A real life cohort of Mepolizumab treatment in severe eosinophilic asthma

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Abstract

Background: Mepolizumab, a monoclonal antibody that interacts with IL-5, was the first anti-IL-5 approved for uncontrolled severe eosinophilic asthma. In several randomised, placebo-controlled trials, treatment with mepolizumab has shown a significant improvement in asthma symptoms and the need to use of oral corticosteroids (OCS). Several studies have correlated blood levels of eosinophil cationic protein (ECP) with the degree of eosinophilic inflammation, which could make it an indirect marker of eosinophilic activity.

Methods: This was a single-centre retrospective study that included all patients diagnosed with severe eosinophilic asthma under treatment with mepolizumab. We recorded the number of exacerbations, daily prednisone intake, asthma control test scores and forced expiratory volume in the first second.

Results: We followed 22 patients, 14 of whom were OCS-dependent with a mean daily dose of 15.85 ± 15.62 mg prednisone. After 12 months, only five continued taking OCS and the mean daily dose was reduced by up to 2.50 ± 3.84 mg ($p < 0.007$). The exacerbation rate at baseline was 2.91 ± 2.27 and decreased to 0.82 ± 1.14 in the following year ($p < 0.001$). ACT scores increased significantly from 16.00 ± 5.85 to 20.71 ± 4.45 after six months ($p = 0.003$). We also observed a decrease in ECP from 81.46 ± 43.99 µg/L to 19.12 ± 18.80 µg/L ($p > 0.001$).

Discussion: These real-life results are consistent with previous clinical trials demonstrating the efficacy and safety of mepolizumab in routine clinical practice for

severe uncontrolled eosinophilic asthma. We observed a significant decrease in blood eosinophil counts and in ECP levels, suggesting a reduction in eosinophil activity following mepolizumab treatment.

Keywords: Asthma; Anti-IL5; Oral systemic corticosteroids; Mepolizumab; Eosinophils.

Impact statement

Our results confirm the efficacy and safety of mepolizumab in routine clinical practice and we observed the significant decrease of ECP, suggesting a reduction in eosinophil activity following mepolizumab treatment.

Manuscript

Background

Asthma is a common chronic airways disease characterised by variable respiratory symptoms and airflow limitation (1). The worldwide prevalence ranges between 1% and 18%, being highest in developed countries (2). Approximately 4% of this total adult asthma population have a severe asthma phenotype, characterised by difficulty in achieving disease control despite high-dose inhaled corticosteroids combined with long-acting b2-agonists (LABAs) or oral corticosteroids (OCS) (3, 4). Such patients may need another type of treatments, such as the new biologic therapies targeting different pathways.

Since omalizumab, the first commercialized biological therapy targeting Immunoglobulin (Ig)E, several antibodies have been developed in the last few years to treat asthma driven by type-2 inflammatory mechanisms, characterised by the production of type-2 cytokines: interleukin (IL)-4, IL-5 and IL-13. IL-5 plays a key role in stimulating the production, recruitment and activation of eosinophil granulocytes (5). Mepolizumab, a humanised IgG1/k monoclonal antibody that interacts with IL-5 by blocking the binding of this cytokine to the alpha subunit of its receptor (6), was the first IL-5 antibody approved by both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for uncontrolled severe eosinophilic asthma. In several randomised placebo-controlled trials, treatment with mepolizumab has shown a significant reduction in exacerbation rates, as well as in the intake of oral corticosteroids and an improvement in the quality of life of these patients (7, 8).

Until now, a blood eosinophil count of $\geq 150/\mu L$ is practically the only available biomarker for selecting asthma patients who would benefit from treatment with mepolizumab (9). In addition, greater treatment effects with increasing blood eosinophil count have been found. Valid biomarkers in asthma are currently needed to provide information about diagnosis, prognosis, clinical outcomes, and other clinical features, but only a few of them have been described and characterised to date (e.g. IgE, Fractional Exhaled Nitric Oxide [FeNO], periostin) (10-12). Several studies have correlated blood levels of eosinophil cationic protein (ECP) to the degree of eosinophilic inflammation, which could make it an indirect marker of eosinophilic activity (12, 13) but this needs further validation in larger populations with severe asthma, its prize is similar to immunoglobuline E test and ECP could be an additional test to include in a laboratory protocol in an asthma clinic.

Few studies have been published to date about real-life experiences and possible criteria for treatment response with mepolizumab. Our aim was to evaluate severe eosinophilic asthma patients treated with mepolizumab in real-world practice and to find potential predictors of response.

