Turk Thorac J 2022; 23(5): 348-354 DOI: 10.5152/TurkThoracJ.2022.22023

Original Article

A Single Center Experience of Super-Responders Among Severe Asthma Patients Receiving Treatment with Mepolizumab

Emel Atayık, Gökhan Aytekin
Department of Immunology and Allergy, Konya City Hospital, Konya, Turkey

Cite this article as: Atayik E, Aytekin G. Mepolizumab super-responders among severe asthma patients receiving Mepolizumab: A single center experience. *Turk Thorac J.* 2022;23(5):348-354.

Abstract

OBJECTIVE: Anecdotal reports among clinicians treating severe asthma patients with novel add-on treatments such as mepolizumab suggest that a fraction of these patients may experience a much more dramatic benefit from these agents than reported in large, randomized controlled studies. Although these patients have been referred to as super-responders in some studies, currently, there is no consensus regarding the nomenclature. Therefore, our aim was to assess the real-life data among patients receiving mepolizumab treatment due to severe eosinophilic asthma, in an effort to determine potential clinical and laboratory differences between super-responders and other group of patients.

MATERIAL AND METHODS: Data from adult patients who received at least four doses of mepolizumab due to persistent severe asthma between Janury 1, 2020, and December 31, 2021, in a Tertiary Allergy Clinic were evaluated in a retrospective manner.

RESULTS: A total of 57 patients with severe asthma receiving mepolizumab treatment were included [female: 38, male: 19]. At 4th- and 12th-month after initiation of mepolizumab treatment, significant differences in forced expiratory volume in 1 second, forced vital capacity, forced expiratory volume in 1 second/forced vital capacity, blood eosinophil count, and serum immunoglobulin E level were detected as compared to baseline ($P < .001$, $P < 0.001$, $P = .027$, $P < .001$, and $P = .035$). Also, at the 12th-month of treatment with mepolizumab, there were significant differences compared to baseline in asthma control test scores, number of asthma exacerbations, non-planned emergency room visits, hospitalizations, and daily need for oral corticosteroids ($P < .001$, for all parameters). Also, there was not a statistically significant difference between super-responders and responders groups in regard to age, gender, duration of disease, duration of mepolizumab treatment, allergen sensitivities, and comorbid conditions (chronic rhinosinusitis, nasal polyps, and aspirin sensitivity).

CONCLUSION: Our results suggest that mepolizumab may be an effective therapeutic option in patients with severe asthma. On the other hand, patients who were considered to be super-responders to mepolizumab treatment were not significantly different from the remaining group of patients (responders). Obviously, further studies are warranted to better define the super-responders among patients with severe asthma who receive mepolizumab treatment.

KEYWORDS: Mepolizumab, severe asthma, FEV1, super-responders, eosinophilic asthma, eosinophil
Received: *February 2, 2022* ***Accepted:*** *June 29, 2022* ***Available Online:*** *August 8, 2022*

INTRODUCTION

Globally, asthma is one of the most common chronic diseases with approximately more than 300 million patients, 5%-10% of whom may have severe asthma (SA). It represents a major cause of disease burden, both for patients and healthcare systems.[1] Patients with SA suffer from asthma attacks despite maximum inhaler therapy. Therefore, significant efforts are being made to determine phenotypic and endotypic characteristics of these patients.[2] Eosinophilic asthma is a SA endotype, and interleukin (IL)-5 contributes to persistent inflammation and the process of eosinophilic asthma within the airways.

Mepolizumab is a monoclonal antibody directed against IL-5, with established efficacy in reducing asthma attacks in patients with severe persistent asthma who have a blood eosinophil count of ≥150 cells/μL.[2-4] It has been approved by the Food and Drug Administration as an add-on or maintenance treatment for eosinophilic SA patients aged ≥ 12 years, and a recommendation has been made to include this drug as a biological agent in existing treatment regimens in patients who are thought to have type 2 inflammation predominantly.[5] Mepolizumab is associated with improvements in asthma control and quality of life and reduces asthma attacks and need for daily corticosteroids independent of the increase in forced expiratory volume in 1 second (FEV1).[5,6] The SterolD ReductIon with mepolizumab Study (SIRIUS) showed that mepolizumab reduces asthma attacks, with a 2.39-fold decrease in the need for corticosteroids as compared to placebo.[3] Again, in the Real-World Mepolizumab in the Prospective Severe Asthma study, mepolizumab injections have been reported to decrease asthma attacks by 69%, emergency room (ER) visits and hospitalizations by 79%, and the median daily corticosteroid dose from 10 mg/day to 5 mg/day.[1]

Anecdotal reports among clinicians treating SA patients with novel add-on treatments such as mepolizumab suggest that a fraction of these patients may experience a much more dramatic benefit from these agents than reported in large, randomized controlled studies. Although these patients have been referred to as super-responders in some studies, currently,

Corresponding author: Emel Atayık, e-mail: emelakinci@yahoo.com

there is no consensus regarding the nomenclature. From a clinical viewpoint, it is important to define and understand the characteristics of these patients and to establish predictors of response.

