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A Comprehensive Evaluation of Mepolizumab Effectiveness in a Real-Life Setting

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Abstract
Introduction: Interleukin-5 (IL-5) is the principal cytokine regulating eosinophil growth, differentiation, activation, and expression. It is a specific target of mepolizumab, an anti-IL-5 monoclonal antibody used in the treatment of severe eosinophilic asthma. This new drug can improve symptoms, reduce asthma exacerbations and steroid use. Few data are available on its efficacy for nasal symptoms. ***Objective:*** To describe the all-round clinical impact of mepolizumab in a real-life setting, evaluating the efficacy and safety of the drug in severe eosinophilic asthma patients. ***Population and Methods:*** We retrospectively collected the clinical and functional data on 27 patients (16 males) affected with severe eosinophilic asthma, diagnosed at the Siena Regional Referral Centre and monitored for 6 months. Clinical, immunological, and functional data at baseline and follow-up were entered in a database together with comorbidities, number of exacerbations, steroid treatment, multiple-flow exhaled nitric oxide, and validated questionnaires. ***Results:*** A significant reduction in asthma exacerbations was observed in all patients after 6 months of the biological therapy ($p = 0.0009$), and 4/6 patients discontinued chronic oral steroids. A significant improvement in ACT, FEV1, SNOT22, and alveolar nitric oxide was observed after 1 month of mepolizumab ($p = 0.003$, $p = 0.007$, $p = 0.047$, and $p = 0.019$, respectively) and maintained after 6 months of treatment. After 6 months, FeNO 50 was reduced as well ($p = 0.030$). Mepolizumab was very well tolerated, and no major side effects were observed. ***Conclusions:*** Our study suggests that mepolizumab is effective in improving control of asthma, lung function parameters, exhaled biomarkers, and nasal symptoms in patients with severe eosinophilic asthma.

Introduction

Asthma is a complex immunoinflammatory disease characterized by chronic airway inflammation and hyperreactivity to different external stimuli. Asthma patients usually report intermittent dyspnea, wheezing,

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and dry cough, while lung function tests (LFTs) may show variable expiratory airflow limitation. Severe asthma is characterized by uncontrolled symptoms even when treated with high doses of inhaled corticosteroids (ICS) and/or oral corticosteroids (OCS), long-acting inhaled β2 agonists, antileukotrienes, and other drugs [1]. Although only 5–10% of asthmatics have severe asthma, it is responsible for 50% of the global social costs of the disease, due to frequent exacerbation episodes leading to emergency department visits and hospitalizations [2].

Biological drugs have been approved for treatment of severe asthma in the last 10 years and are demonstrating reliable effectiveness in terms of asthma control, reduction of exacerbation rate, and need for OCS intake. Interestingly, these new drugs appear to be effective in clusters of severe asthmatics, characterized by particular clinical and immunological features, and have therefore helped to identify specific endotypes of asthma (allergic, eosinophilic, neutrophilic, paucigranulocytic, and mixed) [3–8]. These assumptions have led the way to a personalized approach in the treatment of severe asthma.

Concerning management of the eosinophilic endotype, mepolizumab is a humanized monoclonal of IgG1κ type, which targets human IL-5 and thus prevents its interaction with the α chain of the IL-5 receptor. In randomized clinical trials (RCT), mepolizumab has been demonstrated to produce a significant reduction in exacerbations and steroid intake and to improve asthma control in patients with a peripheral eosinophil count >300 cell/mm^3 [9, 10]. These results have also been reported in real-world studies, confirming the cost-effectiveness and good safety profile of the drug [11, 12].

However, further research is needed to understand its overall effects and to optimize its use in clinical practice, especially concerning the optimal duration of treatment, its effectiveness in upper respiratory tract-related diseases, and prediction of response to treatment [13–15]. In this study, we describe our real-life experience with mepolizumab in a group of patients with severe eosinophilic asthma, focusing on clinical-functional effectiveness, safety, and impact on nasal symptoms and exhaled biomarkers.