Material and methods

Our single-centre retrospective study included all patients diagnosed with severe eosinophilic asthma with inadequate control despite treatment with high-dose inhaled corticosteroids (ICS) combined with long-acting beta 2 agonists (LABA) that had started treatment with mepolizumab, according to its current indication in Spain. They were followed up for at least one year in our difficult-to-control asthma unit at the La Paz University Hospital in Madrid, Spain. For inclusion, patients had to have a blood eosinophil count of at least 150 eosinophils/µL at screening, and/or at least 300 eosinophils/µL at any point in the previous year. Most of our patients had received continuous or near-continuous treatment with OCS.

Patients received subcutaneous injections of mepolizumab 100mg every four weeks over a period of at least 12 months. Throughout this treatment period, the following parameters were recorded at baseline, 4-6 months and 12 months: number of asthma exacerbations, daily intake (mg) of prednisone, forced expiratory volume in the first second (FEV_1), blood eosinophil count, ECP levels, total serum IgE levels, FeNO and asthma control test (ACT) scores. At each injection appointment, patients were asked about the occurrence of adverse effects and subsequently registered.

Statistical analysis.

Statistical analysis regarding categorical variables was stated as absolute numbers (n) and percentages (%), and continuous variables as means ± standard deviation (SD). The evolution of parameters of interest was calculated using generalized linear models. A p-value <0.05 was considered statistically significant. Data analysis was performed with SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

We followed 22 patients with severe eosinophilic asthma in our difficult-to-control asthma unit, starting treatment with mepolizumab. Three patients (13.64%) discontinued treatment before completing 12 months. One of them developed herpes zoster after the second injection of mepolizumab, which resolved properly without sequelae. We believed that this was probably related to the drug. Another patient suffered from nonspecific arthralgias that were not considered clearly related to mepolizumab; and the last case involved a non-responder patient after the eighth administration. Other mild side effects sporadically reported by our patients included headache, low back pain and local irritation at the injection site,

Demographic and clinical characteristics of all patients, including comorbidities, are shown on **Table 1**. In this cohort, rhinitis and chronic rhinosinusitis with nasal polyps were the most frequent comorbidities, with a high prevalence of bronchiectasis (73%). Thirteen patients had previously received omalizumab without success.

Prior to mepolizumab treatment, 14/22 patients were OCS-dependent, with a mean daily dose of 15.85±15.62 mg prednisone or equivalent. After 12 months, only 5/22 continued taking OCS and the mean daily dose was reduced by up to 2.50±3.84 mg (p<0.007) **(Figure 1).** The exacerbation rate at baseline was 2.91±2.27 and decreased to 0.82±1.14 in the following year (p<0.001) **(Figure 2)**. The variation of different clinical parameters from baseline to month 6 and 12 is shown in **Table 2**. Disease control measured by ACT scores significantly increased from 16.00±5.85 to 20.71±4.45 after six months (p=0.003),

although a statistically significant change was not obtained at the 12-month follow-up visit. Regarding lung function, FEV_1 showed an average increase of 238.85 mL after 12 months of treatment, without reaching statistically significant differences compared to baseline (p=0.261). FeNO measurements increased from a mean of 59.99±63.17 parts per billion (ppb) to 73.23±48.28 ppb after 12 months (p=0.604). All these findings are consistent with a dramatic reduction in the blood eosinophil count after one year, from 790.91±549.96 cells/µl to 98.00±90.73 cells/µl (p>0.001). We also observed a significant decrease in ECP, from 81.46±43.99 µg/L to 19.12± 18.80 µg/L, parallel to the reduction in peripheral blood eosinophil count (p>0.001); We observed no significant differences in total IgE at 6 or 12 months.

Discussion

These real-life results are consistent with previous clinical trials showing a clear benefit of this biologic therapy in patients with severe eosinophilic asthma not adequately controlled with high-dose ICS-LABA and/or OCS. A recent article by Bagnasco et al. (14) compared the baseline characteristics of patients treated with mepolizumab in real life with those patients who took part in the main regulatory trials, finding several differences such as improved lung function, higher eosinophil count and treatment with lower doses of prednisone in the former group. This real-world experience is important to support the results of clinical trials and to include new knowledge from clinical practice in guidelines.

The efficacy and safety of mepolizumab have been reported in several clinical trials. In the DREAM study (7), an intravenous formulation resulted in a 48% reduction in clinically significant exacerbations in the active arm versus placebo. In fact, high blood eosinophil counts have been found to play an important role in the risk of asthma exacerbations (15, 16); therefore, one of the key therapeutic goals for these types of drugs is to maintain blood eosinophil numbers below relevant thresholds. In our patients, we observed a significant decrease in blood eosinophil counts and in ECP levels, suggesting a reduction in eosinophil activity. However, there is not sufficient evidence to suggest that a decrease in ECP levels is related to a better response to mepolizumab (17). Regarding lung function, the DREAM study confirmed some other early studies in which there was no significant change in FEV1 during treatment (7,18,19), as was observed in our patients. More recent clinical trials such as MENSA (8) and MUSCA (20) reported

increases of 98 and 120 mL in FEV1 when comparing patients treated with mepolizumab with placebo. In terms of the steroid-sparing effect, the SIRIUS study showed a median percentage reduction of 50% in the glucocorticoid dose in the mepolizumab group, compared to no reduction in the placebo group (21). Similarly, in our study, the number of OCS-dependent patients dropped from 14 to five after one year of treatment.

