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Original Article

Characteristics of Patients with Severe Asthma in Primary and Secondary Care Settings Considered Eligible for Biological Therapy – the Bulgarian RECOGNISE Study

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Abstract

Introduction: Asthma is a major non-communicable disease. It affects both children and adults, but is the most common chronic condition among the former. While inhaled controller drugs stabilize the disease in most asthma patients, there are a certain number of people who suffer from severe asthma, which requires treatment escalation. Oral corticosteroids are usually added, but they are associated with various side effects that may limit their application. The introduction of biologicals targeting inflammatory mediators has opened a new era of asthma treatment highlighting the importance of patient characterization.

Aim: The RECOGNISE study sought to provide real-world insight into the characteristics of patients deemed eligible for biological therapy based on the judgment of the clinical investigator in primary and secondary care settings.

Materials and methods: The RECOGNISE study was a multicenter, observational, cross-sectional, one-visit study to characterize those severe asthma patients who are considered eligible for biological therapy among asthma patients in primary and secondary care settings in Bulgaria. Female and male asthma patients over 18 years of age were enrolled at four sites across the country. Severe asthma diagnosis had to be in agreement with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. Patients provided patient-reported outcomes on asthma control and health-related quality of life (HRQoL). Investigators completed specifically designed electronic case report forms (eCRFs), which included demographics and medical history. Medical history included lung function, biomarkers, comorbidities, exacerbations, Healthcare Resource Utilization (HRU), and prescribed asthma medication in the last 12 months as well as adherence to medication.

Results: Ninety-two severe asthma patients were enrolled in the Bulgarian RECOGNISE study (females prevailing – 65.22%). The median age (range) at diagnosis was 40 (18, 74) years. Most patients were never-smokers (n=72, 78.26%). For eligible patients, the median total EOS blood count was 431.0 cells/μl (n=19) and the blood EOS percentage was 5.95% (n=64). Chronic OCS use (treatment

maintenance with OCS for ≥50% of the previous year) was documented for 30.1% of eligible patients. The results from the Bulgarian RECOGNISE cohort show that 90.2% of the severe asthma patients from the primary and secondary care sites are eligible for treatment with the approved biologicals.

Conclusions: The current findings emphasize how crucial it is for patients with severe asthma to be monitored by an asthma specialist who can determine when it is time to switch to biologicals.

Keywords

asthma specialist, biological therapy, eligibility, severe asthma

INTRODUCTION

Asthma is a non-communicable chronic disease characterized by inflammation and narrowing of the small airways. Although it affects both children and adults, the disease is the most prevalent chronic condition in the former. It is estimated that nearly 300 million people in the world have asthma, and in 2019 asthma was the cause of approximately half a million deaths.[1,2] Across the globe, asthma affects between 1 and 18% of the population of individual countries, with the prevalence being lower in the lowest-income or rural countries. The variable extent of inflammation and airway remodeling in patients results in different combinations of symptoms, which include coughing, wheezing, chest tightness, and airflow limitation.[3,4] Furthermore, the airways of asthma patients are hyper-responsive to a number of triggers, which include exercise and inhaled irritants. It should be noted that the disease onset and severity are determined by a myriad of genetic and environmental factors.[5] A satisfactory disease control is established in most patients through administration of controller drugs, which include inhaled corticosteroids (ICSs), long-acting bronchodilator inhalers (LABAs), leukotriene receptor antagonists (LTRAs), and monoclonal antibody (anti-IgE). However, fractions of patients (less than 10%) suffer from severe asthma with an early-childhood onset through multiallergen sensitization. Severe asthma tends to persist throughout the lifetime of affected patients and is associated with the greatest morbidity and healthcare burden due to its difficult clinical management, regardless of treatment.[5]

The 2014 European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as "asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy". Misdiagnosis and underdiagnosis of asthma, which result in improper treatment choices, increase the avoidable morbidity and mortality rate and thus present a challenge, especially in the low- and middle-income nations.[6] This issue has highlighted the necessity for accurate diagnosis and the exclusion of similar conditions, as emphasized in the above-mentioned set of guidelines. Further, asthma is recognized as a highly heterogeneous condition including a number of phenotypes and subphenotypes. The most notable division would be between Th2-type asthma and non-Th2-type asthma, with the former including severe eosinophilic asthma – up to 70% of the patients.[5-7] The increasing number of novel severe asthma treatment prompted the introduction of these new guidelines, advancing clinical management through disease phenotype identification (clinical as well as molecular) and subsequent evidence-based treatment decisions.[8]

