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Mepolizumab ile Tedavi Edilen Ağır Eozinofilik Astımlı Hastaların Bir Yıllık Gerçek Yaşam Verileri

One Year Real Life Data of Patients with Severe Eosinophilic Asthma Treated with Mepolizumab

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ÖZ

Giriş: Ağır astımı tanılı bazı hastalar, oral kortikosetroidler (OKS) ile birlikte veya bunlar olmaksızın yüksek doz inhale kortikosteroidlerle (IKS) sürekli tedaviye rağmen eozinofilik inflamasyonla ilişkili sık alevlenmeler yaşamaktadır. İnterlökin (IL)-5'e bağlanan ve inaktive eden insanlaştırılmış bir monoklonal antikor olan Mepolizumab'ın ağır eozinofilik astımı olan hastalarda astım kontrol testi (AKT), Periferik kan eozinofil düzeyi (PBEV) ve astım atağı üzerine olan etkisini analiz etmek istedik.

Yöntem: Ağır astım nedeniyle en az 12 ay boyunca 4 haftada bir 100 mg mepolizumab subkutan (sc) uygulanan 27 hastanın başlangıçtaki klinik ve demografik özellikleri kaydedilmiştir. Tedavi öncesi ve sonrası yıllık astım alevlenme sayısı, PBEV ve ACT değişiklikleri karşılaştırılmıştır.

Bulgular: Mepolizumab, tüm hastalarda istatistiksel anlamlı olarak PBEV ve astım alevlenmelerindee azalma ve AKT'de artışa neden olmuştur. PBEV median 910 (IQR: 885) hücre/µL'den 90'a (IQR: 245), [p<0,001], astım alevlenmesi median 4'ten (IQR: 4) 0'a (IQR: 1) [p<0,001]) düşerken ve ACT median 11'den (IQR: 7) 24'e (IQR: 2) [p<0,001] anlamlı şekilde artmıştır.

Sonuç: Tip 2 inflamasyon ile seyreden ağır astım tedavisinde kullanılan mepolizumab, astım kontrolünü sağlamanın yanı sıra PEBV ve astım alevlenmelerini azaltmada da oldukça etkilidir.

Anahtar Kelimeler: ağır astım, mepolizumab, tip 2 enflamasyon

ABSTRACT

Objective: Some patients with severe asthma experience frequent exacerbations associated with eosinophilic inflammation despite continuous treatment with high-dose inhaled corticosteroids (ICS) with or without oral corticocetroids (OCS). We wanted to analyse the effect of Mepolizumab, a humanised monoclonal antibody that binds to and inactivates interleukin (IL)-5, on asthma control test (ACT), peripheral blood eosinophil level (PBEV) and asthma attack in patients with severe eosinophilic asthma.

Method: Baseline clinical and demographic characteristics of 27 patients who were administered 100 mg mepolizumab subcutaneously (sc) every 4 weeks for at least 12 months for severe asthma were recorded. The annual number of asthma exacerbations PBEV and ACT changes before and after treatment were compared.

Results: PBEV decreased significantly from a median of 910 (IQR: 885) cells/µL to 90 (IQR: 245), [p<0.001], asthma exacerbation decreased significantly from a median of 4 (IQR: 4) to 0 (IQR: 1) [p<0.001]) and ACT increased significantly from a median of 11 (IQR: 7) to 24 (IQR: 2) [p<0.001]. Mepolizumab led to a statistically significant reduction in PBEV and asthma exacerbations and an increase in ACT in all patients.

Conclusion: Mepolizumab, which is used in the treatment of severe asthma with type 2 inflammation, is highly effective in reducing PEBV and asthma exacerbations as well as providing asthma control.