Therefore, our aim was to assess the real-life data among patients receiving mepolizumab treatment due to severe eosinophilic asthma, in an effort to determine potential, clinical and laboratory differences between super-responders and other group of patients.

MATERIAL AND METHODS

This retrospective study was conducted between January 1, 2020, and December 31, 2021, in the Allergy and Immunology Department of a Tertiary Care Unit among adult patients who received at least 4 doses of mepolizumab treatment due to severe persistent asthma.

Exclusion criteria were previous treatment with omalizumab due to SA, a diagnosis of asthma-chronic obstructive pulmonary disease overlap, and non-compliance to treatment.

All patients were assessed by chest disease and allergy–immunology specialists. The diagnosis of SA was based on Global Initiative for Asthma guideline criteria.[7,8] Information on the following was retrieved from patient files: age, gender, body mass index (BMI, kg/m^2), duration of asthma, duration of mepolizumab treatment, allergen sensitivity, smoking status, comorbid allergic conditions, presence/absence of nasal polyps and chronic rhinosinusitis, aspirin sensitivity, current/past medications, number of asthma attacks during the 1-year period before and after initiation of mepolizumab treatment, number of unplanned ER visits due to asthma symptoms, number and length of hospitalizations, and daily oral corticosteroid (OCS) dosage. Also, information on the spirometry results before and 4 and 12 months after initiation of mepolizumab treatment was obtained from the automated hospital data management center. Asthma control test (ACT) scores in these periods were recorded. BMI was calculated using the following formula = weight (kg)/height^2 (m).

MAIN POINTS

- Mepolizumab treatment was associated with increases in forced expiratory volume in 1 second and asthma control test scores and decreases in asthma exacerbations, asthma-related emergency room visits, hospitalizations, duration of hospitalization, and need for daily oral corticosteroid.
- In this study, our findings suggest that mepolizumab treatment may have significant effects on many clinical and laboratory parameters in patients with severe asthma.
- Also, this is one of the few studies comparing responders and super-responders among mepolizumab-treated patients with similar demographic, clinical, and laboratory characteristics.
- On the other hand, patients who were considered to be super-responders to mepolizumab treatment were not significantly different from the remaining group of patients in terms of the criteria assessed in our study.

For spirometry assessments, a ZAN 100 spirometer device (Oberthulba, Bavaria, Germany) was used. Forced expiratory volume in 1 second, forced vital capacity (FVC) and the ratio of FEV1/FVC, age, sex, race, and height were recorded for each patient. Asthma was considered well controlled with an ACT score of ≥20, partially controlled with an ACT score of 15-19, and poorly controlled with an ACT score of <15.[9]

Blood samples were drawn from all patients by venipuncture. Abbott Cell Dyn 3700 series (Sheath reagent) and Siemens BN II/ BN ProSpec system (particle-enhanced immunonephelometry) were used for the measurement of whole blood count and quantitative determination of serum immunoglobulin (Ig) E, respectively.

Allergen sensitivity was determined using a skin-prick test that included 8 different allergen categories with 24 inhalant allergens (dog, cat, dust mite, grass, tree, ragweed, mold, and cockroach), or by the detection of any allergen-specific IgE. A wheal diameter of >5 mm with flare at 20 minutes was considered a positive result, and patients were considered as non-atopic in the absence of any reaction to any allergens or in the absence of allergen-specific IgE.[10]

Mepolizumab super-responders were defined as those who had no asthma attack, ER visits, hospitalizations, or need for OCS, with at least 6 point increase in ACT scores and at least 15% increase in FEV1 between the start and end of the study period

The study protocol was approved by the Ethics Committee of Karatay University University (meeting date: July 6, 2020; document no: 2020/013).