As stated in the guidelines' definition, severe asthma may remain uncontrolled even when patients receive the maximally optimized Global Initiative for Asthma (GINA) Step 4 or 5 therapy regimens of medium-/high-dose inhaled corticosteroids with a second controller, in addition to the treatment of contributing factors. To further complicate matter, severe asthma worsens upon decrease or cessation of high-dose regimens.[3]

Clinicopathological features established as important for asthma diagnosis and prognosis include age at onset, sex, allergy, and history of airflow limitation or exacerbations. Severe asthma pathophysiology is defined by the nature of underlying inflammation, with eosinophilic versus non-eosinophilic inflammation representing an important distinction.[9,10] Childhood-onset asthma is distinct from an adult-onset disease, with the former being commonly associated with an IgE-dependent sensitization toward an allergen, while the latter develops independently of an allergen. Exacerbation frequency and the extent of airflow limitation represent other phenotyping bases.[5] Lung function decline and worsening airflow obstruction are particularly prominent in cases of late-onset eosinophilic disease.[11]

While they have been the mainstay for severe asthma treatment, oral corticosteroids (OCS) are associated with considerable side effects, which include the development of metabolic disease (e.g., obesity and diabetes), osteoporosis, cataracts, cardiovascular complications (e.g., hypertension), and adrenal suppression. Use of OCS is also associated with a psychological burden (e.g., anxiety and depression), further compromising the patients' quality of life.[6] Minimization of OCS use has therefore become a major goal within the

clinical treatment of asthma, with advances in phenotyping allowing for more precise disease management, particularly through biologicals targeting immune factors, that is, mainly cytokines and cytokine receptors. Milestones in asthma precision medicine include the introduction of humanized monoclonal antibodies against IgE (e.g., omalizumab) for severe allergic asthma as well as IL-5 and IL-5-targeting antibodies (e.g. mepolizumab, benralizumab) for severe eosinophilic disease, in addition to the more recently developed monoclonals targeting IL-4 and IL-13.[12,13] Early research and clinical trials of anti-IL-5/anti IL-5Rα highlighted the importance of considering immune pathophysiology and disease phenotype stratification.[14,15] More specifically, anti-IL-5 therapy has been demonstrated as particularly effective in those suffering from severe eosinophilic asthma, when used in conjunction with ICS and LABA.[16,17] Further, anti-IL-5 allows for reducing OCS intake.[18,19] As IL-5 is a major mediator of eosinophil activation, blood eosinophil count is an important marker for anti-IL-5 treatment efficacy.[20] Taken together, advances in asthma treatment are inadvertently dependent on the identification of targetable disease features.

Severe asthma precision medicine is no exception to the necessity for effective patient stratification based on clinicopathological features and biomarkers.[21,22] Adequate and timely (early) stratification is often limited to specialized centers where such biologicals are administered. However, epidemiological data on severe asthma patients diagnosed and treated in primary care or other non-specialized settings have been limited.

AIM

In order to provide real-world evidence on the matter, the RECOGNISE study collected the characteristics of patients diagnosed with severe asthma who were evaluated for eligibility for biologic treatment in primary and secondary care settings. Bulgaria was part of the Phase 1 countries in RECOGNISE, along with the Czech Republic, Germany, Greece, Hungary, Poland, Romania, and Slovenia. Phase 2 countries included France, Italy, the Netherlands, and Spain. The present work presents results from the Bulgarian RECOGNISE cohort.

