Real-world outcomes of mepolizumab treatment in severe eosinophilic asthma patients – retrospective cohort study in Slovakia

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Aims. Mepolizumab, a fully-humanized recombinant IgG1 kappa monoclonal antibody directed against IL-5, has shown improved asthma control and lung function in randomised controlled trials. The aim of this study was to evaluate real-world clinical experience in patients with severe eosinophilic asthma treated with mepolizumab in Slovakia.
Methods. A retrospective, non-interventional study based on medical records of all adult asthma patients initiating mepolizumab between November 1, 2017 and January 31, 2019, completing 12 months of treatment. At baseline, general and clinical profile data were recorded 12 months prior to treatment. Primary and secondary endpoints described the results of mepolizumab use at 2, 6, and 12 months after the initiation and compared to baseline. Statistical testing of individual change (in each patient) in selected parameters was performed.
Results. The cohort included 17 patients with particularly severe asthma at baseline, with frequent severe exacerbations (SE, median 5 [IQR 4–6]/patient/year), high blood eosinophil counts (median 0.6x10^9/L), frequent oral corticosteroid (OCS) dependence (82.35%), median dose 15 (IQR 7.5–20) mg/day, impaired lung function, and a spectrum of comorbidities. In a one-year follow-up, the data showed reductions in median SE (0 [IQR 0–1] patient/year, eosinophilia (median 0.175x10^9/L) and OCS maintenance dose (median 6.25 [IQR 2.5–20] mg/day), all statistically significant after 12 months on mepolizumab. Improved and stabilised lung functions throughout the cohort and a reduced incidence of nasal polyposis were observed.
Conclusions. The results provide clinical evidence of mepolizumab efficacy in a real sample of patients with severe asthma when administered in routine care settings in Slovakia.

Key words: severe eosinophilic asthma, exacerbations, mepolizumab, real world evidence, Slovakia

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INTRODUCTION

Asthma is a common, heterogeneous respiratory disease characterized by chronic airway inflammation and hyperresponsiveness to bronchoconstrictors. Several asthma phenotypes with distinct demographic, clinical, and pathophysiological characteristics have been identified, including allergic and non-allergic (eosinophilic) asthma, late-onset asthma, asthma with fixed airflow obstruction, and asthma with obesity[1]. Closer characterization of individual disease phenotypes aims to select the most suitable treatment for a particular patient. Asthma is estimated to affect more than 300 million people worldwide, representing a major global burden in terms of morbidity, reduced quality of life, mortality, and economic costs[2,3]. In Slovakia, 287,000 asthma patients is estimated, 215,000 adults and 6.1% of these have severe persistent disease[4]. The long-term goal of asthma management is to achieve good symptom control and to minimize the risk of exacerbations, fixed airflow obstruction, progression of remodelling, and treatment side effects[1]. Systemic corticosteroids, typically oral (OCS), both intermittent as well as long-term, are used to treat severe asthma as a last resort in an otherwise unsolvable condition. Patients with long-term OCS exposure have a higher prevalence of OCS-related comorbidities such as osteoporosis, hypertension, diabetes, infections, and arthritis and even short-term use is associated with significant side effects[5]. Therefore, the Global Initiative for Asthma (GINA) guidelines emphasize OCS discontinuation if it is no longer required or proves ineffective. Additionally, a triple combination of inhaled corticosteroids (ICS), long-acting muscarinic an-

tagonist (LAMA) and long-acting beta-agonist (LABA) or a biological treatment prior to initiating OCS is currently strongly recommended[1]. The addition of LAMA in step 5, before starting biologics has a pharmacoeconomic aspect, if the patient remains uncontrolled and has exacerbations, the most appropriate biologics should be selected based on phenotypic and eligibility assessment. Asthma management according to GINA guidelines is endorsed by Slovak scientific societies.

In recent years, new molecules have been introduced for the treatment of eosinophilic asthma, especially biologic agents directed against mediators of type 2 immunity, such as omalizumab, reslizumab, and mepolizumab, that have significantly improved the management of severe asthma uncontrolled on standard treatment. In Slovakia, among biologics for the treatment of asthma, only omalizumab and mepolizumab are reimbursed, but in the indication for severe eosinophilic asthma only mepolizumab has been reimbursed since 2019.

