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Phenotypic characteristics of exacerbations in severe asthmatics receiving biological agent treatment

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Abstract
Introduction: Identifying the eosinophilic, neutrophilic, or infectious phenotypes of exacerbations, particularly those occurring during biologic agent therapy, may provide valuable guidance for determining maintenance therapy for patients and preventing recurrent exacerbations. Our study primarily aimed to evaluate the clinical phenotypic features of exacerbations in patients with severe asthma receiving biologic agent therapy.
Methods: The first asthma exacerbation experienced by the patients after the 16th week of biological agent treatment was evaluated in terms of inflammatory phenotype and clinical features. White blood cell counts and C-reactive protein levels, related season, antibiotic use, and hospitalization during the exacerbation were recorded from patients' medical file records.
Results: Data of 75 patients with severe asthma receiving biological treatment were analyzed. Subjects were aged 48.0 (mean) ± 11.0 (standard deviation), and 52 (69.3%) of them were female. Biological agent used in treatment was omalizumab in 53 (70.7%) subjects and mepolizumab in 22 (29.3%) subjects. The majority of exacerbations in asthmatics treated with either biologic agent were eosinophilic. In patients using omalizumab, the median eosinophil count was significantly higher compared to those using mepolizumab (p=0.032).
Conclusion: Phenotyping of asthma exacerbations that persist in spite of biologic therapy will guide treatment adjustments and decisions to switch biologic agents to improve outcomes.

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Introduction

Asthma is a chronic airway disease that affects millions of people worldwide and constitutes a significant public health concern. In 2019, it was estimated that approximately 260 million people globally were diagnosed with asthma.[1] The Global Asthma Report collaboration reported that in the same year, asthma-related mortality reached 461,000 cases.[2] Asthma-related deaths represent the "visible tip of the iceberg" of the global asthma burden, with the majority being preventable. Inadequate disease management remains one of the primary causes of these fatalities.[2]

Severe asthma accounts for approximately 3.7% of individuals with asthma.[3] It is associated with high morbidity and mortality rates and imposes a significant economic burden.[4] Biologic therapies are recommended as adjunct treatments for these patients to help prevent exacerbations, improve symptoms, and reduce the use of inhaled and oral corticosteroids, particularly in corticosteroid-dependent asthma.[3] The management of the disease is affected by multiple factors, including symptom severity, type of inflammation, and treatment response.[5-7]

In contrast to the inflammatory phenotypes in asthmatics, the phenotypes that occur during exacerbations have been less extensively studied.[5] To optimize the management of severe asthma, the use of two broad phenotype classifications—clinical and inflammatory—has been proposed.[8] Identifying the eosinophilic, neutrophilic, or infectious phenotypes of exacerbations, particularly those occurring during biologic agent therapy, may provide valuable guidance for determining maintenance therapy for patients and preventing recurrent exacerbations.

Our study primarily aimed to evaluate the clinical phenotypic features of exacerbations in patients with severe asthma receiving biologic agent therapy. The secondary aim of the study was to identify factors that may contribute to the occurrence and severity of exacerbations.

Material and Methods

Study population and study design

Study population consisted of adult patients diagnosed with severe asthma, who were treated with omalizumab or mepolizumab between 2012 and 2024, and whose data were accessible through the hospital's information management system and/or patient records. The patients were diagnosed with "severe asthma" according to the latest Global Asthma Initiative guidelines. The indications for omalizumab and mepolizumab treatments were determined according to the American Thoracic Society/European Respiratory Society guidelines.[3,9,10] Asthma exacerbation is defined as a condition in which patients experience worsening of one or more of the symptoms of shortness of breath, cough, wheezing, and chest tightness, and requires systemic corticosteroid treatment for at least 3 days.[9]

In our study, the first exacerbation experienced by the patients after the completion of the 16th week of biological agent treatment was evaluated with regard to inflammatory phenotype and clinical features. Patients who were receiving biologic agent therapy but continued to use oral corticosteroid treatment were excluded from the study to avoid potential interference of steroid therapy on peripheral blood measurements. Also, patients who did not experience any exacerbations after starting biologic agent treatment were also excluded from the analysis within the study protocol.