MATERIALS AND METHODS

Study design and participants

The RECOGNISE study was a multicenter, observational, cross-sectional one-visit study aiming at characterization of severe asthma patients who are considered eligible for referral to further clinical assessment for biological therapy among asthma patients in primary and secondary care settings in Bulgaria. Female and male physician-confirmed asthma patients over 18 years of age were enrolled at four sites across the country. Severe asthma diagnosis had to be in agreement with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. This would include asthma necessitating high-dose ICS plus one or more of the following controller drugs over the past 12 months: LABA, leukotriene modifier, theophylline, or continuous/near-continuous OCS (i.e., OCS maintenance for ≥50% of the previous year). Enrolled patients had at least one documented eosinophil (EOS, %) or absolute EOS count from the previous 12 months, in addition to 12 months of documented baseline information (in medical records or requested upon study visit). Medical information included asthma medication, OCS treatment, history of asthma exacerbations (number and severity), and pre-bronchodilator forced expiratory volume in the first second (FEV1). All patients signed an informed consent form, confirming that they understood the purpose of this study as well as the associated procedures. Exclusion criteria included respiratory comorbidities, concurrent asthma biologics (except for stable allergen immunotherapy), acute/chronic conditions that would limit the patient's ability to participate, as well as participation in an ongoing randomized trial that might influence assessment. Category I exacerbations included use of systemic corticosteroids, or temporary increase in a stable oral corticosteroid background dosage for at least 3 days or a single injectable dose of corticosteroids. Category II included an emergency department visit (<24 hours) due to asthma that required systemic corticosteroids. Category III included an inpatient hospital stay (≥24 hours) due to asthma.

The study has been approved by the Ethics Committee for Multicenter Trials of the Bulgarian Ministry of Health, Ref No KI-20/16.02.2017.

Primary and secondary objectives

The primary objective of the study was to describe the characteristics of patients considered eligible or non-eligible for biologic therapy by investigators. Secondary objectives included describing the proportion of patients with severe asthma deemed eligible for biologic therapy, describing the clinicopathological characteristics of severe asthma patients receiving chronic OCS treatment, determining the percentage of severe asthma patients meeting label criteria, describing reasons for eligibility based on the specialty of investigators, describing reasons for patient referral to specialized care for further assessment, and describing exacerbation severity as well as Healthcare Resource Utilization (HRU) among patients with severe asthma.

Exploratory objectives

The RECOGNISE study also had a number of exploratory objectives. These included exploring the percentage of screened patients with asthma and severe asthma considered by investigators as eligible for biologic therapy, describing the proportion of patients deemed eligible by

investigators as well as label criteria, and describing the clinicopathological characteristics of patients with over two OCS bursts for exacerbations in the past year.

Data collection

Data collection was performed in addition to mandated interventions during the physician visit (e.g., examination and treatment). All data collection was carried out on the day of the single study visit. Patients provided patient-reported outcomes on asthma control and health-related quality of life (HRQoL). Investigators completed specifically designed electronic case report forms (eCRFs), which included demographics and medical history. Medical history included lung function, biomarkers, comorbidities, exacerbations, HRU, and prescribed asthma medication in the last 12 months as well as adherence to medication.

Statistical analysis

Descriptive statistical analyses were performed on the collected data. Categorical variables are described via frequency tables. Continuous variables are described using sample statistics (mean, standard deviation, quartiles, median, minimum, and maximum). For continuous endpoint variables, 95% confidence intervals for mean or proportion were also presented. In the current manuscript, data for the enrolled set (ES) of patients is presented. McNemar's test was used to evaluate the agreement between biological therapy label criteria (SPC of the therapies) and physician assessment, with the null hypothesis being that there is agreement and the alternative hypothesis suggesting disagreement.

RESULTS

Basic demographic and clinical characteristics of the cohort

A total of 92 patients were enrolled in the Bulgarian RECOGNISE study. Of these, 32 (34.78%) were male, and 60 (65.22%) were female. The median age (range) at diagnosis was 40 (18, 74) years. Six subjects were excluded: two were excluded due to having a lung function test after enrolment, two had a biomarker test after enrolment, and two had both. Subjects from the Bulgarian cohort had a median height of 165 cm and a median weight of 76 kg (median, BMI=27,9). 41.3% of patients were inactive as per WHO standard categories for the level of exercise, while 50% were partly active, and 7.7% were active **(Table 1)**. Most of the enrolled patients were either employed full-time (n=40, 43.48%) or unemployed (n=42, 45.65%), while 10.87% (n=10) worked part time. Of those employed, 29 (72.50%) did physical work, while 21 (52.50%) did intellectual work. Most patients were never-smokers (n=72, 78.26%), with 10 former and 10 current smokers (10.87% each). Chronic OCS use was reported in 25 (27.17%) of enrolled patients.