Mepolizumab is a humanized immunoglobulin G 1/κ monoclonal antibody that specifically binds to and inactivates interleukin-5, a cytokine central to the eosinophil growth, proliferation, activation and survival[6]. Compared with placebo, mepolizumab is associated with significant reduction in annual exacerbations, dependence and daily dose of OCS and a reduction in blood and sputum eosinophil counts[7-10], improvements in health-related quality of life (HRQoL), asthma control, lung function and shows a favourable long-term safety profile[8,9] in patients with severe eosinophilic asthma. In Slovakia, mepolizumab is indicated for the treatment of severe eosinophilic asthma as a subcutaneous injection, but real-world evidence (RWE) was lacking at the time of the study.

We conducted a retrospective study based on the medical records of all mepolizumab-treated patients with severe eosinophilic asthma (general sample). The primary objectives of this study were to characterize the profile of all patients with severe asthma treated with mepolizumab in Slovakia at defined time points and intervals, and to describe the results of mepolizumab use in a one-year follow-up. Secondary objectives were to evaluate the difference in annual number of severe exacerbations (SE), in blood eosinophil counts, forced expiratory volume in 1 second (FEV1), and required maintenance dose of OCS, respectively, at baseline compared to follow-up.

METHODS

Study design

This was a non-interventional retrospective cohort study that evaluated the chronological medical records of patients long-term followed by their specialists (pulmonologists and/or clinical immuno-allergologists). The data were collected from the electronic and physical medical records into a standardized case report form. The study population consisted of a general (non-selective) sample, i.e. all mepolizumab treated asthma patients in outpatient clinics in Slovakia who met the eligibility criteria. This was a case-crossover study, with a self-controlled design, where each patient acts as his or her own control.

Participants and setting

Data of all adult patients (≥18 years) diagnosed with severe eosinophilic asthma (ICD-10 codes: J45.0, J45.1, J45.8 or J45.9) with the first mepolizumab administration (index date) between November 1, 2017 and January 31, 2019, completing 12 months of mepolizumab treatment with continual adherence (taking ≥13 injections), were collected. As mepolizumab was not included in the List of reimbursed drugs in Slovakia at that time, approval by the health insurance company was required for reimbursement when the indication was fulfilled according to the Summary of Product Characteristics (SmPC).

Patient characteristics and measurements were collected at four time points: at baseline, defined as the last available medical check-up prior to the first mepolizumab administration (index date), and at three follow-up time points at 2, 6 and 12 months (i.e. the 3rd, 7th and 13th injection of mepolizumab) after the index date. In addition, two 12-month time periods before (baseline period) and after (follow-up period) setting to mepolizumab were captured (to quantify the number of SE per year). The study also included descriptive data at the time of asthma diagnosis, a record of any biological use at any time in the past before the index date, and the occurrence of selected comorbidities at any time before or after mepolizumab therapy.

The study complied with all applicable laws and subject privacy requirements. Each participating centre granted permission to use medical chart data in a non-interventional case-crossover study. There was no direct contact with the subject or primary collection of individual data, no patient identifiers were included, and the protocol did not interfere with physicians' decisions on patient care management. The results are summarized in tabular form omitting subject identification and the study was approved by the local ethics committee.

Variables and measurement

At the defined times and periods, the following variables were captured. The demographics recorded at diagnosis included anonymized patient ID, sex, date of birth and year of diagnosis, and at baseline only, weight, height (BMI) and smoking status. Past use of biological agents was recorded in the period prior to the index date for any time before index date. Clinical characteristics of patients captured at baseline and at three follow-up times (2, 6 and 12 months after index date) involved forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), Tiffeneau index (FEV1/FVC), blood eosinophil counts and OCS daily dose of prednisone-equivalent were captured. The prednisone-equivalent dose of OCS was calculated as the dose of both prednisone and methylprednisolone (4 mg of methylprednisolone being equivalent to 5 mg of prednisone).

For each 12-month period, before (baseline period) and after (follow-up period) the index date, the total num-

ber of SE and SE requiring hospitalisation was recorded. SE was defined as worsening of asthma requiring the use of OCS and/or hospitalization and/or emergency department visits despite daily high doses of ICS and LABA. To quantify the number of severe exacerbations (SE) per year, absolute and per patient number of SE was calculated. The incidence of selected comorbidities (allergic rhinitis, chronic obstructive pulmonary disease – COPD, gastroesophageal reflux, nasal polyps and obesity) was recorded at any time before or after the index date.

Sample size and bias

Although the studied population was relatively small (n=17), it represented the general cohort of all patients who met the inclusion criteria, i.e. of all patients with eosinophilic asthma treated with mepolizumab in a defined period. No subjects were excluded from the group.