The information of the patients included in our study was accessed through the hospital information management system and the patients' age, gender, smoking history, obesity, and atopy information were noted from the information recorded in the patient files.

Again, the patients' medical history regarding white blood cell counts and C-reactive protein (CRP) results, the season in which the exacerbation occurred, and antibiotic use and hospitalization during the exacerbation were recorded from the patient file records. According to the World Health Organization classification, individuals with a body mass index of 30 or higher are considered obese patients.[11] To determine whether exacerbations in patients with severe asthma are eosinophilic or neutrophilic, a laboratory value of 100/μL for eosinophils, 7700/μL for neutrophils, and a neutrophil percentage cutoff value of 70% were used.[12,13]

Statistical analysis

Data presentation for categorical variables was performed using frequencies and percentages, while numerical data were presented using means and standard deviations or medians and minimum–maximum values. For numerical variables, the normality of distribution was tested using theKolmogorov–Smirnov test. Normally distributed data were reported as mean ± standard deviation, while nonnormally distributed data were reported as median and minimum-maximum values.

Statistical analysis was conducted by SPSS 22 software. Continuous variables were compared using independent sample *t*-test if normally distributed, whereas with the Mann–Whitney U test, otherwise. For the comparison of categorical data, the Yates Chi-square test (Continuity Correction) and Fisher's Exact test were used. The statistical significance level was considered as $p < 0.05$.

Results

Medical records of 135 patients diagnosed with severe asthma treated with biologic agents were reviewed. Of these, 46 patients did not experience any exacerbations after initiating biologic agent therapy. In addition, 14 patients who benefited from biologic therapy but could not completely discontinue low-dose maintenance steroid treatment were excluded from the study. As a result, data of 75 patients diagnosed with severe asthma receiving biological treatment were analyzed.

The mean age of the study population was 48.0 ± 11.0 (mean ± standard deviation), and 52 (69.3%) of them were female. Among the patients, 70.7% (n=53) were using omalizumab, and 29.3% (n=22) were using mepolizumab.

The characteristics of the 75 patients included in the study are given in Table 1.

The comparison of variables such as age, gender, the season in which the exacerbation occurred, smoking history, obesity status, eosinophilic/neutrophilic exacerbation distribution, atopy status, the necessity of antibiotic use, hospital admission, WBC, neutrophil, neutrophil percentage, median eosinophil value, and CRP with the biological agents used by patients during their first asthma exacerbation is presented in Table 2. More than half of the exacerbations were eosinophilic both in patients using omalizumab and in patients using mepolizumab (69.8% and 54.5%, respectively). In patients using omalizumab, the median eosinophil count was significantly higher compared to those using mepolizumab (310.0 (10–3690), 145.0 (40–1410) respectively; p=0.032). No statistically significant differences were found between the omalizumab and mepolizumab groups for other variables.

Discussion

Determining the phenotypic characteristics of asthma exacerbations will guide the prevention of recurrent attacks and the shaping of treatment management in severely ill patients receiving biologic agent treatment. In this study, which included 53 omalizumab- and 22 mepolizumab-treated severe asthmatic patients, it was observed that eosinophilic inflammation was dominant in both groups in the first asthma exacerbation that occurred after the 16th week of treatment. The median eosinophil count was higher in patients receiving omalizumab than in those receiving mepolizumab. There was no difference in the distribution of inflammatory types of exacerbations, CRP levels, need for antibiotic use, and frequency of hospitalization between the two biologic agent treatment groups.

Objectively endotyping patients with severe asthma by measuring type 2 inflammatory biomarkers is an important way to unravel the mechanisms underlying respiratory diseases, prevent asthma attacks, and most importantly provide a precision-based approach by selecting the appropriate treatment for each patient. However, this task is becoming increasingly complex as the diversity of biological treatments increases day by day.[14]

Table 1 Demographic and clinical data of the study population (n = 75).