Table 1. Basic demographic characteristics of enrolled patients (n=92)

	Bulgaria N (%)
Number of patients	92 (100.00)
Height, cm	
Mean (SD)	165.25 (8.17)
Median (range)	165 (148, 194)
Q1, Q3	160, 170
Weight, kg	
Mean (SD)	77.85 (14.91)
Median (range)	76 (44, 115)
Q1, Q3	67.5, 88
Level of exercise (WHO standard categories)	
Inactive	38 (41.30)
Partly active	46 (50.00)
Active	8 (8.70)

Demographic and basic clinical characteristics based on eligibility

Median age at diagnosis was 40 years for eligible and 41 years for non-eligible patients, based on physician assessment. Most patients in both eligibility-based subgroups were female (66.3% of eligible and 55.6% of non-eligible patients). All patients of the Bulgarian cohort were white. 48.2% of eligible and 22.2% of non-eligible patients were not employed, 41.0% and 66.7% worked full-time, 10.8% and 11.1% worked part-time. Of those who were employed, 22.9% and 22.2% did intellectual work, while 28.9% and 55.6% did physical work. Most patients from both eligibility-based groups were never-smokers (78.3% of eligible and 77.8% non-eligible patients). The median number of pack years of former and current smokers was 10 for eligible and 21 for non-eligible patients **(Table 2)**.

Asthma-related clinical characteristics based on eligibility

The median total EOS count was 431.0 cells/µl for eligible (n=19) and 360 cells/µl for non-eligible (n=2) patients and the blood EOS count (in percent %) was 5.95% for eligible (n=64) and 6.00% for non-eligible (n=7) patients. The median total white blood cell count was 8,480 cells/µl (n=64) and 9,500 cells/µl (n=7). The median IgE count was 96.8 UI/ml for eligible (n=8) and not available for non-eligible patients. The FeNO level for Bulgarian patients was not determined. Chronic OCS use (treatment maintenance with OCS for ≥50% of the previous year) was documented for 30.1% of eligible patients and was not documented for non-eligible patients. Short courses of systemic corticosteroids (≥3 days) were documented for 84.3% and 77.8% of eligible and non-eligible patients, respectively. The median

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Table 2. Demographic and basic clinical characteristics based on eligibility

	Eligible N (%)	Non-eligible N (%)	Total N (%)
Number of patients	83 (100.00)	9 (100.00)	92 (100.00)
Age at diagnosis, year			
N	83	9	92
Mean (SD)	39.57 (15.70)	44.56 (14.43)	40.05 (15.57)
Median (range)	40 (1, 74)	41 (28, 71)	40.00 (1, 74)
Q1, Q3	30, 54	34, 53	32, 53.5
Sex			
Male	28 (33.73)	4 (44.44)	32 (34.78)
Female	55 (66.27)	5 (55.56)	60 (65.22)
Ethnicity			
White	83 (100.00)	9 (100.00)	92 (100.00)
Employment status			
Full-time	34 (40.96)	6 (66.67)	40 (43.48)
Part-time	9 (10.84)	1 (11.11)	10 (10.87)
Not employed	40 (48.19)	2 (22.22)	42 (45.65)
Work type			
Physical work	24 (28.92)	5 (55.56)	29 (31.52)
Intellectual work	19 (22.89)	2 (22.22)	21 (22.83)
Smoking status			
Former	9 (10.84)	1 (11.11)	10 (10.87)
Current	9 (10.84)	1 (11.11)	10 (10.87)
Never	65 (78.31)	7 (77.78)	72 (78.26)
Number of pack-years (years smoking × packs per day)			
N	18	2	20
Mean (SD)	13.67 (7.08)	21 (5.66)	14.40 (7.18)
Median (range)	10 (3, 25)	21 (17, 25)	13.00 (3, 25)
Q1, Q3	10, 20	17, 25	10, 20

prebronchodilator FEV1 was 1,390 ml in eligible (n=83) as well as non-eligible (n=9) patients. Most patients in both eligibility-based subgroups adhered to asthma medication (97.6% and 88.9%, respectively). A history of atopy was documented for 50.6% of eligible and 77.8% of non-eligible patients.