Population and Methods

All patients with severe eosinophilic asthma treated with mepolizumab at our center between October 2018 and January 2020 were enrolled in the study. Diagnosis of severe asthma was according to international guidelines [1]; all patients were diagnosed and monitored at Siena Regional Referral Centre for Rare Interstitial Lung Diseases, according to the center's protocol. The dose of mepolizumab was 100 mg s.c. every 4 weeks.

Clinical and demographic features, functional parameters, immunological data, and multiple-flow fractional exhaled nitric oxide (FeNO) were recorded prospectively and entered in an electronic database designed for data analysis. Any side effects related to mepolizumab were also recorded. Immunological data included serum total IgE and specific IgE, autoantibodies (including ANCA), peripheral eosinophil count, and the corresponding percentage.

Patients filled in the Asthma Control Test (ACT) at baseline and during follow-up [16]. Another disease-specific questionnaire (22-item Sino-Nasal Outcome Test [SNOT22]) was also answered by patients suffering from chronic rhinosinusitis with nasal polyposis (CRSwNP) [17]. Clinical data, LFTs, FeNO assessment, and questionnaires were recorded at baseline (T0) and after 1 and 6 months of therapy (T1 and T6, respectively).

Lung Function Tests

The following lung function parameters were recorded according to ATS/ERS standards using a Jaeger body plethysmograph with corrections for temperature and barometric pressure: forced expiratory volume in 1 s (FEV1), FVC, FEV1/FVC, total lung capacity (TLC), residual volume (RV), transfer factor of the lung for carbon monoxide (TLCO), and TLCO/alveolar volume (VA) [18, 19].

FeNO Assessment

Nitric oxide measurements were performed with an electrochemical analyzer (model Hypair FeNO Medisoft Cardioline Exp'air, 2010) according to ATS recommendations for online measurement of FeNO in adults [20]. The analyzer was sensitive from 1 to 500 ppb NO with a resolution of 1 ppb. All measurements were made at an ambient NO concentration of <10 ppb. Exhaled NO was measured during slow exhalation from total lung capacity against a positive pressure in the range of 5–20 cm H_2O. Exhalation flow rate was kept constant by a biofeedback visual display. FeNO was measured at flow rates of 50, 100, 150, and 350 mL/s. For each flow rate, at least 2 technically satisfactory measurements were performed, and in the case of a difference of more than 10% between these measurements, a third measurement was taken. The flow-independent NO parameters, CaNO and maximum airway flux of NO (J'awNO), were calculated by the device software using the linear model endorsed by the recent ERS technical standard [21]: CaNO and J'awNO were the *Y*-intercept and the slope of the linear relationship between flow rate and FeNO × flow product, respectively. For each patient, the linear relationship was evaluated between the three points (100, 150, and 350 mL/s) of NO flux versus flow.

Statistical Analysis

All data were expressed as mean ± SD, unless otherwise indicated. Statistical analysis and graphs were performed with GraphPad Prism version 5.0 software for Windows (GraphPad Software, La Jolla, CA, USA) using nonparametric tests. A p value ≤0.05 was considered significant.

Table 1. Demographic, clinical, immunological, and functional parameters of study population at baseline and after 1 and 6 months of treatment with mepolizumab

