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RESEARCH ARTICLE

Clinical profile of comorbidities in patients with severe asthma undergoing benralizumab biologic therapy

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Objective: This study aims to analyze the comorbidity profile of patients with severe asthma undergoing benralizumab therapy in a Romanian academic center, focusing on the impact of these comorbidities on disease management.

Methods: A retrospective analysis was conducted on 34 adult patients with severe asthma treated with benralizumab between 2020 and 2025 at the Pneumology Department of Mures County Clinical Hospital. Demographic, clinical, functional, and biological parameters were analyzed, including comorbidities, lung function tests, eosinophil counts, fractional exhaled nitric oxide, and Asthma Control Test scores. Non-parametric statistical tests were applied, with significance set at $p<0.05$.

Results: The study revealed a complex comorbidity profile. Cardiovascular diseases were most prevalent: hypertension was found in 91.2% of patients, ischemic heart disease in 47.1%, and heart failure in 17.6%. Pulmonary comorbidities included bronchiectasis (41.2%), pneumonia (82.4%), and obstructive sleep apnea (8.8%). ENT comorbidities were also frequent, with nasal polyposis in 35.3% and chronic rhinosinusitis in 32.4%. Metabolic conditions such as obesity (26.5%) and type 2 diabetes (29.4%) were common. Despite this burden, benralizumab therapy resulted in significant improvements in lung function, symptom control, and biomarkers, with eosinophil depletion, FeNO reduction, and improved ACT scores ($p<0.001$).

Conclusions: Patients with severe asthma treated with benralizumab present a high prevalence of cardiovascular, pulmonary, and metabolic comorbidities. Benralizumab therapy proved effective in reducing airway inflammation and improving clinical control, regardless of the comorbidity load. A multidimensional, personalized management approach remains essential for optimizing outcomes in this population.

Keywords: severe asthma, benralizumab, comorbidities, eosinophilic asthma, biologic therapy

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Introduction

Although it accounts for only about 5–10% of all asthma cases, patients with severe asthma are responsible for a significant percentage of the socioeconomic burden of the disease, due to direct and indirect medical costs, as well as reduced quality of life.

In Romania, recent data estimate a prevalence of asthma between 4% and 6% in the adult population, with a significant increase in the number of patients with severe forms over the past decade [1]. New therapeutic perspectives were offered to patients with eosinophilic or allergic phenotypes by the introduction of biological therapies into clinical practice. Benralizumab, a humanized monoclonal antibody against the IL-5 receptor α, binds with high affinity to eosinophils and basophils, inducing apoptosis through antibody-dependent cell-mediated cytotoxicity (ADCC). This results in a rapid and sustained depletion of circulating and tissue eosinophils, thereby reducing exacerbations and improving lung function in eligible patients. Access to benralizumab has been available in Romania since 2021 through the National Severe Asthma Programme, but actual data on the clinical characteristics of treated patients, particularly in terms of associated comorbidities, remain limited. Comorbidities such as chronic rhinosinusitis with nasal polyposis, obesity, gastroesophageal reflux (GERD), anxiety or depression [2] have a negative influence on asthma control and can alter the response to biological treatment [3, 4]. Bronchiectasis may develop as a result of chronic lung disease and may be the result of long-term uncontrolled asthma [5]. Severe asthma has a significantly higher prevalence of bronchiectasis, with an average of 36.6% compared to 3% in mild forms of the disease [6].

There are a number of extrapulmonary comorbidities that independently affect the progression of asthma. This highlights the importance of individualized disease management strategies that look beyond the lung system. In severe asthma, physical inactivity, obesity, symptoms of anxiety and depression, and systemic inflammation have been shown to be independently associated with a greater impairment of quality of life [2, 7, 8].

In this context, this study aims to analyze the profile of comorbidities in patients with severe asthma treated with benralizumab in an academic medical center in Romania, thus contributing to a better understanding of the clinical

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peculiarities of local practice and to the optimization of personalized therapeutic strategies.