Statistical analyses of all study data recorded in the study form were performed using International Business Machines Statistical Package for the Social Sciences 20.0 statistics software (Chicago, Ill, USA). The normal distribution of discrete and continuous numerical variables was tested with Kolmogorov–Smirnov test. Descriptive statistics for discrete and continuous numerical variables were expressed as mean ± standard deviation or median (minimum–maximum), while categorical variables were expressed as the number of cases and (%). Categorical variables were assessed with chi-square test, while continuous variables were assessed using *t*-test or Mann–Whitney *U* test. Dependent variables with normal distribution were compared using paired-samples' *t* test, while those without normal distribution were compared with Wilcoxon test. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

A total of 57 patients with SA receiving mepolizumab treatment were included [female: 38 (66.7%), male: 19 (32.3)]. The mean age of participants was 45.11 ± 14.74 years, the median duration of asthma was 10 years (2-30 years), and the mean duration of mepolizumab treatment was 8 months. Non-smokers comprised 91.2% of the study population, while 64.9% had non-allergic asthma and 35.1% had allergic asthma. Related comorbid conditions included chronic rhinosinusitis in 84.2%, nasal polyps in 61.4%, and aspirin sensitivity in 36.8%. Overall, 56.9% of the patients had poorly

controlled asthma. Table 1 summarizes the demographic and clinic characteristics of the study population.

At the 4th- and 12th-month after the initiation of mepolizumab treatment, significant differences in FEV1, FVC, FEV1/FVC, blood eosinophil count, and serum IgE level were detected as compared to baseline ($P < .001$, $P < 0.001$, $P = .027$, $P < .001$, and $P = .035$, respectively) (Figure 1). Also, at 12th-month treatment with mepolizumab, there were significant differences compared to baseline in ACT scores, number of asthma exacerbations, non-planned ER visits, hospitalizations, length of hospital stay, and daily need for OCS ($P < .001$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, and $P < .001$, respectively) (Table 2) (Figure 2). At least, 50% reduction in asthma exacerbation frequency, number of ER visits, and daily OCS need was noted after 1 year treatment with mepolizumab in 84.2% of the patients ($n = 48$). Also, at least 50% reduction in the number of hospitalizations was found in 89.5% of the patients ($n = 51$) and at least 50% reduction in the duration of hospital stay was observed in 86% of the patients ($n = 49$) after 1 year treatment with mepolizumab. The median change in ACT scores with 1 year mepolizumab treatment was 6 (range: 0-13), and the median change in FEV1 was 19% (range: 0-51).

Table 1. Demographic, Clinical, and Laboratory Characteristics of Patients

Parameters	Results
Age (years)	45.11 ± 14.74
Gender, female (n, %)	38 (66.7)
BMI (kg/m^2)	27.83 ± 4.45
Duration of disease (years)	10 (2-30)
Duration of treatment (months)	8 (4-24)
Non-smoker (n, %)	52 (91.2)
Diagnosis (n, %)	
Allergic asthma	20 (35.1)
Non-allergic asthma	37 (64.9)
Allergen sensitivity (n, %)	
Non-atopic	36 (63.2)
House dust mite	9 (15.8)
Mold	5 (8.8)
Pollen mixture	5 (8.8)
Animal dander	2 (33.5)
Accompanying allergic disease (n, %)	
None	16 (28.1)
Allergic rhino-conjunctivitis	39 (68.4)
Chronic urticaria	2 (3.5)
Chronic rhinosinusitis	48 (84.2)
Nasal polyps	35 (61.4)
Aspirin sensitivity	21 (36.8)
Asthma treatment (n, %)	
ICS+LABA+ LTRA	25 (43.9)
ICS+LABA+ LTRA + tiotropium	6 (10.5)
ICS+LABA+ LTRA + theophylline	6 (10.5)
ICS+LABA+ LTRA + tiotropium+ theophylline	20 (35.1)
Asthma control	
Well-controlled asthma	-
Partially controlled asthma	23 (40.4)
Poorly controlled asthma	34 (59.6)

BMI, body mass index; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LTRA, leukotriene receptor antagonists.

Asthma control was achieved in 91.3% of the patients ($n = 52$) with 1-year mepolizumab treatment (79% well-controlled asthma, n = 45; 12.3% partially controlled asthma, n = 7) (Table 2).

Then, the study population was categorized into 2 groups as super-responders and responders. Figure 3 and 4 show the change in FEV1, FVC, ACT score, serum IgE, and blood eosinophil counts before and after mepolizumab treatment. There was not a statistically significant difference between 2 groups in regard of age, gender distribution, BMI, duration of disease, duration of mepolizumab treatment, allergen sensitivities, and comorbid conditions including chronic rhinosinusitis, nasal polyps, and aspirin sensitivity (Table 3).

DISCUSSION

Our findings suggest that mepolizumab treatment may have significant effects on many clinical and laboratory parameters in patients with SA. Also, this is one of the few studies comparing responders and super-responders among mepolizumab-treated patients with similar demographic, clinical, and laboratory characteristics.