Like other studies that use data from medical records, there is a risk of bias due to missing data (information bias). To avoid this, only patients who started treatment within a defined time period that provided a minimum of 12 months of baseline and who completed a full 12 months of treatment were enrolled. For each parameter, the number of patients with a record is indicated. For comorbidities, confounding factors or interactions that may introduce a bias, such as concurrent treatment for a comorbid condition, were not recorded. Hence these parameters are limited to descriptive analysis of intra-subject changes.

Quantitative variables and statistical analysis

Primary outcomes were analysed by descriptive statistics. All continuous variables were described using standard statistical measures: number of observations, mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum values (range). All categorical variables were summarized as absolute and relative frequencies (percentage). Blood eosinophil counts

Table 1. Basic patient's characteristics at the diagnosis and baseline.

Patient's characteristics	Total (n = 17)
Age at diagnosis, years	
Mean (SD)	37.12 (13.82)
Median (IQR)	35 (32–51)
Range	3–53
Age at baseline, years	
Mean (SD)	51.02 (10.81)
Median (IQR)	51.87 (45.19–59.10)
Range	27.94–65.30
Female, n (%)	14 (82.35%)
BMI at baseline, kg/m^2	
Mean (SD)	31.02 (7.30)
Median (IQR)	32.6 (24.56–36.33)
Range	18.78–42.46
18.5–24.9 (normal weight), n (%)	5 (29.41%)
25.0–29.9 (overweight), n (%)	3 (17.65%)
≥ 30 (obese), n (%)	9 (52.94%)
Smoking status at baseline*	
Non-smoker, n (%)	14 (82.35%)
Ex-smoker, n (%)	3 (17.65%)
Smoker, n (%)	0 (0%)
Ex-smokers at baseline (n = 3) – time since last smoking, month	
Mean (SD)	213.33 (111.16)
Median (IQR)	252 (88–300)
Range	88–300
Biologic use anytime before index date, n (%)	3** (17.65%)
Patients with prior biologic use (n = 3) – time since last administration to the index date (months)	
Mean (SD)	94.04 (80.87)
Median (IQR)	138.58 (0.69–142.85)
Range	0.69–142.85
Discontinuation of mepolizumab treatment, n (%)	0 (0%)

*Non-smokers – never smoked regularly and did not smoke at all in the last year; ex-smokers – have not smoked at least one month; **Omalizumab reported in all 3 patients.
BMI, body mass index; IQR, interquartile range; SD, standard deviation.

were analysed as continuous as well as a categorical variable. The physiological value was considered below or equal $0.300x10^9$/L, and an increased value ≥$0.301x10^9$/L, determined from the indication restrictions of mepolizumab in Slovakia.

Secondary outcomes included changes from baseline in disease outcome during follow-up. For statistical testing of individual change in blood eosinophil counts, FEV1 and OCS daily dose, the measured values for each patient were compared at different time points. The nonparametric Sign test was chosen to test the effect of treatment at the selected time points. $\alpha = 0.05$ was taken as statistically significant. Data were processed and analysed using Microsoft Excel 2013 Professional, STATISTICA 13 software.

In the analysis of each parameter, only patients with a record were included. Primary and secondary outcomes were described for all patients.

RESULTS

Participant characteristics and comorbidities

The study cohort consisted of a total of 17 patients, the majority were female (82.4%). Diagnosis of asthma occurred at the median age 35 (IQR 32–51) years, however the average age at the first mepolizumab administration was higher, median 51.87 (IQR 45.19–59.10) years. More than a half of the patients (52.94%) were obese and 17.65% were overweight. Non-smokers made up 82.35% of

Table 2. Number of severe exacerbations of asthma (SE) in patients; absolute and relative (%) individual change in SE counts; baseline vs. follow-up period.

Characteristics	Baseline period (12 months)	Follow-up period (12 months)
Patients with at least one SE (n = 17)		
Yes, n (%)	15 (88.24%)	5 (29.41%)
No, n (%)	2 (11.76%)	12 (70.59%)
Patients with at least one SE requiring hospitalization		
Yes, n (% of patients with at least one SE, n = 15)	6 (35.29%)	1 (5.88%)
No, n (% of patients with at least one SE, n = 15)	11 (64.71%)	16 (94.12%)
Number of SE – total		
SE, n	74	6
SE requiring hospitalization, n (% of total SE, n = 74)	14 (18.92%)	1 (16.67%)
Number of SE – per person		
Patients with record, n	17	17
Mean (SD)	4.35 (1.97)	0.35 (0.61)
Median	5	0
IQR	4–6	0–1
Range	0–7	0–2
	Baseline *vs*. follow-up period	
Absolute individual change in number of SE		
Patients with record, n	17	
Mean (SD)	−4.00 (2.18)	
Median	−4.00	
IQR	(−6)–(−3)	
Range	((−7.00)–1.00)	
P-value (Sign test)	0.0012	
Relative individual change in number of SE		
Patients with record, n	16*	
Mean (SD)	-86.35% (0.2678)	
Median	−100.00%	
IQR	(−100.00%)–(−77.50%)	
Range	(−100.00%)–0.00%	