Parameters	Baseline	T1	T6	*p* value
N	26	26	18	
Male, %	17 (65.3)	17 (65.3)	11 (61.1)	
Age, years	56.4±11.7	56.4±11.7	54.3±12.8	
Smoking status, packs/year	6.9±9.5	6.9±9.5	6.8±9.1	
Current	2	2	1	
Former	13	13	8	
Never	11	11	9	
BMI, kg/m^2	25.6±4.7	25.6±4.7	24.4±6.1	
Age at onset, years	36.5±16.6	36.5±16.6	36.5±16.5	
Comorbidities				
CRSwNP	14			
CRSnNP	2			
Allergic rhinitis	8			
AERD	3			
GERD	7			
Obesity	7			
Bronchiectasis	2			
Immunological data				
Total serum IgE, IU/mL	408.3±911.6			
Eosinophil cell count, cell/mm^3	904.4±628.7	140.6±80.6	75±54.8	<0.0001
(%)	(10.6±6)	(1.8±1.1)	(1±0.7)	<0.0001
Clinical features				
Moderate-severe exacerbations, *n*	3.8±2.7		0.4±0.5	0.0009
ACT score	16.1±4.8	20.1±3.3	21.8±3.5	0.0016
SNOT22 score	40.5±21.9	21.6±13.2	23.6±13.2	0.0179
ICS dosage, μg/day[a]	561.7±403.3	561.7±403.3	512.3±312.4	0.5282
OCS dosage, mg/day[b]	3±4.8	2.8±4.9	0.3±1.1	0.0211
PFTs				
FEV1, L	2.5±0.9	2.8±1	2.9±1	0.0278
(%)	(86.5±22.9)	(87.2±21.4)	(92.9±22.6)	0.3929
FVC, L	3.6±1	3.8±1.1	3.9±1.1	0.7857
(%)	(92.9±31.8)	(98.1±17.3)	(97.2±22)	0.7000
FEV1/FVC	69.7±11.6	72.6±9.9	72.4±10.4	0.1327
PEF, L/min	6.8±2.4	7.4±2.7	7.4±2.9	0.1778
(%)	(88.4±22.4)	(95.1±24.1)	(96.1±25.8)	0.4563
FEF 25–75%, L/s	1.8±1.3	2.2±1.5	2.8±2.3	0.16.32
(%)	(52.3±32.8)	(72.8±43.4)	(65.5±35.9)	0.4250
DLCO, %	90.2±20	92.6±9.9	88.2±15.6	0.8895
KCO, %	102.1±22.6	100.8±12.3	101.5±16.4	0.9256
Multiple-flow FeNO analysis				
FeNO 50, ppb	75.6±29.1	77.7±52.2	54.2±51.1	0.0307
FeNO 100, ppb	56.8±26.1	53.2±35	40.7±37.8	0.1870
FeNO 150, ppb	40.3±16.6	37.7±23.7	26.7±24.8	0.0689
FeNO 350, ppb	19.1±6	17.3±10.1	11.3±6.2	0.0099
J'awNO, nL/min	215.5±85.5	204.9±137	133.3±99.4	0.0476
CaNO, ppb	8.3±3.3	6.2±5.8	4.5±2	0.0048

p values were calculated through nonparametric analysis. CRSwNP, chronic rhinosinusitis with nasal polyps; AERD, aspirin-exacerbated respiratory disease; GERD, gastroesophageal reflux disease; ACT, Asthma Control Test; SNOT22, 22-item Sinonasal Outcome Test; ICS, inhaled corticosteroids; OCS, oral corticosteroids; FEV1, forced expiratory volume in 1 s; ppb, parts per billion. [a] Beclomethasone equivalent. [b] Prednisone equivalent.

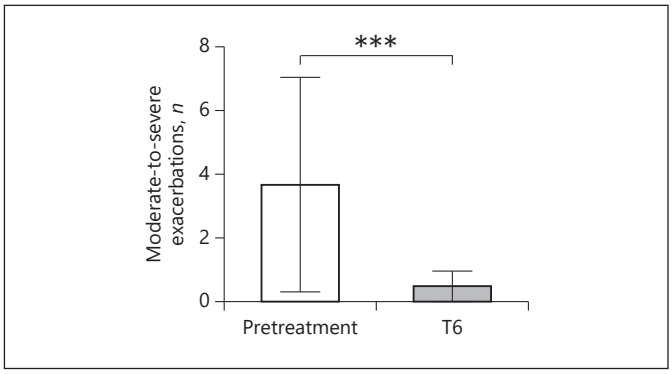

Fig. 1. Number of moderate-to-severe exacerbations before treatment and after 6 months of therapy.