Mepolizumab treatment was associated with increases in FEV1 and ACT scores and decreases in asthma exacerbations, asthma-related ER visits, hospitalizations, duration of hospitalization, and need for daily OCS. Gibson et al[11] also showed that mepolizumab was able to reduce asthma exacerbations and improve asthma control, quality of life, and lung functions in patients with severe eosinophilic asthma, despite the presence of comorbid conditions. Similarly, Taiile et al[12] reported 86.2% reduction in asthma exacerbations following 12 and 24 weeks of treatment with mepolizumab. In a study from Spain, a 87% of reduction in 1 year was found in patients with severe eosinophilic asthma treated with mepolizumab.[13] In our study, 84.2% of the patients experienced at least 50% reduction in asthma exacerbations after 1 year of mepolizumab therapy. In MEpolizumab as adjunctive therapy iN patients with Severe Asthma (MENSA) randomized controlled study, asthma attacks were reduced by 42% following at least 32 weeks of mepolizumab therapy,[14] while 24 weeks of treatment with mepolizumab in MUSCA randomized controlled study (Mepolizumab adjUnctive therapy in subjects with Severe eosinophiliC asthma) was associated with a significant improvement in ST George's Respiratory Questionnaire.[15]

Although the clinical benefit associated with mepolizumab treatment in SA patients is independent of FEV1,[5,16] it has also been shown to increase FEV1 and ACT scores.[17] For instance, Schleih et al[18] reported a 5.31 point increase in ACT

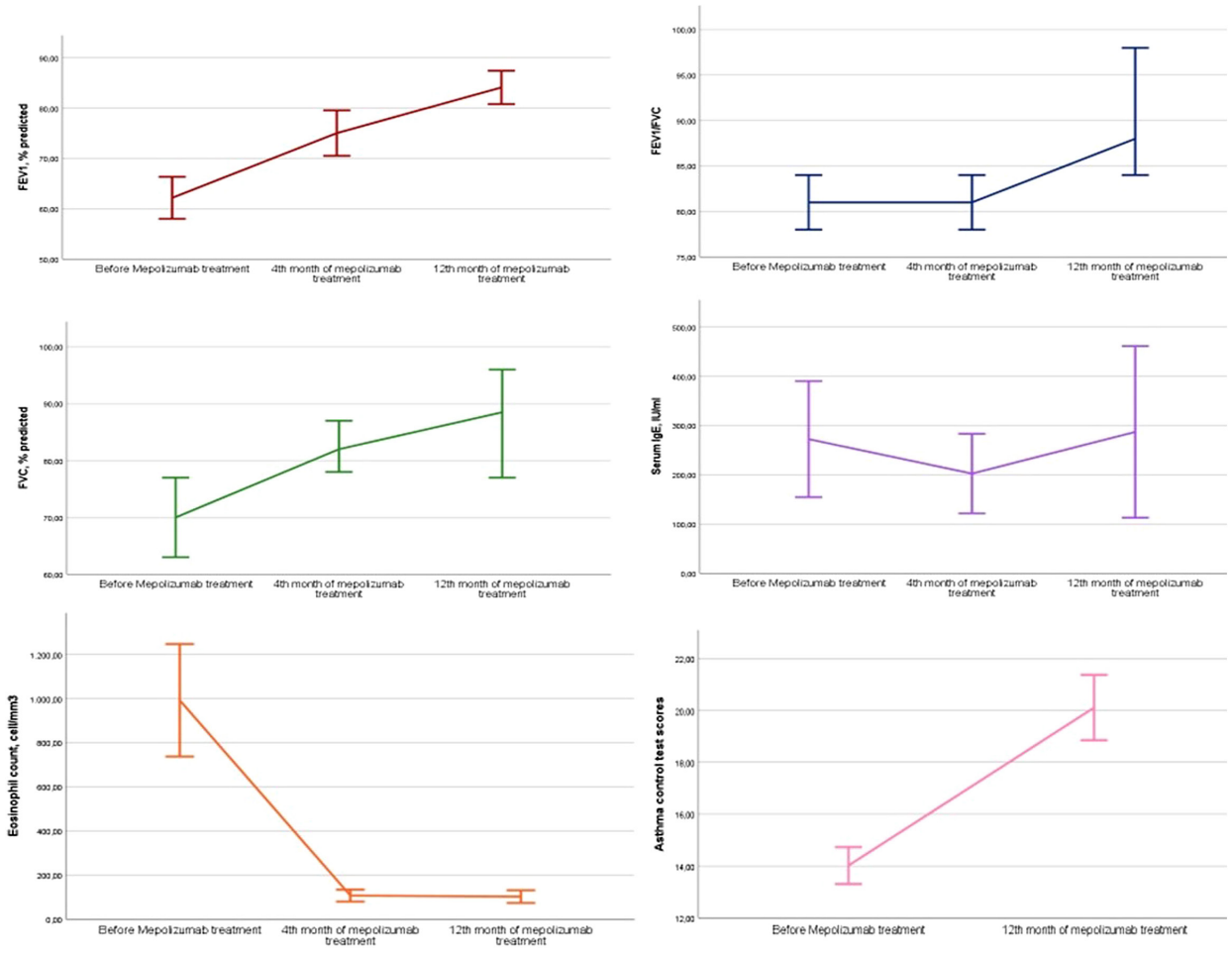

Figure 1. Change in clinical and laboratory parameters during mepolizumab treatment. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2. Change in Clinical and Laboratory Parameters During Mepolizumab Treatment