Results from the clinical trials are consistent with those in patients treated with mepolizumab in real life. Rhinitis and nasal polyps were the most frequent comorbidities in our study, as was reported by Bagnasco et al. (22), although we observed a higher prevalence of bronchiectasis (73%) in our patients, we think it is due to our Asthma Clinic Protocol where every patient is studied with chest computed tomography, however, not all bronchiectasis presented clinical implications in asthma. In 2020, we published a retrospective study(23) performed in patients of our difficult-to-control asthma unit obtaining a similar prevalence of bronchiectasis (60.4%) measured by chest computed tomography. Regarding other comorbidities, one of our patients had a confirmed diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) that was satisfactorily controlled with mepolizumab 100mg every four weeks, despite the results of several open-label or placebo-controlled studies where the effectiveness in the induction and maintenance of remission in EGPA was under mepolizumab 300mg subcutaneously once a month (23-25).

Some real-world studies evaluating the efficacy of mepolizumab, such as Pelaia et al. (26), have demonstrated a significant reduction in the annual asthma exacerbation rate (from 3 to 0), with a concomitant reduction in OCS doses (from 6.25 mg/day of prednisone to 0mg/day), which is similar to our findings. The REDES study (27), a multicentre trial that evaluated mepolizumab efficacy in eosinophilic asthma, found that exacerbation rates decreased by 77.5% and that 50.6% of patients did not suffer any exacerbations during the 12 months of treatment. In addition, 47.8% of the patients were able to discontinue OCS treatment and the mean daily dose was decreased by 59.9%. In turn, the REALITI A study (28) found a reduction in exacerbation rates of 69%, from 4.63 to 1.43 (p<0.001) and the daily OCS dose decreased from 10mg/day pre-treatment to 5mg/day after 21 weeks.

A potential cause of discrepancies with these anti-IL5 drugs could be the assessment of treatment response. Global Initiative for Asthma (GINA) Guidelines recommend re-evaluating treatment response to adjust medications according to response (29). Some authors propose the establishment of response criteria for evaluation of treatment. Drick

et al. (30) recommended an initial follow-up of six months, in order to identify response criteria. In this study patients were divided into two groups: responder and non-responder; having as a primary criterion the *improvement of subjective condition* (including their subjective asthma-related symptoms, quality of life, number of exacerbations and improvement of physical fitness), as well as lung function and eosinophils in peripheral blood. Some scientific societies have proposed a response-criteria based on previous studies (31).

In real-world settings, only approximately 30% of severe asthma patients are OCS-dependent, with many patients using OCS in short courses of treatment rather than continuously (32). In our study, only one patient discontinued treatment with mepolizumab due to lack of efficacy, and that was after the eighth dose. In this patient, we observed a notable decrease in the peripheral eosinophil count, therefore this biomarker should not be used in isolation for response assessment. Consistent with previous studies and clinical trials, adverse events were rare and mostly mild in our study, allowing most of the patients to complete treatment for at least a year (33). We measured inflammatory biomarkers such as FeNO and serum ECP, finding different behaviours, but no significant association with clinical improvement was observed. Unlike some previous studies, we did not observe significant improvement in lung function. Although the small population size is one of the major limitations of this study, our results reinforce those previously reported in regulatory clinical trials and in the few published real-world studies.

 In conclusion, the results from our single-centre study confirm the efficacy and safety of mepolizumab in routine clinical practice. As reported in previous trials and real-life setting studies, we observed a significant decrease in peripheral blood eosinophilia, asthma exacerbations, OCS intake and an improvement in asthma control, accompanied by the excellent safety profile and tolerability of the drug.

Conflicts of interest

The authors certify that none of them have any conflicts of interest.

Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Information revealing the patient's identity has been avoided. All patients have been identified by numbers or aliases and not by their real names.

<u>Study approval statement</u>: Ethics approval was not required because it was a retrospective and observational study. We did not change our daily clinical practice.

<u>Consent to publish statement:</u> The study participants have given their written informed consent to publish their case (including publication of images).

The protocol was approved by local regulatory ethics committee (PI-2932).

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Table 1. Baseline demographic and clinical characteristics of severe asthmatics patients.