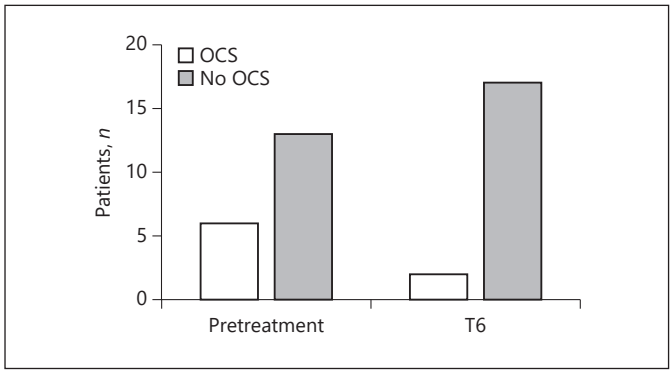

Fig. 2. Number of patients with oral corticosteroid administration before and after 6 months of therapy with mepolizumab. OCS, oral corticosteroids.

Results

Twenty-six patients with severe eosinophilic asthma (17 males, age 56.4 ± 11.7 years) were enrolled in the study. As reported in Table 1, there was a predominance of males, and 14/26 patients (53.8%) were current or former smokers. Concerning medical comorbidities, 14 patients (53.8%) had CRSwNP, while 8 (30.7%) suffered from allergic rhinitis. Gastroesophageal reflux disease (GERD), nonallergic rhinosinusitis, and bronchiectasis were reported by 7, 2, and 2 patients, respectively. Among those with allergic rhinitis, 3 had previously been treated with omalizumab.

At baseline, our patients reported more than 3 moderate-to-severe exacerbations of asthma in the 6 months before starting mepolizumab, despite high daily doses of ICS plus long-acting inhaled β2 agonists. Six patients (22.2%) were taking OCS as maintenance therapy. Among other control options, 13 patients (48.1%) were treated with tiotropium and 10 (37%) with montelukast. Poor asthma control was demonstrated by a clinically significant reduction in ACT score. Regarding basal functional assessment, our population showed mild obstructive impairment of lung volumes, associated with a significant reduction in FEF 25–75, while no alterations in diffusion capacity were observed.

At T1, all patients repeated clinical assessment, blood eosinophil count, LFTs, FeNO assessment, and questionnaires. As expected, there was an abrupt reduction in peripheral blood eosinophil count (p = 0.0005). We observed a significant improvement in ACT score (p = 0.0030), associated with a significant increase in postbronchodilator FEV1, FEV1/FVC, and FEF 25–75 (p = 0.0070, p = 0.0263, and p = 0.0294, respectively), but not in postbronchodilator PEF (p = 0.3048). SNOT22 values were significantly reduced (p = 0.0079). Regarding exhaled breath biomarkers, FeNO 50 and CaNO levels both decreased, although only the latter reached statistical significance (p = 0.3792 and p = 0.0445, respectively), while J'awNO showed no significant differences (p = 0.5186).

At T6, data were available for 18 patients (69.2%). We observed a significant reduction in moderate-to-severe exacerbation rate with no hospitalizations or emergency room visits (p = 0.0009) (Fig. 1). This was associated with a decrease in mean daily OCS intake (p = 0.0211). Four out of 6 patients permanently discontinued OCS maintenance therapy after 67.5 ± 15.6 days of therapy (Fig. 2). No differences in ICS dose were found (p = 0.5282). Compared to baseline values, the significant improvement in postbronchodilator FEV1, ACT, CaNO, and SNOT22 observed at T1 was also confirmed at T6 (p = 0.0278, p = 0.0016, p = 0.0048, and p = 0.0179), while a significant reduction in FENO 50 and J'awNO was only reached at T6 (p = 0.0307 and p = 0.0476, respectively) (Fig. 3). Two patients (7.4%) discontinued mepolizumab due to lack of efficacy after 146 and 115 days of treatment.

Concerning safety, no hypersensitivity reactions were observed. Drug-related side effects are listed in Table 2; they were reported in 6 patients (22.2%) and were mild, not requiring any specific medication.