Parameters	Before Mepolizumab Treatment	4th-Month Mepolizumab Treatment	12th-Month Mepolizumab Treatment	*P*
FEV1, % predicted	62.18 ± 15.70	75.04 ± 17.01	84.11 ± 12.52	**<.001**
FVC, % predicted	68 (35-89)	82 (46-98)	90 (51-124)	**<.001**
FEV1/FVC	81 (58-106)	81.5 (64-108)	88 (76-110)	**.027**
ACT scores	14 (8-20)	-	22 (12-24)	**<.001**
Asthma exacerbations	4 (2-12)	-	1 (0-6)	**<.001**
Unplanned ER visits	4 (1-12)	-	0 (0-6)	**<.001**
Hospitalization	1 (0-12)	-	0 (0-2)	**<.001**
Duration of hospitalization (days)	5 (0-12)	-	0 (0-12)	**<.001**
Eosinophil count (/mm^3)	850 (120-6880)	80 (10-450)	80 (20-390)	**<.001**
Serum IgE level (IU/mL)	119 (17-2500)	122 (16-1130)	161 (22-1869)	**.035**
OCS (mg/day)	4 (0-16)	-	0 (0-4)	**<.001**
Asthma treatment				**.042**
Well-controlled asthma	-		45 (79)	
Partially controlled asthma	23 (40.4)		7 (12.3)	
Poorly controlled asthma	34 (59.6)		5 (8.8)	

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACT, asthma control test; ER, emergency room; OCS, oral corticosteroids; Ig, immunoglobulin. $P < 0.05$ was considered statistically significant.

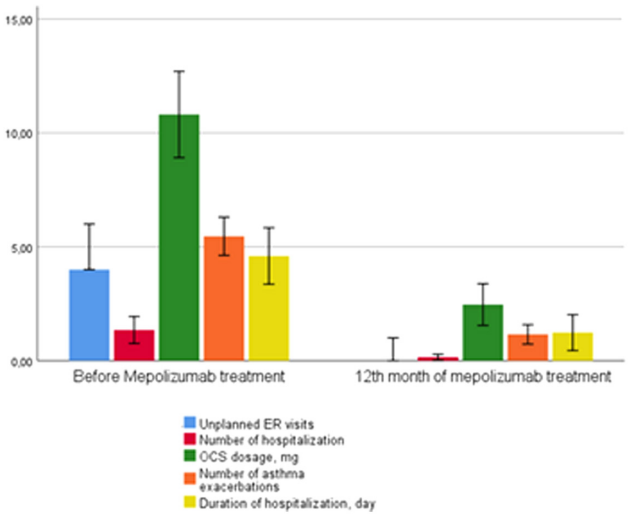

Figure 2. Change in the number of hospitalizations, asthma exacerbations, unplanned ER visits, duration of hospitalization, and daily OCS dosage during mepolizumab treatment. ER, emergency room; OCS, oral corticosteroids.

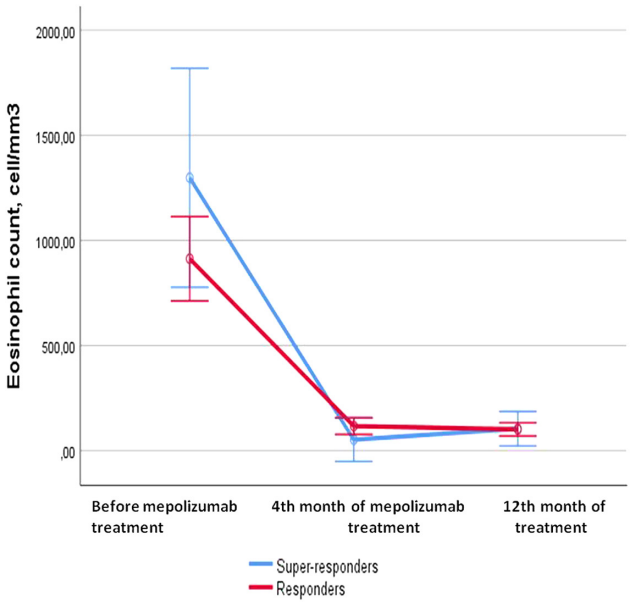

Figure 4. Blood eosinophil count in super-responders and responders during omalizumab treatment.