*One patient had a change from 0 to 1 SE, which is not appropriate for relative (%) expression, therefore this case was not included and it is more appropriate to consider the results of frequency changes.
IQR, interquartile range; SD, standard deviation; SE, severe exacerbation of asthma.

Table 3. Pulmonary functions (FEV1, FVC, FEV1/FVC), blood eosinophil counts and oral corticosteroid (OCS) daily dose, at baseline; 2, 6 and 12 months follow-up times.

Characteristics	Baseline	2 months after	6 months after	12 months after
FEV1 (%)				
Patients with record, n	17	16	17	17
Mean (SD)	66.26% (0.25)	66.41% (0.23)	65.94% (0.25)	73.7% (0.33)
Median	61%	68.6%	71%	67%
IQR	45%–84%	47.5%–83.5%	47%–81%	46.1%–92%
Range	35%–106%	28%–106%	29%–114.7%	30%–162%
FVC (%)				
Patients with record, n	17	16	17	17
Mean (SD)	78.98% (0.19)	81.83% (0.25)	81.56% (0.28)	80.44% (0.23)
Median	69%	82.15%	74%	78.9%
IQR	68%–96%	71%–93.5%	71.2%–89.2%	69%–103%
Range	49%–112%	38%–135%	36%–148%	35%–113%
Tiffeneau index (FEV1/FVC)				
Patients with record, n	17	16	17	17
Mean (SD)	0.83 (0.237)	0.807 (0.142)	0.811 (0.171)	0.894 (0.217)
Median	0.82	0.826	0.82	0.882
IQR	0.685–0.928	0.760–0.890	0.674–0.940	0.794–0.945
Range	0.522–1.544	0.519–1.025	0.417–1.019	0.569–1.434
Blood eosinophil counts (x 10^9/L) – continuous				
Patients with record, n	17	14	15	16
Mean (SD)	0.707 (0.365)	0.321 (0.457)	0.139 (0.147)	0.183 (0.146)
Median	0.6	0.105	0.1	0.175
IQR	0.51–0.72	0.07–0.39	0.05–0.2	0.08–0.219
Range	0.3–1.83	0–1.59	0.01–0.59	0–0.55
Blood eosinophil count (x 10^9/L) – categorical, n (%)				
0.000 – 0. 300 x 10^9/L	1 (5.88%)	10 (58.82%)	14 (82.35%)	14 (82.35%)
≥ 0.301 x 10^9/L	16 (94.12%)	4 (23.53%)	1 (5.88%)	2 (11.76%)
Not measured	0 (0%)	3 (17.65%)	2 (11.76%)	1 (5.88%)
OCS* dose, (mg/24 h) per patient in daily maintenance therapy				
Patients with record, n (%)	14 (82.35%)	12 (70.59%)	10 (58.82%)	10 (58.82%)
Mean (SD)	16.61 (10.99)	12.19 (7.43)	10 (7.82)	10.5 (8.64)
Median	15	10	6.25	6.25
IQR	7.5–20	5–20	2.5–20	2.5–20
Range	5–40	5–25	2.5–20	2.5–25

*As a dose of prednisone equivalent (in addition to prednisone calculated also from methylprednisolone)
FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; OCS, oral corticosteroid; SD, standard deviation.

the population. Most patients (82.35%) had not received any other biologic therapy prior to mepolizumab, three patients previously used omalizumab, with the last dose administered in one patient less than a month before, and in two cases approximately 12 years before index date. All patients persisted on mepolizumab treatment for the full 12 months (Table 1). The asthma condition at baseline was rather severe, as illustrated by the incidence of severe exacerbations (SE) averaging 4.35 SE per year (Table 2), OCS dependence in 82.35% of patients, high blood eosinophil count, in only one patient in the physiological range (<0.300x10^9/L), as well as impaired lung function (Table 3).