Discussion

In this real-life study, we described a population with severe eosinophilic asthma treated with mepolizumab, a direct IL-5 inhibitor, recently approved in Italy. As expected, our results confirmed the effectiveness of the drug

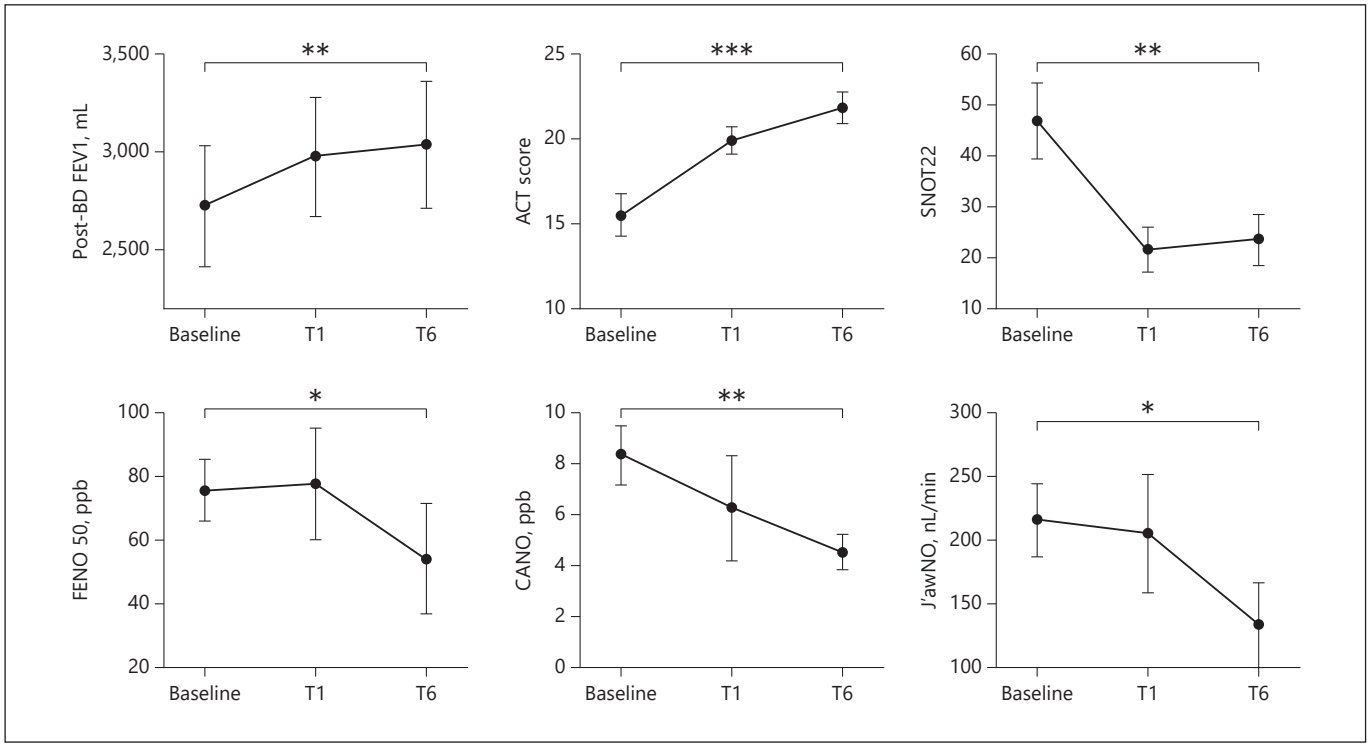

Fig. 3. Baseline, T1, and T6 values of postbronchodilator (post-BD) FEV1 (mL), ACT scores, SNOT22, FENO 50 (ppb), CANO (ppb), and J'awNO (nL/min).