Keywords: severe asthma, mepolizumab, type 2 inflammation

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INTRODUCTION

Asthma is a major public health problem affecting more than 330 million people worldwide. Especially severe asthma, which is difficult to control, creates a serious socioeconomic burden (1). Asthma control may be difficult due to inappropriate inhaler technique, patient non-compliance, smoking or other comorbidities (gastroesophageal reflux, obesity, rhinitis, etc.). Difficult-to-treat asthma is defined as asthma that cannot be controlled despite moderate or high-dose inhaled corticosteroid (ICS) treatment, usually in combination with a second controlling agent such as a long-acting beta agonist (LABA) or maintenance oral corticosteroid (OCS). Despite the provision of correct inhaler technique and adherence to the inhalers, control of deteriorating factors and triggers, patients who needed high dose ICS/LABA ± other controller agents to control the disease or remained uncontrolled were considered to have severe asthma (2). Severe asthma, which affects 3.7-7% of all asthmatic patients, requires frequent hospital admission, resulting in significant deterioration in the quality of life of patients and their relatives, as well as high morbidity and economic burden on societies (3). To perform real precision and personalized medicine, it started with phenotyping of patients and continued with endotyping linked to inflammation characteristics and cellularity. Recent studies have shown that severe asthma can be divided into two phenotypes: asthma with type 2 inflammation (T2 high) and asthma with no characteristics of type 2 inflammation (T2 low). Peripheral blood eosinophil value (PBEV) (>150 cells/μL), rise in the exhaled fraction of nitric oxide (FeNO>20 ppb), sputum eosinophilia (>2%) and the presence of an atopy marker (perennial aeroallergens positive skin tests and/or presence of specific IgE) are typical markers of type 2 inflammation (4). In recent years, many biological agents that have been proven to be significantly effective in the treatment of severe asthma, both in providing asthma control and in reducing the number of attacks, are included in Global Initiative for Asthma (GINA) step 5 treatment (5). One of the main targets of these drugs is eosinophils, which are observed to be cells that are usually increased in the blood of severe asthmatic patients. Mepolizumab, an anti-IL-5 monoclonal antibody, is a biological agent approved by the United States of America (USA) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in patients with T2 high severe asthma (6). In Türkiye, Mepolizumab was authorized in severe asthma towards the end of 2019. The link between IL-5 and eosinophils is actually well known, as this cytokine is required for the maturation of precursors in the bone marrow and the subsequent release of mature cells into the blood. The production and stimulation of IL-5 is triggered by TH2 (T helper) and ILC2 (innate lymphoid cells), which in turn are activated mainly by signals from epithelial cytokines such as IL-25, IL-33 and TSLP (Thymic stromal lymphopoietin). Mepolizumab is an anti-IL-5 antibody that controls the proliferation, maturation and activity of eosinophils (7,8). In this article, we wanted to share our experience with the efficacy of mepolizumab in patients with severe eosinophilic asthma.

MATERIALS AND METHODS

In this single-center, observational and retrospective study, patients who received subcutaneous mepolizumab 100 mg every 4 weeks for severe asthma for at least 12 months or longer between January 2020 and April 2022 were evaluated. The eligibility criteria for treatment were:

1. ≥18 years old with a diagnosis of severe asthma
2. PBEV ≥300 cells/μL (in patients using systemic steroids for a long time, ≥150 cells/μL under treatment)
3. Unresponsive to high-dose ICS-LABA and/or leukotriene receptor antagonist treatment
4. Patients with a history of at least two exacerbations in the last year (requiring at least 3 days of systemic corticosteroid therapy). (9,10)

A total of 27 patients with severe asthma who met the above criteria were included in the study. Of the 27 patients, 3 had been previously treated with omalizumab and switched to mepolizumab due to lack of response to treatment, while 24 had not been previously treated with any other biological agent. Pre-treatment ACT, PBEV, annual number of asthma attacks, serum total IgE levels, atopy status according to skin prick test (SPT) results and body mass index (BMI) were recorded. ACT, PBEV and number of asthma exacerbations before and after treatment were compared. In addition, all patients were divided into subgroups according to BMI (obese: BMI≥30 kg/m2 vs nonobese: BMI<30 kg/m2), atopy status [SPT(+) vs SPT(-)], serum total IgE level (≥100 IU/L vs <100 IU/L) and PBEV (>500 cells/μL vs ≤500 cells/μL) and the increase in ACT and decrease in asthma exacerbations before and after treatment were compared.