Of the selected comorbidities, before starting on mepolizumab, patients most often suffered from allergic rhinitis (76.47%), obesity and nasal polyposis (52.94%, both), gastroesophageal reflux (29.41%) and COPD (17.65%). A reduction in the incidence of nasal polyposis (to 11.76%) was observed after starting treatment with mepolizumab, but more detailed analysis of the course of nasal polyposis was not the aim of the study. In addition, there was a decrease in the presence of clinical symptoms of allergic rhinitis (to 64.71%) and reflux (to 23.53%), but no change in obesity or COPD was recorded in the follow-up.

Change in severe exacerbations

In the baseline period, 15/17 patients (88.24%) experienced at least one SE and 6 of them required hospitalisation. In the follow-up, the occurrence of any SE decreased substantially to 5 patients (29.41%) with only one person in the need of hospital stay. The yearly mean number of SEs per person decreased from 4.35 [SD 1.97] to 0.35 [SD 0.61] SE/patient/year, corresponding to −91.89% change, median reduction was from 5 [IQR 4–6] to 0 [IQR 0–1] SE/patient/year, therefore −100% reduction.

Table 4. Individual changes in blood eosinophil counts, forced expiratory volume in 1 s (FEV1) and oral corticosteroids (OCS) daily dose over time; baseline vs. 2, 6 and 12 months follow-up times.

Characteristics	2 months after vs. baseline	6 months after vs. baseline	12 months after vs. baseline
Individual change in blood eosinophil counts (x 10^9/L) over time			
Patients with record, n	14	15	16
Mean (SD)	−0.416 (0.458)	−0.581 (0.385)	−0.543 (0.308)
Median	−0.460	−0.480	−0.455
IQR	(−0.650)–(−0.200)	(−0.720)–(−0.400)	(−0.685)–(−0.355)
Range	(−1.440)–0.370	(−1.620)–0.080	(−1.280)–(−0.071)
P-value (Sign test)	0.0614	0.0019	0.0002
Individual change in FEV1 (%) over time			
Patients with record, n	16	17	17
Mean (SD)	−1.54% (0.17)	−0.32% (0.20)	7.44% (0.19)
Median	0.5%	−6.0%	6.9%
IQR	(−13.9%)–6.5%	(−9.0%)–8.0%	(−5.0%)–11.0%
Range	(−39.0%)–29.1%	(−32.0%)–47.5%	(−24.0%)–57.0%
P-value (Sign test)	0.7893	0.6276	0.1456
Individual change in OCS dose (mg/24 h)			
Patients with record, n	12	10	10
Mean (SD)	−3.438 (4.860)	−6.750 (7.910)	−6.500 (7.656)
Median	−0.625	−5.000	−5.000
IQR	(−5.0)–0.0	(−10.0)–0.0	(−7.5)–0.0
Range	(−15.000)–0.000	(−22.500)–0.000	(−22.500)–0.000
P-value (Sign test)	0.0412	0.0412	0.0233

FEV1, forced expiratory volume in 1 second; IQR, interquartile range; OCS, oral corticosteroid; SD, standard deviation.

The evaluation of the observed overall decrease in frequency of SE after one year of mepolizumab was approached through the descriptive analyses and statistical testing of individual changes in SE count in each patient respectively and assessed as an absolute, as well as relative (%) change. On average (mean=median), the number of SE decreased by four severe episodes in follow-up, statistical testing confirmed a significant decrease in the absolute number of SE in follow-up compared to baseline (P=0.0012). Relative individual change in the number of SE was on average (median) −100.00% (IQR (−100.00%)–(−77.50%)) after one year on treatment (Table 2).

A total of 15 patients achieved a decrease in SE, including two individuals who showed a reduction from 7 to 0 and 5 to 2 SE, respectively. The study cohort included two patients with zero SE pre-mepolizumab. In the follow-up, one patient (who discontinued omalizumab 12 years ago) experienced a single SE (not requiring hospitalization) and one remained free of SE. Both patients were cortico-dependent for the entire course of the study.

Change in blood eosinophils counts and FEV1

Expected decrease and thus an improvement towards physiological values was observed in eosinophilia, where the median blood eosinophil counts decreased from 0.6x10^9/L at baseline to 0.175x10^9/L in one year after index date. Fourteen (82.35%) patients reached a low range eosinophil counts (<0.300x10^9/L) 12 months after, compared to only one case at baseline (Fig. 1A, 1B, Table 3). A statistically significant decrease (as a change in individual patients) in the blood eosinophil counts were confirmed by testing after 12 months and 6 months on treatment compared to baseline (P=0.0019; P=0.0002, respectively), but not in 2 months to baseline (P=0.0614) (Fig. 2A, Table 4). FEV1 remained stable during the treatment period, with the median of the individual change in FEV1 not statistically significant (P>0.05) at baseline vs. all reference times (Fig. 2B, Table 4).