Asthma medication

At least one asthma medication used currently and/or in the last 12 months was documented for all patients from both eligibility-based subgroups **(Table 3)**. Of the eligible patients with asthma medication, none used prior asthma medication, 63% used current asthma medication, and 37% used prior as well as current asthma medication. Of the non-eligible patients, 55.6% used current asthma medication, and 44.4% used prior and current asthma medication. Based on the Anatomical Therapeutic Chemical (ATC) Classification System, most frequently used asthma medications were 'drugs for obstructive airway diseases' (R03) and corticosteroids (across different therapeutic subgroups). Most frequently used drugs for obstructive airway diseases were adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics (in 77.8% of eligible and 88.9% of non-eligible patients), selective beta-2-adrenoreceptor agonists (75.3% and 88.9%), anticholinergics (58% and 66.7%), leukotriene receptor antagonists (40.7% and 66.7%), glucocorticoids (23.5% and 22.2%), and xanthines (23.5% and 11.1%). Together with the glucocorticoids for obstructive airway diseases, systemic corticosteroids (H02) were the most frequently used corticosteroids (glucocorticoids in 38.3% of eligible and 33.3% of non-eligible patients; corticosteroids for systemic use in 6.2% of eligible patients), followed by locally acting intestinal corticosteroids (A07; 6.2% of eligible patients), and nasal corticosteroids (R01; 6.2% of eligible patients). Systemic antibiotics were also frequently used among patients of the Bulgarian cohort.

Table 3. Asthma medication used currently or in the last 12 months based on eligibility

	Eligible N (%)	Non-eligible N (%)	Total N (%)
Patients with asthma medication currently and in the last 12 months (total)	81 (100.00)	9 (100.00)	90 (100.00)
Patients with prior asthma medication only*			
No	81 (100.00)	9 (100.00)	90 (100.00)
Patients with concomitant asthma medication only**			
No	30 (37.04)	4 (44.44)	34 (37.78)
Yes	51 (62.96)	5 (55.56)	56 (62.22)
Patients with prior and concomitant asthma medication			
No	51 (62.96)	5 (55.56)	56 (62.22)
Yes	30 (37.04)	4 (44.44)	34 (37.78)
Patients with asthma medication of unknown date only***			
No	81 (100.00)	9 (100.00)	90 (100.00)

Exacerbations

A history of asthma exacerbations in the last 12 months was documented for 95.2% of eligible and 88.9% of non-eligible patients, with a median number of 1 and 2 exacerbations, respectively. Category I exacerbations were documented for 45.8% and 66.7% (median number of category I exacerbations of 1 and 1); category II exacerbations for 22.9% and 22.2% (median number of category II exacerbations of 1 and 1.5); and category III exacerbations for 45.8% and 55.6% (median number of category III exacerbations of 1 for both), respectively.

Healthcare resource utilization (HRU)

All patients visited a physician in the last 12 months (100% of eligible and non-eligible patients). GP visits were documented for 44.6% and 55.6%, specialist visits for 100% in each subgroup (mainly an asthma specialist (97.6% and 100%), respectively. Hospitalizations in the last 12 months were documented for 55.4% of eligible and 55.6% of non-eligible patients; 19.3% and 44.4% had an emergency visit; 18.1% and 22.2% had been on sick leave **(Fig. 1)**. The median number of secondary specialists and emergency visits was 4 for eligible and 6 for non-eligible patients. Visits to