Methods

This retrospective study included 34 patients who were treated in the Pneumology Department of the Mures County Clinical Hospital between 2020 and 2025 and benefited from the Ethics Committee agreement with the number 937/23.01.2025. Inclusion criteria were: age ≥18 years, confirmed diagnosis of severe asthma according to GINA 2024 criteria, eligibility for biologic therapy with benralizumab, and availability of complete clinical and follow-up data. Exclusion criteria were: diagnosis of other chronic pulmonary diseases (COPD, interstitial lung disease, pulmonary fibrosis), active malignancy, pregnancy or breastfeeding, and lack of informed consent.

The patients were examined through day hospitalization, continuous hospitalization or in the specialized ambulatory of Mures County Clinical Hospital. All participants expressed informed consent to participate in the study.

IBM SPSS Statistics version 26.0.0 was used to perform statistical analysis. Hetograms, Q-Q plots, and the Shapiro-Wilk test for normality were used to test for non-parametric data distribution, which was confirmed. The median (Q25-Q75) was used to express all quantitative data results. Frequency analysis was used to analyze qualitative data, with results expressed in n (%). Differences between the study groups were analyzed through the Mann-Whitney test or Kruskal Wallis test for independent samples, Wilcoxon test or Friedman's test accordingly for related samples and the Chi-Square test, respectively, setting the significance limit at a = 0.05.

For the patients included in the study, the following parameters were analyzed: demographic data (age, gender), time from the asthma diagnosis or from the onset of symptoms, associated comorbidities, respiratory functional samples (spyrometry), biomarkers (number of serum eosinophils, FeNo, Ig E). Comorbidities were identified based on prior documented diagnoses in the patients' medical records at baseline (before benralizumab initiation), complemented by additional evaluations when required. Cardiovascular comorbidities were confirmed through specialist consultation (cardiology), pulmonary conditions by pneumologists, and ENT disorders by otolaryngologists. Metabolic comorbidities (diabetes, obesity, dyslipidemia) were recorded based on laboratory findings and documented diagnoses. This multidisciplinary approach ensured accurate classification of comorbidities. For overtime evaluation, T0 represents baseline (before initiation of benralizumab), T1 represents the 3-month evaluation, T2 the 6-month evaluation, and T3 the 12-month evaluation.

Results

The study included 34 patients with severe asthma and benralizumab therapy. The mean age was 68 years (58-73), BMI (kg/m2) was 27.45 (23.09-33.36). All the subjects were non-smokers. The percentage of men was 44.1% and the majority came from urban areas 22 (64.7%). The median age of onset of asthma was 50 (37-59).

In decreasing order of frequency, the ENT comorbidities were allergic rhinitis (29.4%), nasal polyposis (35.3%) and rhinosinusitis (32.4%). Pulmonary comorbidities were bronchiectasis (41.2%), pneumonia (82.4%) and OSAS (8.8%). Metabolic Comorbidities were dislipidemia (32.4%), obesity (26.5%) and type 2 diabetes (29.4%).

The prevalence of cardiovascular comorbidities varied considerably among the study group. High blood pressure (hypertension) was overwhelmingly common in the benralizumab group, affecting 91.2% (31/34) of patients. Other cardiovascular conditions such as ischemic heart disease was present. Valvulopathies and congestive heart failure were observed in approximately 17–18% of benralizumab patients. No cases of pulmonary hypertension or atrial fibrillation were recorded. These findings highlight a significantly higher burden of hypertension among patients treated with benralizumab, pointing toward a higher prevalence of cardiovascular risk factors in those receiving the former biologics (Table I).

The symptoms patients reported were consistent with the comorbidities recorded. Thus, all patients reported dyspnea, cough, limitation of daily activities, nocturnal symptoms and fatigue. Other high-frequency symptoms were wheezing (94.1%), expectorative cough (94.1%), thoracic constriction (91.2%), nasal congestion (67.6%), rhinorrhea (70.6%) and headache (61.8%).