Change in OCS daily dose

At baseline, 14 (82.35%) patients were OCS-dependent, and at follow-up times some patients discontinued OCS, either temporarily or completely until the end of the study period (Fig. 1C, Table 3). However, mepolizumab had a strong effect on reducing OCS daily consumption, from a median 15 (IQR 7.5–20) mg/24 h at baseline to 6.25 (IQR 2.5–20) mg/24 h at 12-months follow-up. All patients either had a dose reduction or their dose did not change, meaning no patient required a higher dose of OCS, compared to the last follow-up time. Testing confirmed a statistically significant individual decrease in OCS daily dose in patients at all reference follow-up times to baseline (P≤0.05) (Fig. 2C, Table 4).

DISCUSSION

RWE data inform health-care professionals about aspects of treatment that could not be assessed in standard randomised control trials (RCT), e.g. due to population restrictions, different treatment patterns or the exclusion of patients with comorbidities[11]. Although clinical trials

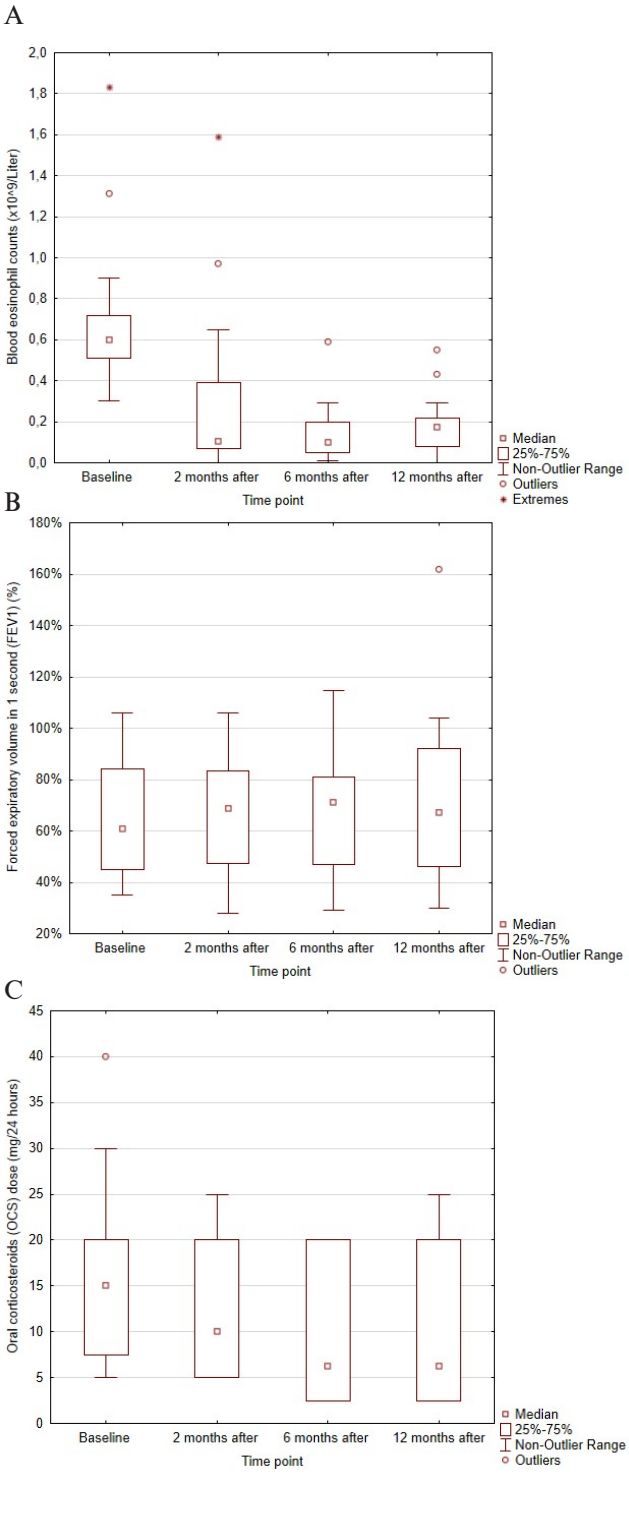

Fig. 1. Descriptive statistics of medians (IQR). A. Blood eosinophil counts. B. Forced expiratory volume in 1 second (FEV1). C. Oral corticosteroids (OCS) daily dose, at baseline; 2, 6 and 12 months follow-up times. C. two patients discontinued OCS at 2 months after and one patient at 6 months after, until the end of follow-up, one patient interrupted OCS treatment at 6 months after, but at 12 months after had a record of OCS treatment again, one patient discontinued OCS at 12 months after.