This study was approved by both the Scientific Committee of our hospital (04.02.2021-202). Data were collected from the hospital database. Adverse events were documented. For statistical analyses (IBM-SPSS software, v25.0), t-independent and Mann-Whitney tests were used to compare parametric and non-parametric independent samples, respectively, while paired-t and Wilcoxon tests were employed to evaluate differences between intervals within the same variable, as appropriate. p-values <0.05 were considered statistically significant.

RESULTS

A total of 27 patients were enrolled in the study, mean age of 45.48±11.260 years [23-65 years] and 17 were female (63%). The mean BMI was 28.49±5.29 kg/m2 [19.14-41.02 kg/m2], with 10 patients (37%) obese (BMI ≥30 kg/m2). Total serum IgE (median 220 kU/L, min.-max: 15-1436 kU/L) was ≥100 kU/L in 20 patients (74.1%), with 13 patients (48.1%) showing positive skin prick testing (SPT) . Rhinitis (n = 15; 55.6%) and gastroesophageal reflux disease (GERD) (n=9; 33.3%) were the most common comorbidities (Table 1).

Regarding mepolizumab's efficacy (Fig. 1A), PBEV significantly decreased from a median of 910 (IQR:885) cells/μl to 90 (IQR:245), [p < 0.001], asthma attack decreased from median of 4 (IQR:4) to 0 (1) [p<0.001]) as well as ACT significantly increasing from a median 11 (IQR:7) to 24 (IQR:2) [p<0.001].

A sub-analysis was attempted comparing changes in ACT improvement and exacerbation rate after 12 months of treatment in patients with baseline PBEV ≥500 cells/μL vs <500 cells/μL, BMI ≥30 kg/m2 vs <30 kg/m2, positive vs negative SPT, total serum IgE100 IU/L vs <100 IU/L (Fig. 1B). There was a statistically significant difference (p < 0.05) between the groups of SPT (+) vs SPT (-) regarding exacerbation reduction per year.

No patient required hospitalisation due to asthma attack while receiving Mepolizumab treatment. Mepolizumab was well tolerated. Only one adverse event was reported: a headache that resolved spontaneously within 2 hours.

Table 1. Baseline Demographic and Clinical Characterization	
Baseline Characterictic	
Total number of patients	27
Age, years, Mean ±SD; [min.-max.]	45.48±11.260 [23-65]
Sex,male/female, n(%)	17(63)/10(37)
BMI, kg/m^2 Mean ±SD; [min.-max.]	28.49±5.29 [19.14-41.02]
Smoking status,n (%) • Non-smoker • Ex-smoker • Current smoker	 18(66.7) 8(29.6) 1(3.7)
Age of Asthma onset, years, Mean ±SD; [min.-max.]	32.85±31.00 [6-60]
Total serum IgE, kU/L,Median[min.-max.]	220 (15-1436)
PBEV, cells/µl, Mean±SD; [min.-max.]	1060.37±880.00 [120-2840]
FEV$_1$, mL., Mean±SD; [min.-max.]	2083.56±863.76 [580-3660]
Positive skin prick test,n (%) • House dost mite,n • Pollens,n • Poly-sensitized,n	12(44.4) 8 6 2
Comorbidities, n(%) • Rhinitis • GERD • NSAID hypersensitivity • Nasal Polyposis	 15 (55.6) 9 (33.3) 4 (14.8) 2 (7.4)
ACT,Mean±SD; [min.-max.]	10.59±3.587 [5-17]
Previous Omalizumab,n(%)	3(11.11)
Data presented as n(%), mean±SD and median(IQR) as appropriate. BMI, body mass index; PBEV,Peripheral blood eosinophil value; FEV$_1$, forced expiratory volume in one second; GERD, gastroesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drugs, ACT, Asthma control test	