Age; years (mean ± SD)	48.0±11.0
Female gender	52 (69.3)
Biological agent	
Omalizumab	53 (70.7)
Mepolizumab	22 (29.3)
Smoking history	26 (34.7)
Obesity	32 (42.7)
Atopy	
None	24 (32.0)
Perennial	31 (41.3)
Seasonal	2 (2.7)
Mixed	18 (24.0)

Data are given as n(%), unless otherwise stated. SD: standart deviation.

Asthma has been one of the best known pulmonary pathologies for years. It is characterized by airway inflammation, bronchial hyperreactivity, and usually reversible bronchial obstruction. However, in spite of rapid developments in asthma treatment, approximately 10% of patients have severe uncontrolled asthma although treated with high-dose inhaled corticosteroids and ß2-adrenergic agonists.[15,16] This group of patients also experience frequent unpredictable severe exacerbations requiring courses of corticosteroids and/or hospitalizations.[17] Three classes of monoclonal antibodies targeting type 2 inflammatory pathways are currently available to treat severe asthma. These agents, antiIgE, anti-IL-5/Rα, and anti-IL-4Rα, provide patient benefits by reducing OCS, decreasing exacerbation rates, and improving asthma control.[18,19] Furthermore, agents targeting epithelial cytokines known as “alarmins” (TSLP, IL-25, and IL-33) have recently been developed as new options for treating asthma for patients with unmet needs.[20]

With the increasing variety of biologic treatments, uncertainty has emerged regarding agent selection, recognition of treatment failure, and appropriate steps and timing for switching from one biologic to another.[21] In spite of all these biological agent options, inadequate clinical response has been reported in 10% of patients receiving biological treatment.[22] The concept of “asthma remission” needs to be defined very well during treatment with biologicals. The definition of remission includes various aspects of the disease such as symptoms, exacerbations, lung function, and airway inflammation. Failure to achieve remission is an indication that another monoclonal antibody should be used.[21,23] In this context, knowing the nature of exacerbations in severe asthmatic patients treated with biologics is very important for the future treatment plan. The present study results reveal that most of the patients treated with both omalizumab and mepolizumab had eosinophilic exacerbations. The exacerbation endotypes following eosinophilic inflammation were noneosinophilic and nonneutrophilic, eosinophilic and neutrophilic, and neutrophilic exacerbations. The distribution of exacerbation endotypes did not show statistically significant differences between patients using omalizumab and mepolizumab. The fact that most of the exacerbations in severe asthmatics using omalizumab or mepolizumab treatment are of the eosinophilic endotype suggests that the use of biologics that will better control eosinophilia in the ongoing treatment of these patients will be beneficial.

In the present study, there were no statistically significant differences in terms of hospitalization rates, need for antibiotic use, and serum CRP levels during asthma exacerbations in patients using omalizumab and mepolizumab.

The median eosinophil count recorded during exacerbations in patients treated with mepolizumab was significantly lower compared with patients treated with omalizumab. This is consistent with recent large-scale studies on the effects of omalizumab and mepolizumab on peripheral blood eosinophil counts, which have shown that eosinophil counts were significantly higher in patients treated with omalizumab than in patients receiving mepolizumab.[24,25]

Table 2 Comparison of clinical and laboratory parameters during the first exacerbation after 16 weeks of biological treatment in subjects treated with omalizumab and mepolizumab (n = 75).