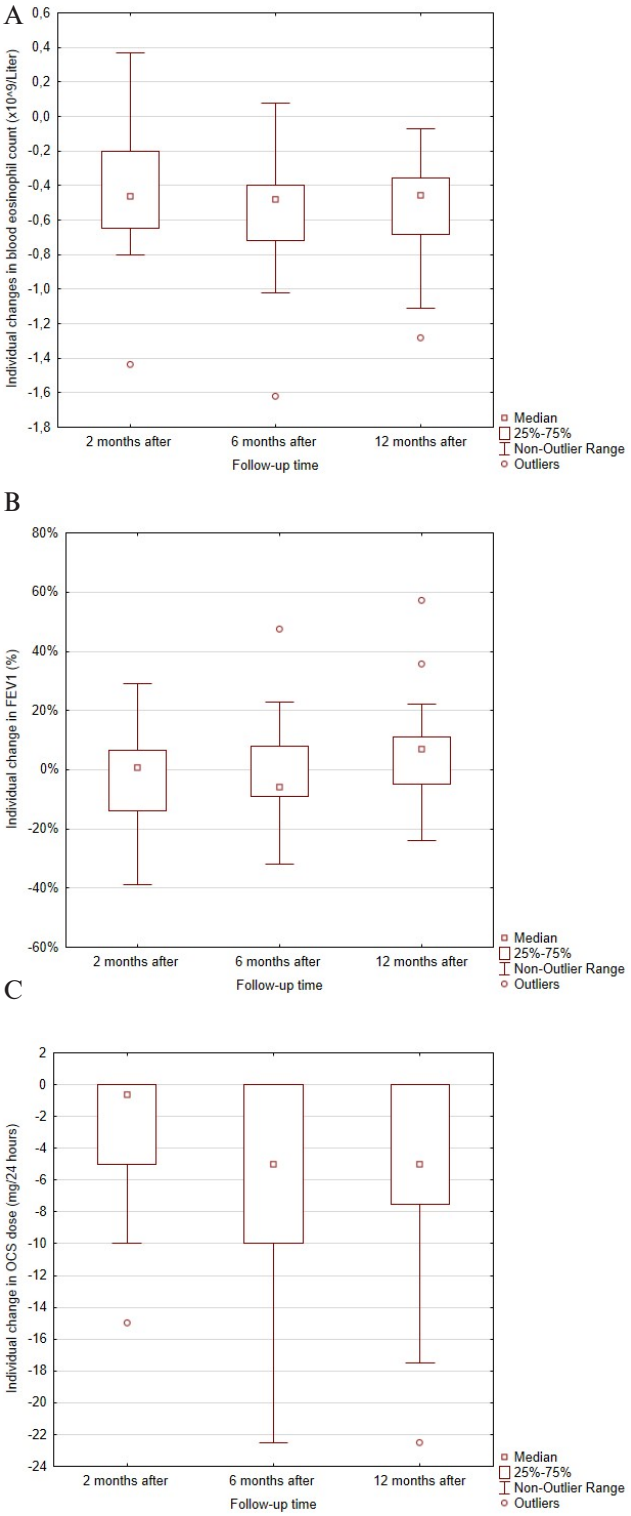

Fig. 2. Descriptive statistics of medians (IQR). A. Individual changes in blood eosinophil count. B. Individual changes in FEV1. C. Individual changes in oral corticosteroids (OCS) daily dose over time; at baseline *vs*. 2, 6 and 12 months follow-up times.

have high internal validity, they do not replicate real-world conditions[12]. The population studied in this retrospective study includes patients with particularly severe eosinophilic asthma, with frequent occurrence of SE, a spectrum of comorbidities (nasal polyps, obesity, reflux) and receiving maintenance OCS pre-mepolizumab. Previous RWE studies from European countries showed a similar broader spectrum of common airway and systemic comorbidities in severe asthma patients treated with mepolizumab[13] compared with those typically enrolled in controlled trials[14].