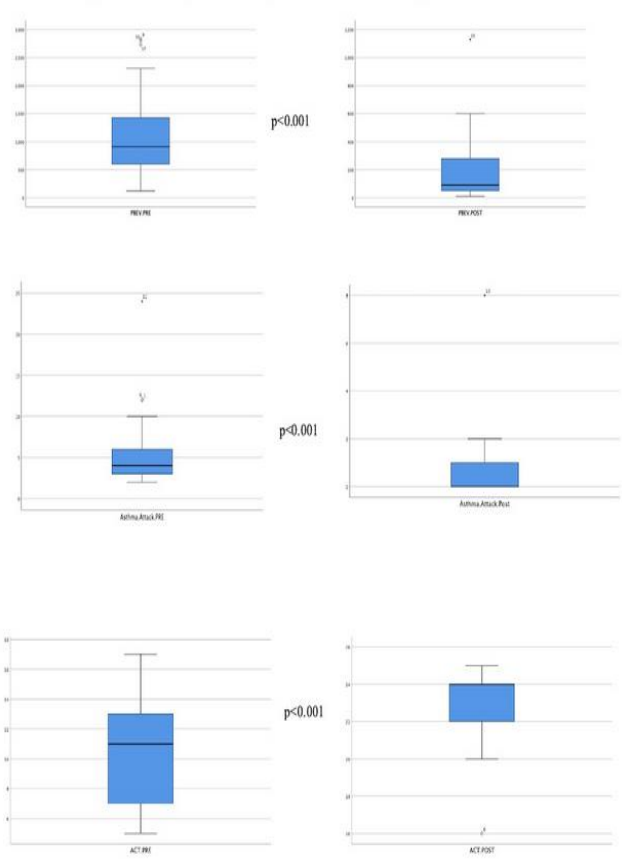

Figure 1A. PBEV, asthma attack, ACT before and after mepolizumab treatment

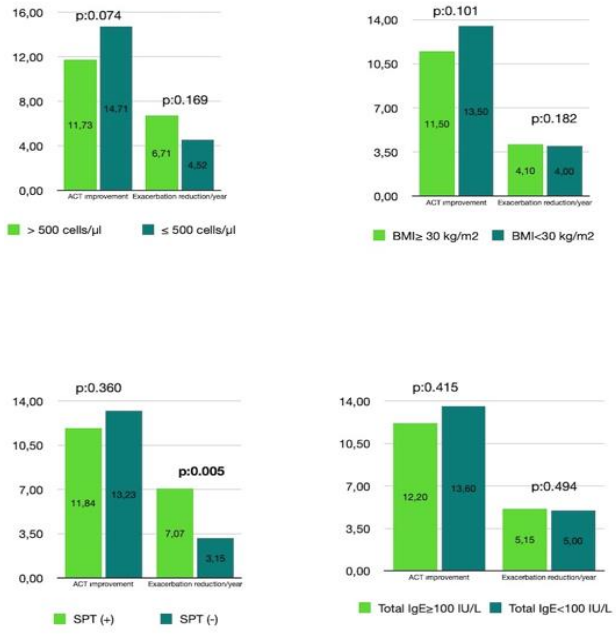

Figure 1B. Evaluation of the efficacy of mepolizumab with subgroup analyzes

DISCUSSION

In this study, patients with severe eosinophilic asthma were administered 100 mg mepolizumab sc every 4 weeks for at least 12 months and all patients showed a statistically significant increase in ACT as well as a decrease in asthma attacks and PEBV. In a randomised, double-blind study by Elisabeth H. Bel et al. (11) involving 135 patients with severe eosinophilic asthma, mepolizumab caused a clinically significant reduction in patients' use of OCS and had a significantly beneficial effect on exacerbations, asthma control and quality of life. Again, in the MENSA study with a large patient participation, it was observed that mepolizumab decreased PEBV as of week 4, reached the lowest level around week 12 and the decrease in PEBV was maintained during the study period (10). Similarly, in our study a statistically significant decrease in PEBV was found after mepolizumab.