	Omalizumab (n = 53)	Mepolizumab (n = 22)	p
Age; years (mean ± SD)	47.8 ± 10.9	48.5 ± 11.5	0.804
Female gender	36 (67.9)	16 (72.7)	0.892
Smoking history	19 (35.8)	7 (31.8)	0.946
Obesity	23 (43.4)	9 (40.9)	1.000
Exacerbation season			
Winter	17 (32.1)	9 (40.9)	0.775
Spring	10 (18.9)	2 (9.1)	
Summer	11 (20.8)	5 (22.7)	
Autumn	15 (28.3)	6 (27.3)	
Exacerbation type			
Eosinophilic	37 (69.8)	12 (54.5)	0.097
Neutrophilic	4 (7.5)	1 (4.5)	
Both eosinophilic and neutrophilic	6 (11.3)	3 (13.6)	
Noneosinophilic nonneutrophilic	6 (11.3)	6 (27.3)	
WBC count (/μL); median (min-max)	8700.0 (4890-19200)	8470.0 (3700-15750)	0.749
Neutrophil (/μL); median (min-max)	4740.0 (2400-13100)	5475.0 (2500-8950)	0.930
Neutrophil % (mean ± SD)	57.9 ± 10.9	60.9 ± 12.2	0.290
Eosinophil count (/μL); median (min-max)	310.0 (10-3690)	145.0 (40-1410)	0.032
CRP (mg/dL); median (min-max)	4.5 (0.1-76.5)	4.6 (0.5-115)	1.000
Antibiotic use	28 (52.8)	8 (36.4)	0.296
Hospitalization	6 (11.3)	1 (4.5)	0.666

Data are given as n (%), unless otherwise stated. WBC: White blood cell, CRP: C-reactive protein, SD: Standard deviation.

When evaluating the limitations of our study, the retrospective design and the fact that it was conducted in a single center can be considered major constraints. In addition, the biomarkers to be used for endotype determination in patients with severe asthma have been clearly defined in the GINA 2025 guidelines.[3] According to these recommendations, the cut-off value for peripheral blood eosinophil count as an indicator of type 2 inflammation is 150 cells/μL. However, this threshold has not yet been clearly established in patients receiving biologic therapy. A study published in 2021 reported that peripheral eosinophil levels may be suppressed during biologic treatment and, therefore, used a cut-off value of 100 cells/μL to define peripheral eosinophilia in this patient population.[10] In addition, since our study was retrospective, the exact timing of blood sample collection was unknown, and potential within-day variations in eosinophil counts could not be considered. Based on this finding, our study adopted the same cut-off value to avoid overlooking eosinophilic exacerbations. Although the lack of a universally accepted threshold in the literature represents a limitation of our study, we believe that our findings provide a valuable reference and foundation for future research in this field.

The strengths of our study include the limited number of investigations addressing the phenotypes of asthma exacerbations and the comprehensive, multidimensional evaluation of exacerbations, which enhances the significance of our findings. Moreover, our study provides foundational data that may serve as a reference for future research focusing on exacerbations in patients receiving biologic therapy.

Conclusion

Identifying the clinical and inflammatory phenotypes of ongoing asthma exacerbations in spite of biologic therapy can guide treatment optimization, improve patient outcomes, and inform the selection and adjustment of biologic agents. Although some patients with severe asthma may benefit from biologic therapy, this patient population is highly heterogeneous. Therefore, further comprehensive studies examining exacerbations under biologic therapy are warranted.

Data Availability

The data set used and/or analyzed during the present study is available upon reasonable request.

Ethics Statement

The study was conducted in accordance with the ethical standards outlined in the Helsinki Declaration and its subsequent amendments, and it was approved by Ankara Atatürk Sanatoryum Training and Research Hospital Ethics Committee (Approval Date: 12.06.2024, Approval Number: 2024-BÇEK/86).

Disclaimers

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Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

KA and FA constructed the research hypothesis; HÇT, ÖA, OT, FDÇ, MY, ÖG, GTVS, and KA contributed substantially to data collection; HÇT, KA, and FA performed data analysis and interpretation; HÇT, KA, and FA substantially contributed to the writing of the manuscript. All authors have contributed substantially to obtaining the results and preparation of the manuscript in accordance with ICMJE criteria. All authors have reviewed the final manuscript, contributed to essential revisions, and approved the manuscript.

Conflict of Interest

All authors declare that no conflict of interest may have influenced either the conduct or the presentation of the research. Also, they declare not to have any conflicts of interest that may have influenced directly or indirectly the content of the manuscript.

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