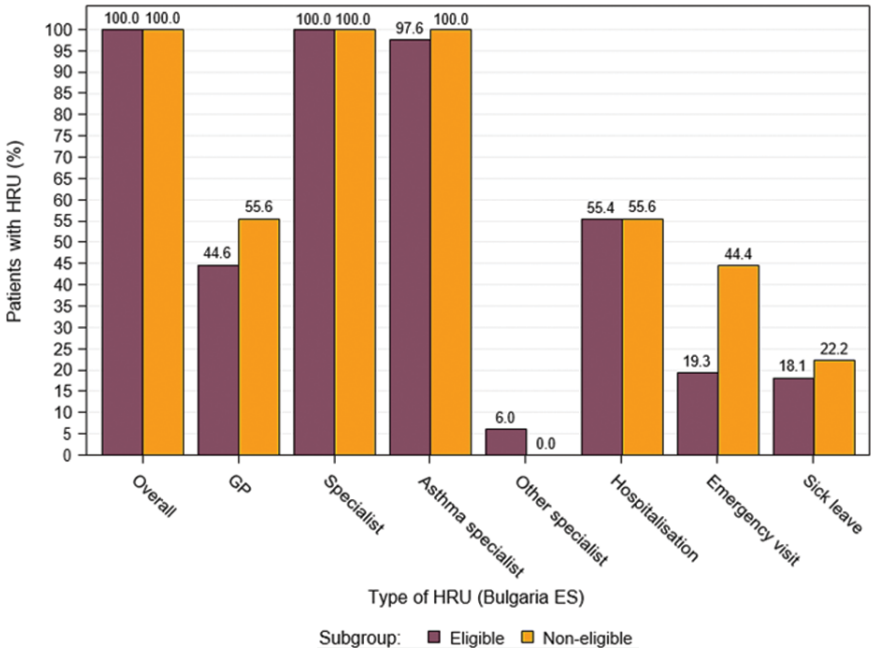

Figure 1. Proportion of patients with healthcare resource use (HRU) stratified by eligibility (patient-based) (Bulgaria ES). Overall percentage represents patients with at least one HRU.

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a GP (median of 4 and 5) were more common than to an asthma specialist (median of 3 for both), while the latter were more common than visits to another specialist (median of 2 for eligible patients). The median number of emergency visits was 1 and 1.5 for eligible and non-eligible patients, respectively. The median number of days in hospital was 5 and 8, respectively, while the median number of days on sick leave was 10 and 7.5. The median number of days of HRU was 4 for eligible and 8 for non-eligible patients.

Comorbidities and Charlson Comorbidity Index (CCI)

The most frequent comorbidities among Bulgarian patients were untreated cataracts (4.8% of eligible and 22.2% of non-eligible patients), untreated osteoporosis (4.8% and 11.1%), treated congestive heart failure (3.6% and 22.2%), treated GI conditions (2.4% and 11.1%), and untreated moderate to severe chronic kidney disease (2.4% for eligible patients). Other treated and untreated comorbidities that were neither OCS-related nor part of the Charlson Comorbidity Index (CCI) were reported for 44.6% and 3.6% of eligible as well as in 44.4% and 22.2% of non-eligible patients, respectively.

For the majority of patients (91.6% of eligible and 100% of non-eligible), the documentation of CCI-relevant comorbidities was complete (i.e. all respective comorbidities were answered with 'yes' or 'no'). Among these patients, congestive heart failure (6% and 22.2%), diabetes (uncomplicated; 13.3% of eligible patients), and moderate to severe chronic kidney disease (3.6% of eligible patients) were most common. Median CCI was 0 for both eligible and non-eligible patients. The median age-adjusted CCI (ACCI) was 2 for eligible and 3 for non-eligible patients. Most patients had an ACCI of 0 to 3 (42.2% and 33.3% had an ACCI of 0 or 1, while 38.6% and 44.4% had an ACCI of 2-3); for 2.4% and 11.1%, the ACCI was ≥6 **(Table 4)**. The median estimated 10-year survival based on the ACCI was 90.2% for eligible and 77.5% for non-eligible patients **(Fig. 2)**.

Questionnaires

All patients had valid questionnaires for both HRQoL (SGRQ) and asthma control (ACQ-6).[23,24] With scores of the SGRQ ranging from 0–100% (lower scores indicate less impairment and better HRQoL), the mean total score (95% CI) was 60.7% (56.9–64.4%) for eligible and 55.7% (39.8–71.7%) for non-eligible patients. Mean scores in the symptom domain were 70.8% (67.7–74.0%) and 65.7% (50.2–81.2%), those in the activity domain were 64.5% (60.2–68.8%) and 57.8% (40.7–74.8%), and those in the impact domain were 55.3% (50.8–59.9%) and 51.6% (34.8–68.3%), respectively **(Fig. 3)**. Mean ACQ-6 scores (95% CI), with lower scores indicating better asthma control, were 3.2 (2.9–3.4) for eligible and 2.9 (1.8–3.9) for non-eligible patients. 3.6% of eligible patients had well-controlled asthma (score ≤0.75), 6% and 11.1% of eligible and non-eligible patients had partly controlled asthma (score >0.75 – <1.5), 90.4% and 88.9% had not well-controlled asthma (score ≥1.5).