scores with 6 months of mepolizumab treatment. Caminati et al[19] observed a 6-point change in ACT scores and a 5% change in FEV1 with 6 month omalizumab treatment. In another study, 12 months of treatment with mepolizumab resulted in a ≥3-point increase in ACT scores in 80.65% of the patients and a ≥200 mL increase in FEV1 in 54.84.% of the patients. In the current study, 1-year treatment with mepolizumab was associated with a 6-point increase (0-13) in ACT scores and 19% change (0-51) in FEV1.

An important clinical benefit of mepolizumab is related to its ability to reduce the daily OCS dose, that is. the steroid-sparing effect. In the randomized, controlled SIRIUS study, 6 months of treatment with mepolizumab allowed 54% of the patients to reduce their daily steroid dose by at least 50% as compared to the baseline.[3] Montero-Perez et al[13] reported that 60% of their patients had reduced daily steroid requirements with mepolizumab therapy. Again, in another report, at least 50% reduction in daily corticosteroid dose was achieved in 33% and 62.5% of the patients after 6 and 12 months of treatment with mepolizumab, respectively.[12] Among our patients, 84.2% experienced at least a 50% reduction in daily OCS dose with 1-year treatment of mepolizumab, in line with the previously published figures.

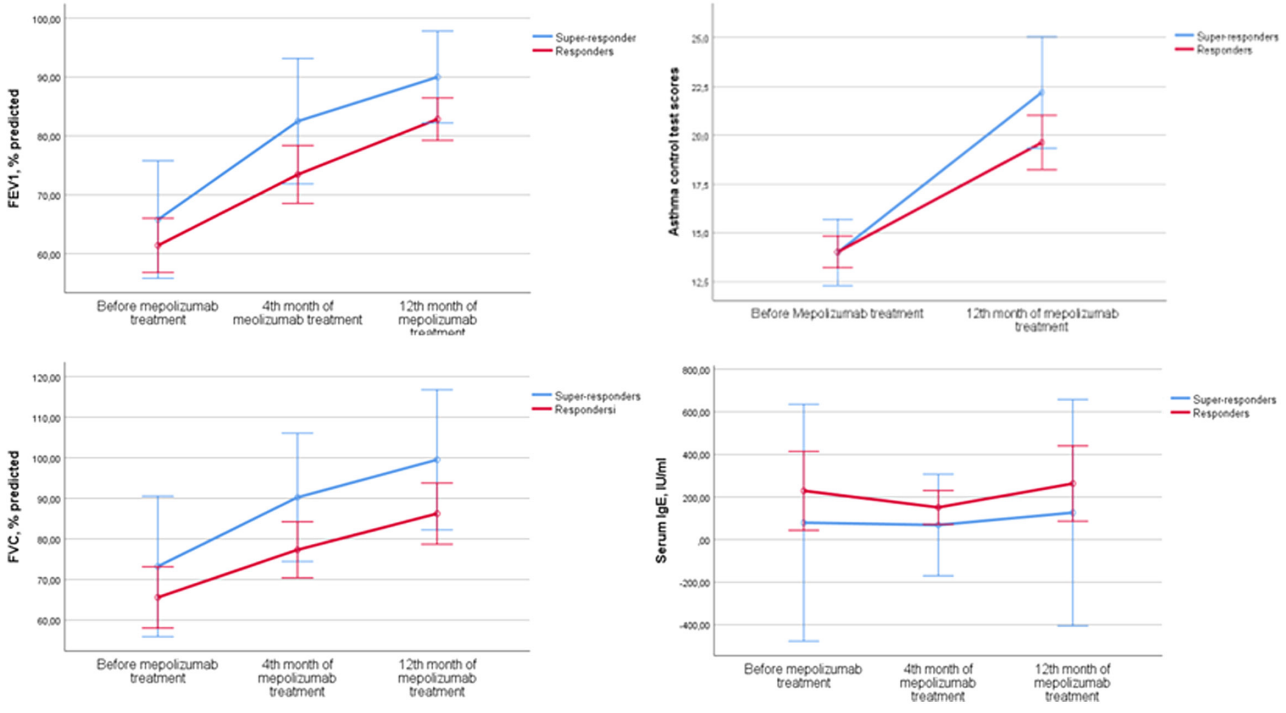

Figure 3. Change in clinical and laboratory parameters among super-responders and responders during mepolizumab treatment. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3. Comparison of Clinical and Laboratory Characteristics Among Super-Responder Patients Versus Responder Patients