It is well known that OCS treatment is associated with a wide range of adverse events (diabetes, osteoporosis, cardiovascular adverse events, infections, etc.). Unfortunately, in clinical practice, OCSs are used quite frequently and for long periods of time to control disease in patients with severe asthma. Recent studies have shown that increasing the dose of ICS also causes many systemic side effects (cataracts, adrenal suppression, fractures and diabetes, etc.). The magnitude of the increased risk across these systemic adverse effects is probably clinically significant for doses >250 to 500 µg/day of fluticasone propionat or equivalent (12). In asthmatic patients, add-on biological agent therapy should be considered in cases where disease control cannot be achieved despite conventional treatment. Patients treated with mepolizumab have also been shown to have a 90% to 100% reduction in the dose of OCS compared to placebo (9). In the study by Nair et al.(13), prednisolone use decreased by 83.8±33.4% in the mepolizumab group, whereas this rate was 47.7±40.5% in the placebo group (p:0.04).

Considering that obesity is one of the confounding factors of severe asthma, we analysed the effect of mepolizumab on ACT and asthma exacerbation in obese and non-obese subgroups and found that mepolizumab had similar efficacy in both groups. In a study by Kritikos et al. (14), patients with severe asthma were divided into subgroups according to comorbidities [obesity, nasal polyps, Aspirin- exacerbated respiratory disease (AERD) and Allergic Bronchopulmonary Aspergillosis (ABPA), Asthma-Chronic obstructive pulmonary disease overlap ACO] and analysed. Accordingly, mepolizumab was effective in all BMI categories (obese and non-obese) and was associated with a reduction in PBEV and significant improvements in asthma symptom control and lung function.

When we analysed the patients in subgroups according to laboratory parameters, it was shown that mepolizumab provided asthma control and reduced exacerbations independently of serum total IgE and PBEV levels. However, when patients were analysed according to their SPT results and atopy status, the improvement in ACT was similar in both groups, while the annual reduction in asthma exacerbations was statistically significantly higher in the non-atopic group.

In the study comparing mepolizumab with placebo in the treatment of patients with severe asthma selected according to omalizumab eligibility criteria, it was shown that mepolizumab significantly reduced asthma exacerbations compared to placebo, regardless of serum total IgE level and atopy status of patients. In the same study, it was found that mepolizumab effectively reduced asthma exacerbations compared to placebo (25% to 66% reduction in exacerbations) when categorised according to pretreatment serum total IgE and PBEV levels. However, the reduction in exacerbations was numerically lower in patients with blood eosinophil counts <300 cells/µL and serum total IgE ≤170 IU/mL (15). As a result, mepolizumab is a highly effective treatment option for managing severe asthma, both in reducing asthma exacerbations and in achieving symptom control. However, this study demonstrated that mepolizumab significantly reduced annual asthma exacerbations more prominently in the SPT(+) group compared to the SPT(-) group.

Studies have not reported serious effects of mepolizumab such as cardiac, thromboembolic or ischaemic events. the most commonly reported adverse events were headache and nasopharyngitis. Local injection site reactions have also been observed in some patients (11). In our study, only 1 patient complained of headache.

The most important limitations of our study is limited number of patients. However, it has an important added value in providing real world evidence about the effect of mepolizumab in a cohort of Türkiye severe eosinophilic asthmatic patients

Ethics Committee Approval: Ethical approval was obtained from University of Health Sciences Süreyyapaşa Chest Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (04.02.2021 date and 202 number).

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