Table 4. Charlson Comorbidity Index* stratified by eligibility

	Eligible N (%)	Non-eligible N (%)	Total N (%)
Number of patients	83 (100.00)	9 (100.00)	92 (100.00)
Charlson Comorbidity Index (CCI)			
N	76	9	85
Mean (SD)	0.46 (0.94)	1.22 (1.99)	0.54 (1.11)
Median (range)	0 (0, 6)	0 (0, 6)	0 (0, 6)
Q1, Q3	0, 1	0, 2	0, 1
Age-adjusted Charlson Comorbidity Index (ACCI)			
N	76	9	85
Mean (SD)	1.91 (1.61)	2.78 (1.92)	2 (1.65)
Q1	1.00	1.00	1.00
Median (range)	2 (0, 9)	3 (1, 7)	2 (0, 9)
Q1, Q3	1, 3	1, 3	1, 3
ACCI categorical			
0 - 1	35 (42.17)	3 (33.33)	38 (41.30)
2 - 3	32 (38.55)	4 (44.44)	36 (39.13)
4 - 5	7 (8.43)	1 (11.11)	8 (8.70)
≥6	2 (2.41)	1 (11.11)	3 (3.26)

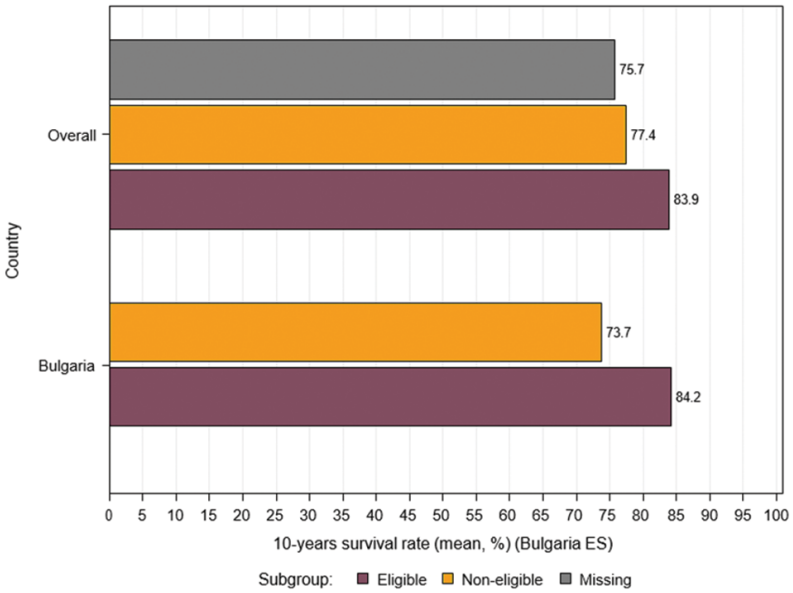

Figure 2. 10-year survival rate (mean, %) (Bulgaria ES).

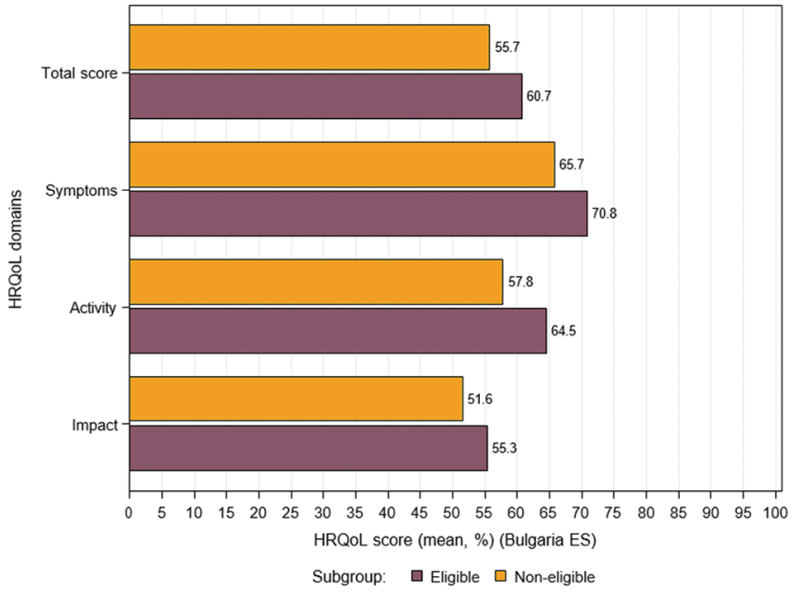

Figure 3. Questionnaires- HRQoL- Domain and total scores stratified by eligibility (Bulgaria ES).