Our observations in the Slovak population are consistent with a post hoc analysis of phase IIb/III RCT with mepolizumab, which showed that mepolizumab reduces exacerbations, and improves asthma control, HRQoL and lung function in patients with severe eosinophilic asthma despite comorbid conditions, including upper respiratory conditions, psychopathologies, cardiovascular conditions, gastroesophageal reflux disease, diabetes mellitus, and obesity[15]. RWE studies have also confirmed the clinical benefit of mepolizumab beyond RCT settings in patients with severe asthma and various comorbid conditions that may complicate holistic patient management[16].

Patients on mepolizumab treatment for 12 months showed a statistically significant reduction, 86.35% on average, in the number and severity of asthma SE, compared to an equally long baseline period prior to treatment.

Consistent with the known pharmacological activity of mepolizumab, a decrease in blood eosinophil counts during the follow-up period was observed, with the median values falling within the reported normal ranges of circulating eosinophil levels in a healthy adult European population, as reported Hartl et al. 2020 (median [5%–95% CI] 120 [30–330] cells/μL in males and 100 [30–310] cells/μL in females) (ref.[17]). This is in line with the described long-term ability of mepolizumab to normalize rather than completely deplete the blood eosinophil compartment[18]. Although peripheral blood eosinophil counts are an easy point-of-care biomarker, eosinophils are predominantly and primarily tissue-based cells. Despite clearly demonstrated effectiveness of anti-eosinophilic therapies in asthmatic patients with increased peripheral blood eosinophils, there are probably subgroups of patients who could benefit from these treatment options, despite normal or even low eosinophils in the peripheral blood[19].

From the second month after starting mepolizumab, patients achieved a statistically significant decrease in OCS consumption, which persisted throughout the observation period. The significant reduction in daily OCS doses at 6 and 12 months into the mepolizumab treatment can be explained by the fact that the protocol did not specify how to proceed with OCS dose reduction and that physicians delayed OCS dose decrease, also due to lack of experience in real clinical practice.

Due to their severe and long-lasting asthma, associated with irreversible changes in the lungs, no significant improvement in functional parameters was expected in the studied patients, but stabilization of asthma (or no deterioration) was expected and confirmed.

We observed decrease (not statistically tested) in the incidence of nasal polyposis after mepolizumab administration for one year. This observation is consistent with the demonstrated positive effect of mepolizumab in ameliorating the condition, however, the reason for this reduction was not determined, i.e. it is not known whether their incidence was reduced in direct relation to the administration of mepolizumab, or whether the patients had polyps surgically removed at the time of follow-up etc. Recently Phase III mepolizumab RCT SYNAPSE trial confirms that mepolizumab treatment improved nasal polyp size and nasal obstruction in patients with recurrent severe chronic rhinosinusitis compared with placebo[20].

Due to the required approval of insurance company at the time of the mepolizumab indication, the patients had to strictly meet the criteria specified in SmPC and all of them were in a severe condition. After treatment they all showed at least one of the described benefits, i.e. lowering number of SE incidences, eosinophil count decrease and those dependent on corticosteroids could reduce their daily consumption or even stop the OCS treatment. This may affect the future prognosis of the patients, who could avoid development of steroid associated cardiovascular and metabolic comorbidities.

The main limitation of this study is the relatively small number of patients, which limits the power of the study and statistical comparisons between groups. The cohort included all severe eosinophilic asthma patients treated with mepolizumab in Slovakia at that time, which can be considered as a strength of the study.

The study includes all patients treated in Slovakia with mepolizumab at the time of the study and thus represents cohort of patients with early access to the treatment. This study may not be fully representative of patients with severe asthma outside this region due to the small sample size and possible selection bias (patients were selected by their physician at the time of mepolizumab availability in Slovakia and the treatment was approved by their insurance company). The generalizability of the findings outside the Slovak healthcare system may be limited.

CONCLUSION

The study demonstrated that patients eligible for the mepolizumab treatment in Slovakia were patients with very severe eosinophilic asthma, with advanced remodelling and irreversible bronchial changes, often complicated by various comorbidities. Moreover, a significant proportion of these patients required treatment with systemic corticosteroids with the high risk of long-term consequences and complications. Treatment with mepolizumab resulted in a decrease of the number of blood eosinophils, reduction of asthma exacerbations and corticosteroid use. Lung functions remained stable during the treatment period. The data provide the first clinical evidence of the efficacy of mepolizumab when administered in routine care in Slovakia. The results are consistent with other

RWE studies of mepolizumab treatment in different geographical locations.

ABBREVIATIONS

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; IQR, interquartile range; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids; RWE, real-world evidence; SD, standard deviation; SE, severe exacerbation.

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