Characteristics	Mepolizumab Patients (n=22)
Age (years)	55.77±15.03
Female, n (%)	15 (68)
Smoking history, n (%)	
Active smoker	1 (5)
Former-smoker	10 (45)
Non-smoker	11 (50)
Body mass index	25.39±5.34
Continuous OCS therapy, n (%)	14 (64)
Mean daily dose of prednisone or equivalent at baseline (mg)	15.85±15.62
Blood Eosinophils (cells/μl)	790.91±549.96
FEV_1 (l) (pre-BD)	1.93±0.88
FeNO (ppb)	59.99±63.17
Total IgE (kU/L)	214.96±211.54
ECP (μg/L)	81.47±43.99
ACT	16.00±5.85
Comorbidities, n (%)	
Rhinitis	14 (64)
Rhinosinusitis	17 (77)
Nasal polyps	12 (55)
Gastroesophageal reflux	10 (46)
Bronchiectasis	16 (73)
Obstructive Sleep Apnea Syndrome	7 (32)
Aspirin-Exacerbated Respiratory Disease (confirmed)	2 (9)
Psychiatric disorder (Depression/Anxiety)	6 (27)
Asthma and COPD overlap (ACO)	1 (5)
Eosinophilic granulomatosis with polyangiitis (confirmed)	1 (5)

ACT: Asthma control test; BD: Bronchodilator; COPD: Chronic obstructive pulmonary disease; ECP: Eosinophil cationic protein; FeNO: Fractional Exhaled Nitric Oxide; FEV1: Forced expiratory volume in the first second; IgE: Immunoglobuline; OCS: Oral corticosteroids

Table 2. Variation of different clinical parameters from baseline to month 6 and 12. All data are expressed in mean and standard deviation (SD).
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	Peripheral blood eosinophil count (cells/μl)	ECP (μg/L)	Total IgE (kU/L)	ACT	FEV$_1$ (ml)	FeNO (ppb)
Baseline	790.91±549.96	81.47±43.99	214.96±211.54	16.00±5.85	1,930.41±880.29	59.99±63.17
6 months	114.00±99.07	22.38±19.08	128.12±128.77	20.71±4.45	2,295.63±634.61	54.95±43.45
12 months	98.00±90.73	19.12±18.80	160.26±108.57	18.50±5.27	2,169.26±677.75	73.23±48.28

ECP= Eosinophil cation protein; ACT= Asthma Control Test; FEV$_1$ (ml)= Exhaled Expiratory Volume during the first second; FeNO= Fractional Exhaled Nitric Oxide

Figure 1. Effect of mepolizumab on OCS intake. Mean daily prednisone doses (mg) assessed at baseline, six months and after a year of treatment. (p<0.007)
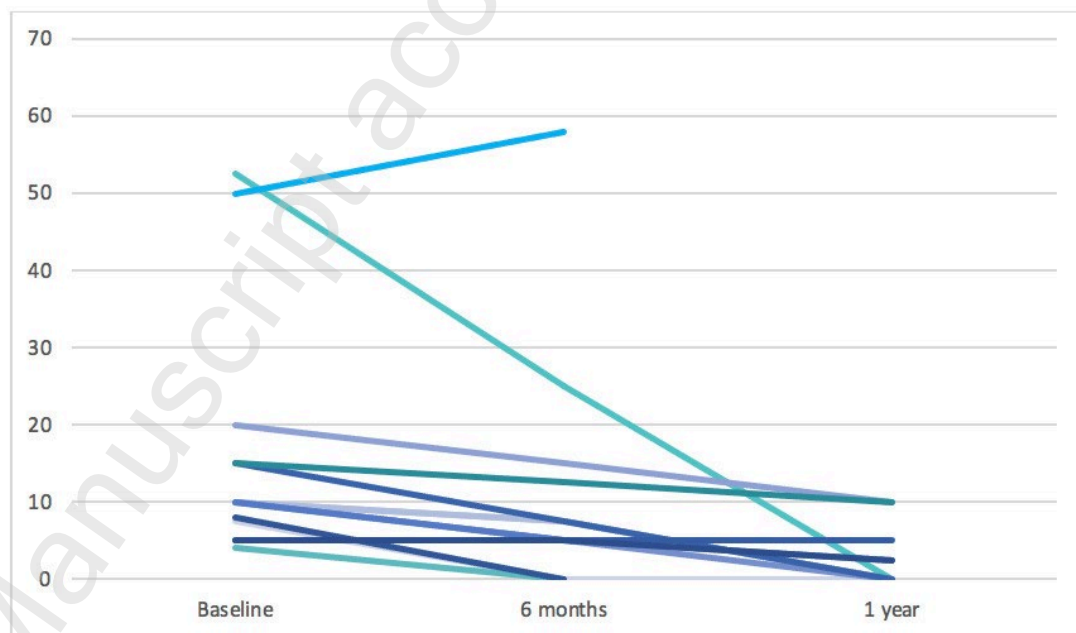
Figure 2. Exacerbation rate at baseline and after a year of treatment with mepolizumab. (p<0.001)