proportion of our patients had peripheral nervous system involvement (8/14). We observed a remarkable reduction in peripheral neuropathy during treatment with mepolizumab, as confirmed by other case reports (28, 29). In addition, in our study, we didn't observe difference in the rate of remission between ANCA negative (10/14) or positive patients (4/14), though the subgroups were too small to draw conclusions. However, these findings support the results observed in larger series (7, 19). Nevertheless, other Authors suggest a better response to mepolizumab in ANCA-negative patients, maybe reflecting the more prominent eosinophilic phenotype (14, 24, 28). In ANCA associated vasculitis (AAV), particularly in EGPA, patients' clinical evaluation must consider not only disease activity (for example by BVAS index), but also cumulative organ damage due to both disease burn and long-term detrimental effects of treatments, mainly OCS. In this regard, infections are the second most common cause of death in AAV, and they are specifically related to OCS dose (31, 32). Other side effects related to OCS include osteoporosis, bone fractures, diabetes, and cardiovascular events, highlighting the need for glucocorticoid-sparing therapy (33, 34). Therefore, the OCS sparing effect of mepolizumab could allow to reduce damage index and side effects related to long-term OCS therapy. Finaly, the MARS study evaluated the long-term safety and effectiveness of mepolizumab 300 mg in 118 EGPA patients from real-world in Japan. During a 48-week follow-up period, the authors didn't report significant difference with data observed in the Japan post marketing surveillance (18). In our study, no patients discontinued the drug or experienced adverse events during treatment, confirming the good safety profile of the drug. Our study has some limitations, mainly related to its retrospective design and the small statistical sample. Despite a careful data collection and the systematic assessment of clinical parameters, some data were missing and a little degree of heterogeneity in clinical management among centers cannot be excluded. Moreover, as well as in the MIRRA trial, the BVAS index is used to calculate the EGPA vasculitis activity, although this tool is not specifically validated for EGPA, and we cannot exclude that the BVAS score might be biased by chronic or persistent damage. Finally, according to the small sample size no statistically significant conclusions could be deduced. On the other side, our study has also several strengths, mainly the long follow-up period up to 60 months. In conclusion, our data support the long-term effectiveness of mepolizumab and in particular are suggestive for an excellent safety profile of this drug among patients with EGPA. In the nearest future, sustained remission in EGPA without the use of steroids may be an achievable goal in clinical practice. Long-term studies in

larger populations could allow to confirm the usefulness and the safety of mepolizumab in the treatment of EGPA with different phenotypes of disease and its glucocorticoid-sparing effect on both asthmatic and vasculitic symptoms.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author Contribution: G.C., M.S., A.M. conceived of the presented idea. G.C., M.S., A.M., P.C., E.O., C.G., S.C., B.B., D.G. contributed to the design and implementation of the research and to the data collection. G.C. wrote the manuscript with support from M.S. and A.M. A.M., M.S., D.G. Supervised the project. All authors discussed the results and contributed to the final manuscript.

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