Table 2. Safety profile in our study population

Side effects	6/26 patients
Headache, *n* (%)	5 (19.2)
Asthenia, *n* (%)	3 (11.5)
Drowsiness, *n* (%)	3 (11.5)
Hypotension, *n* (%)	1 (3.8)
Nausea, *n* (%)	1 (3.8)

in terms of reduction of exacerbation rate, and consequently need for systemic steroids, and also in terms of improvement of asthma control and functional parameters. There have been many reports in the literature on the efficacy of mepolizumab from RCTs and real-life studies [22, 23]. Our study contributes to the topic, confirming that mepolizumab is very effective in reducing respiratory symptoms, the number and severity of exacerbations, and OCS intake, enabling significant health gains in patients with severe eosinophilic asthma. Moreover, our data further underline the rapidity of action of mepolizumab: its positive effects on respiratory parameters, such as ACT, CaNO, and FEV1, were already significant after the first dose, as previously described [14], and were maintained throughout the observation time. These data are interesting and suggest that these parameters could be early predictors of sustained response to mepolizumab. In confirmation of this hypothesis, two of our patients discontinued treatment due to lack of efficacy and neither showed a significant improvement in ACT, CaNO, or FEV1 at T1. Unfortunately, our sample size was too small to fully investigate this aspect.

We also observed a significant impact of mepolizumab on CRSwNP in terms of reduction of symptom burden, quantified by SNOT22. CRSwNP is a common comorbidity in eosinophilic asthma and can be predictive of a better response to mepolizumab in terms of asthma control and reduction of respiratory exacerbations [24]. However, the effect of mepolizumab in the management of CRSwNP is still unclear. Some reports have raised concerns about its real effectiveness for CRSwNP outcomes [25, 26]. Our results are in line with previous reports in the literature: in particular, a post hoc analysis of the MUSCA study demonstrated a significant decrease in SNOT22 values after 24 weeks of treatment, reporting a mean score reduction similar to ours (11.8 vs. 13.1) [27]. On this question, a single RCT reported good efficacy with 750 mg i.v. mepolizumab in reducing the need for

sinus surgery for nasal polyposis, confirming its therapeutic potential for CRSwNP [28]. A RCT is currently underway to evaluate the effectiveness of 100 mg subcutaneous mepolizumab and is likely to clarify the role of this drug in CRSwNP management (identifier: NCT03085797).

Concerning exhaled biomarkers, to our knowledge this is the first study to perform multiple-flow FeNO analysis in severe asthma patients treated with mepolizumab. FeNO 50 is widely accepted in asthma as a useful biomarker for prediction of exacerbation and compliance with inhalation therapy [29], while CaNO has been proposed in the literature as a reliable biomarker of small airway inflammation [29, 30]. In line with our results, previous studies have reported a significant decrease in FeNO 50 after at least 6 months of mepolizumab treatment [31, 32], but no differences after the first dose [33]. This result was further confirmed by J'awNO, a flow-independent marker of bronchial NO flux, that showed the same pattern. Interestingly, we observed that CaNO levels significantly declined as well, but in contrast to FeNO 50 and J'awNO, the decrease was already evident at T1. Therefore, our results suggest that mepolizumab may promptly reduce distal inflammation, alleviating small airway obstruction and contributing to clinical and functional improvement. Since the small airways, associated with in loco overexpression of inducible NO synthase [34], are directly involved in the pathogenesis of severe asthma, our data are of interest.

In conclusion, our study provides further evidence of the effectiveness and safety of mepolizumab in a real-life population of severe asthmatics. We also report a significant improvement of CRSwNP symptoms, to be confirmed in the ongoing trial. The early reduction of CaNO is new and interesting and is worth investigating as a biomarker of small airway inflammation in asthma patients.

Statement of Ethics

All subjects gave their written informed consent to the study. The study was approved by the local ethics committee (C.E.A.V.S.E.) (code number 180712).

Disclosure Statement

The authors have no conflicts of interest to declare.

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The authors did not receive any funding.

Author Contributions

P.C. conceived the study and supervised all aspects of the study; L.B. and M.d. performed data analysis; M.P. and F.P. interpreted the results; E.M., A.R., A.F., and V.B. collected the data and built the database; and P.S. and E.B. drafted the paper.

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