In the benralizumab-treated subgroup, the improvements over the course of therapy were pronounced and statistically significant across multiple parameters. Lung function demonstrated marked recovery; FVC increased from a median of 61% (53–72%) at baseline (T0) to 94% (83–107%) at T3, with a p-value less than 0.001, indicating substantial enhancement of pulmonary volume. Similarly, FEV1 improved from 48% (36–58%) to 80% (72–93%) ($p<0.001$), reflecting improved airflow and airway patency. The inspiratory Tiff index showed an increase from 60 to 67, representing better airway stability, while MEF50% increased from 18% to 46%, highlighting significant positive changes in small airway function.

A hallmark of treatment efficacy was the significant reduction in eosinophilic infiltration; median eosinophil counts decreased from 750 x10^3/μL (460–1035) at baseline to essentially zero (T2, and T3), with $p<0.001$. This near-complete depletion of eosinophils confirms the tar-

Table I. Cardiovascular comorbidities

Cardiovascular Comorbidities	Benralizumab (n=34)	p*
High blood pressure	31 (91.2%)	<0.001
Ischemic heart disease	16 (47.1%)	0.27
Valvulopathies	6 (17.6%)	0.48
Congestive heart failure	6 (17.6%)	0.48
Pulmonary hypertension	0 (0%)	-
Atrial fibrillation	0 (0%)	-

*Chi-square test

geted anti-eosinophil mechanism of benralizumab. Alongside, FeNO levels reduced from a median of 34 ppb at baseline to 18 ppb (11–21) at T3, with a p-value <0.001, indicating decreased airway inflammation. Clinically, the ACT score, which measures asthma control, improved significantly from 12 (11–14) at baseline to 25 (24–25) at T3, again with p<0.001, showcasing improved symptom management. The number of exacerbations dropped from a median of 3 (2–3) to zero (p<0.001), corresponding to a significant decrease in disease activity and exacerbation risk (Table II).

Exploratory analyses did not reveal statistically significant correlations between the number of comorbidities, age, and the degree of lung function improvement during follow-up, most likely due to the small sample size and the retrospective nature of our study. Larger cohorts and prospective research would be required to clarify these relationships.

Discussions

The results of our study confirm that patients with severe asthma treated with benralizumab present a complex comorbidity profile, with a high prevalence of cardiovascular, respiratory, and metabolic conditions. These findings are consistent with international literature, which indicates that patients with severe asthma have a significantly increased risk of multiple comorbidities [9], negatively impacting disease control and therapeutic response [4,6].

One of the most important observations of this study is the extremely high prevalence of arterial hypertension (91.2%) [7]. This result is higher than those reported in other European cohorts. For example, some studies reported a prevalence of 56% for hypertension in patients with severe asthma receiving biologic therapy [10,11]. These differences could be attributed to the older age of patients in our cohort and possibly to more rigorous cardiovascular comorbidity monitoring, given the recent access to biologic therapy in Romania. Similarly, in the study by Kavanagh et al. [12,13], hypertension was present in 43% of patients treated with benralizumab, while ischemic heart disease was reported in 18%, placing our results above the reported average and suggesting a higher cardiovascular burden in our population.

Regarding pulmonary comorbidities, the presence of bronchiectasis in 41.2% of patients is consistent with the meta-analysis conducted by Zhang et al. [6], which estimated a mean prevalence of bronchiectasis in severe asthma of approximately 36.6%, significantly higher than in mild forms of the disease (3%). This association indicates that uncontrolled chronic inflammation can lead to tissue remodeling and irreversible airway damage [2,4]. Our results strengthen the need for systematic screening for bronchiectasis in patients with refractory severe asthma.

ENT comorbidities were also frequent, particularly nasal polyposis (35.3%) and chronic rhinosinusitis (32.4%), which correspond to the eosinophilic patient profile described in the CALIMA [14] and SIROCCO [15] trials, where benralizumab demonstrated superior efficacy in reducing exacerbations in subgroups with nasal polyposis. Agache et al. [4,16], in the EAACI recommendations, emphasize the importance of assessing ENT comorbidities when selecting patients for biologic therapy, especially in the T2-high phenotype.