	Super-responders (n = 10)	Responders (n = 47)	*P*
Age (years)	39 ± 14.02	48.02 ± 13.64	.108
Gender, female (n, %)	7 (70)	31 (66)	.805
BMI (kg/m^2)	26.09 ± 3.96	28.20 ± 4.51	.176
Duration of disease (years)	8 (3-15)	10 (2-30)	.242
Duration of treatment (months)	12 (4-19)	8 (4-24)	.298
Diagnosis (n, %)			.710
Allergic asthma	3 (30)	17 (36.2)	
Non-allergic asthma	7 (70)	30 (63.8)	
Allergen sensitivity (n, %)			.936
Non-atopic	7 (70)	29 (61.7)	
House dust mite	1 (10)	8 (17)	
Mold	1 (10)	4 (8.5)	
Pollen mixture	1 (10)	4 (8.5)	
Animal dander	0 (10)	2 (4.3)	
Accompanying allergic disease (n, %)			.558
None	4 (40)	12 (25.5)	
Allergic rhino-conjunctivitis	6 (60)	33 (70.2)	
Chronic urticaria	0	2 (4.3)	
Chronic rhino sinusitis	9 (90)	39 (47)	.580
Nasal polyps	8 (80)	27 (57.4)	.183
Aspirin sensitivity	5 (55.6)	16 (38.1)	.690
Blood Eosinophil count (cell/mm$^{3)}$	875 (360-6880)	795 (120-2390)	.500
Serum IgE (IU/mL)	99 (38-907)	136 (17-2500)	.908

BMI, body mass index; Ig, immunoglobulin.

Super-responders among patients receiving mepolizumab treatment represent a relatively new concept, with no clear-cut consensus on its definition.[20-22] Upham et al[22] attempted to define the super-responders using a modified Delphi process. Accordingly, the minor criteria included the absence of asthma exacerbations, major improvement in asthma control, and absence of the need for ACS, and the minor criteria included a 75% reduction in asthma exacerbations, well-controlled asthma, and ≥500 mL increase in FEV1. Improvement in at least 3 criteria with 2 of them being in the major criteria category was defined as super-responder. In Kavanagh et al's[21] study involving 99 patients with severe eosinophilic asthma and receiving mepolizumab therapy, a ≥50% reduction in asthma exacerbations and OCS need was used to define super-responders, although these authors failed to identify any clinical, laboratory, and demographic differences between super-responders and responders in terms of age, gender, atopy status, smoking status, and blood eosinophil parameter. In Harvey et al's[20] study involving 309 patients with eosinophilic asthma, patients with maximum Asthma Control Questionnaire (ACQ) scores (25% of the study population), and those with well-controlled asthma after 6 months of treatment with mepolizumab were defined as super-responders. As compared to responders, super-responders were more likely to be females, have lower baseline BMI and shorter duration of asthma, have higher frequency of nasal polyps, be non-smokers, and have higher IgE levels. On the other hand, the criteria used to define super-responders by Eger et al[23] included asthma control with 2 years of treatment with anti-IL-5 therapy, no use of OCS within the past 3 months, FEV1 ≥ 80% predicted, FENO < 50 ppb, and well control of comorbidities such as chronic rhinosinusitis and nasal polyps. Super-responders in that study had shorter asthma history, adult-onset asthma, higher baseline FEV1, and lower BMI and were more likely to be free of nasal polyps. In our study, super-responders and responders were comparable in terms of demographic, spirometric, or laboratory parameters. Due to a lack of consensus regarding the definition of super-responders, all patients experiencing dramatic improvements in any of the assessed parameters were considered to be super-responders in our study. Thus, our super-responder patients consisted of those with no asthma exacerbation, ER visits, hospitalizations, and OCS requirement following mepolizumab treatment and those with at least 6-point increase in ACT scores and ≥15% increase in FEV1. Due to the adoption of different criteria for super-responders, the study results may also vary. Furthermore, the pathogenesis of asthma is particularly complex in patients with severe asthma, and treatment outcomes may be determined not only by the endotypes but also by the phenotypic characteristics of the patients.[24,25] Therefore, the identification of

patients with pure eosinophilic endotype among the overall population of asthmatic patients may be a challenging task.

In conclusion, our results suggest that mepolizumab may be an effective therapeutic option for patients with SA, consistent with the published data. On the other hand, patients who were considered to be super-responders to mepolizumab treatment were not significantly different from the remaining group of patients in terms of the criteria assessed in our study. Obviously, further studies are warranted to better define the super-responders among patients with SA who receive mepolizumab treatment.