At the metabolic level, obesity (26.5%) and type 2 diabetes (29.4%) were commonly encountered in our cohort, in line with literature data [12,17], which report a prevalence of 25–40% for obesity in populations with severe asthma. These comorbidities have been associated in other studies with a poorer response to inhaled corticosteroids and a mixed inflammatory profile, supporting the choice of non-IgE-dependent biologic therapy [18].

The high comorbidity burden observed in our cohort has important clinical implications. First, systematic cardiovascular screening should be integrated in the routine management of patients eligible for biologics, particularly in elderly patients. Second, the frequent association with bronchiectasis highlights the need for regular imaging and microbiological assessment to optimize antibiotic strategies and prevent exacerbations. Third, the coexistence of ENT comorbidities such as chronic rhinosinusitis and nasal polyposis suggests a multidisciplinary approach with ENT specialists to enhance disease control. Finally, metabolic disorders like obesity and type 2 diabetes require lifestyle interventions and metabolic monitoring, as they may negatively influence asthma outcomes. These findings underline that a comprehensive, multidisciplinary follow-up is warranted in patients receiving biologic therapy.

The effectiveness of benralizumab in our cohort was remarkable, with significant improvements in lung function (median FEV1 increases over 30%), reductions in FeNO and eosinophil counts to zero, and a significant increase in ACT score. These outcomes are comparable to those re-

Table II. The improvements over the course of therapy

Study group (N=34)	T0	T1	T2	T3	p
FVC (%)	61 (53-72)	70 (62-88)	83 (72-96)	94 (83-107)	<0.001[a]
FEV1 (%)	48 (36-58)	62 (51-72)	67 (60-78)	80 (72-93)	<0.001[a]
ITiff	60 (51-68)	67 (69-72)	70 (60-75)	67 (61-75)	<0.01[a]
MEF50 (%)	18 (12-37)	30 (22-52)	36 (24-55)	46 (31-67)	<0.001[a]
Eosinophils (*103/µl)	750 (460-1035)	0 (0-100)	0 (0-0)	0 (0-0)	<0.001[a]
FeNO (ppb)	34 (25-45)	-	-	18 (11-21)	<0.001[b]
ACT score	12 (11-14)	21 (18-23)	23 (21-24)	25 (24-25)	<0.001[a]
Exacerbations	3 (2-3)	0 (0-0)	0 (0-0)	0 (0-0)	<0.001[a]

[a] Friedman test; [b] Wilcoxon test

ported in the literature and in observational studies such as that by González-Barcala et al. [19], where benralizumab led to a 70–80% reduction in exacerbations and significant improvement in quality of life, even in patients with multiple comorbidities [20,21].

An important aspect to highlight is that, despite the significant comorbidity burden, the therapeutic response was maintained, supporting the use of benralizumab as an effective and safe option, regardless of complex comorbidity profiles, especially in elderly or multi-morbid patients [22].

The limitations of our study include the small sample size, the lack of a control group, and its retrospective design, which may affect the generalizability of the results. Nevertheless, this study represents one of the few Romanian investigations specifically exploring the comorbidity profile in the context of benralizumab therapy and provides relevant data for local clinical practice.

Conclusion

Patients with severe asthma treated with benralizumab in our cohort presented a high prevalence of cardiovascular, respiratory, and metabolic comorbidities. Despite this comorbidity burden, benralizumab therapy was associated with significant improvements in lung function, airway inflammation, and symptom control. While our findings provide preliminary insights into the comorbidity profile of Romanian patients receiving biologic therapy, larger and prospective studies are required to better clarify the relationship between comorbidities, disease progression, and treatment outcomes. Until then, our results support the importance of a multidimensional, personalized management strategy in severe asthma.

Authors' contribution

CM (Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Writing—Original Draft Preparation, Writing—Review and Editing, Visualization, Supervision, Project Administration)
DH (Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing, Visualization)
MAV (Software, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing)
HKS (Software, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing)
ESI (Software, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing)
MBI (Software, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing)
AS (Software, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing)
GJ (Software, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing)
CEB (Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Review and Editing, Visualization, Supervision, Project Administration)

Conflict of interest

None to declare.

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