Ethics Committee Approval: This study was approved by Ethics committee of Karatay University, (Approval No: 2020/013).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.A.; Design – E.A., G.A.; Supervision – G.A.; Funding – E.A.; Materials – E.A. Data Collection and/or Processing – E.A.; Analysis and/or Interpretation – E.A., G.A.; Literature Review – E.A., G.A.; Writing – E.A., G.A.; Critical Review – E.A., G.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Harrison T, Canonica GW, Chupp G, et al. Real-world mepolizumab in the prospective severe asthma REALITI-A study: initial analysis. *Eur Respir J*. 2020;56(4). [CrossRef]
2. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651-659. [CrossRef]
3. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197. [CrossRef]
4. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360(10):973-984. [CrossRef]
5. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with BioLogicals (Benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of BioLogicals in severe asthma. *Allergy*. 2020;75(5):1023-1042. [CrossRef]
6. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;9: CD010834. [CrossRef]
7. Asthma management and prevention for adults and children older than 5 years. *GINA Updated 2021*. Available at: www.ginaasthma.org
8. Diffucult-to-treat and severe asthma in adolescent and adult patients Diagnosis and Management. *GINA 2021*. Available at: wwwginaasthmaorg
9. Nguyen VN, Chavannes N, Le LT, Price D. The Asthma Control Test (ACT) as an alternative tool to Global Initiative for Asthma (GINA) guideline criteria for assessing asthma control in Vietnamese outpatients. *Prim Care Respir J*. 2012;21(1):85-89. [CrossRef]
10. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test - European standards. *Clin Transl Allergy*. 2013;3(1):3. [CrossRef]
11. Gibson PG, Prazma CM, Chupp GL, et al. Mepolizumab improves clinical outcomes in patients with severe asthma and comorbid conditions. *Respir Res*. 2021;22(1):171. [CrossRef]
12. Taillé C, Chanez P, Devouassoux G, et al. Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme. *Eur Respir J*. 2020;55(6). [CrossRef]
13. Montero-Pérez O, Contreras-Rey MB, Sánchez-Gómez E. Effectiveness and safety of mepolizumab in severe refractory eosinophilic asthma: results in clinical practice. *Drugs Context*. 2019;8:212584. [CrossRef]
14. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556. [CrossRef]
15. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5(5):390-400. [CrossRef]
16. Renner A, Marth K, Patocka K, Idzko M, Pohl W. Effectiveness of mepolizumab therapy in patients with severe eosinophilic asthma: Austrian real-life data. *Pulm Pharmacol Ther*. 2020;64: 101946. [CrossRef]
17. Cameli P, Bergantini L, d'Alessandro M, et al. A comprehensive evaluation of mepolizumab effectiveness in a real-life setting. *Int Arch Allergy Immunol*. 2020;181(8):606-612. [CrossRef]
18. Schleich F, Graff S, Nekoee H, et al. Real-word experience with mepolizumab: does it deliver what it has promised? *Clin Exp Allergy*. 2020;50(6):687-695. [CrossRef]
19. Caminati M, Cegolon L, Vianello A, et al. Mepolizumab for severe eosinophilic asthma: a real-world snapshot on clinical markers and timing of response. *Expert Rev Respir Med*. 2019;13(12):1205-1212. [CrossRef]
20. Harvey ES, Langton D, Katelaris C, et al. Mepolizumab effectiveness and identification of super-responders in severe asthma. *Eur Respir J*. 2020;55(5). [CrossRef]
21. Kavanagh JE, d'Ancona G, Elstad M, et al. Real-world effectiveness and the characteristics of a "super-responder" to mepolizumab in severe eosinophilic asthma. *Chest*. 2020;158(2): 491-500. [CrossRef]
22. Upham JW, Le Lievre C, Jackson DJ, et al. Defining a severe asthma super-responder: findings from a Delphi process. *J Allergy Clin Immunol Pract*. 2021;9(11):3997-4004. [CrossRef]
23. Eger K, Kroes JA, Ten Brinke A, Bel EH. Long-term therapy response to anti-IL-5 biologics in severe asthma-A real-life evaluation. *J Allergy Clin Immunol Pract*. 2021;9(3):1194-1200. [CrossRef]
24. Schoettler N, Strek ME. Recent advances in severe asthma: From phenotypes to personalized medicine. *Chest*. 2020;157(3):516-528. [CrossRef]
25. Han YY, Zhang X, Wang J, et al. Multidimensional assessment of asthma identifies clinically relevant phenotype overlap: A cross-sectional study. *J Allergy Clin Immunol Pract*. 2021;9(1): 349-362.e18. [CrossRef]