Secondary objectives

Patient characteristics based on chronic OCS use

Patients with chronic OCS use were less frequently unemployed (44.0% and 46.3% of patients with versus without chronic OCS use, respectively), and had a higher number of pack-years (median of 20 and 10, respectively). Respective median IgE counts were 94.9 and 227.5 UI/ml. Short courses of systemic corticosteroids (at least three days) were documented for 80.0% and 85.1% of patients with versus without chronic OCS use. Adherence to asthma medication was documented for 96% versus 97.0%, and 68.0% versus 47.8% had a history of atopy.

Asthma medication, exacerbations, and HRU based on chronic OCS use

For 25 (100%) and 65 (100%) of patients with versus without chronic OCS use, at least one asthma medication used currently and/or in the last 12 months was documented; 60.0% and 63.1% used current asthma medication; 40.0% and 36.9% used prior and current asthma medication. The most frequently used corticosteroids that were more common in patients with chronic OCS use were systemic glucocorticoids (38.3% vs. 33.3%) and glucocorticoids for obstructive airway diseases (23.5% vs. 22.2%).

Asthma exacerbations in the last 12 months were documented for 100% and 92.5% of patients with versus without chronic OCS use (the median number of exacerbations

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was 2 and 1, respectively). The greater part of patients with category I and II exacerbations were those with chronic OCS use, while the opposite was true for category III exacerbations. With regard to HRU, 40.0% and 61.2% of patients with versus without chronic OCS use were hospitalized in the last 12 months; 32.0% and 17.9% had an emergency visit; 8.0% and 22.4% had been on sick leave. The median number of doctor and emergency visits for patients with and without chronic OCS use was 4. The median numbers of GP visits were 5 and 4, while the median numbers of visits to specialists and asthma specialists were the same for both subgroups (median of 3 in both cases). The median number of days in hospitalization was 6.5 and 5, while the median number of days of HRU was 0 and 5 for patients with versus without chronic OCR use, respectively.

Comorbidities based on chronic OCS use

With respect to the most frequently documented comorbidities, untreated osteoporosis was more common in patients with chronic OCS use (8% vs. 4.5%), as also observed for treated congestive heart failure (7.5% vs. 5.4%). Both treated and untreated comorbidities that were neither OCS-related nor part of the CCI were more common in patients without chronic OCS use. All frequently documented comorbidities of patients with a complete CCI, only diabetes was more common in patients without chronic OCS use. Fewer patients with chronic OCS use had a low ACCI (0–1; 32.0% vs. 44.8%). The mean SGRQ total score (95% CI) was 60.0% (52.7–67.3%) for patients with chronic OCS use and 60.2% (55.9–64.5%) for those without. Higher symptoms and impact scores were observed for patients with chronic OCS use, while activity scores were higher in those without chronic OCS use). Asthma seemed to be less well controlled in patients with chronic OCS use. The mean ACQ-6 score (95% CI) was 3.2 (2.9–3.4) in patients with chronic OCS use and 2.9 (1.8–3.9) in patients without. Not well-controlled asthma (score ≥1.5) was observed in 90.4% and 88.9% of patients in these subgroups, respectively. Based on currently approved EU labels for biological therapy (i.e. SmPCs for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab), 51% (n=47) of patients in the Bulgarian cohort were eligible for biological therapy. McNemar's test was used to determine whether label criteria and clinical judgment of the investigator agreed. Overall, McNemar's test suggested discordance between clinical judgment and label criteria ($p<0.0001$). All Bulgarian patients were enrolled by specialists, all of whom were pulmonologists. Main reasons for referral for biological therapy according to the investigator were 'high-risk patients' in 41.3% of cases, 'corticosteroid treatment' (high dose, long-term use & side effects) in 40.2%, and 'add-on specialist treatment' in 7.6%. The reason was unknown in 9.8% of cases.

Exploratory objectives

1.14% of all screened patients with asthma (n=7,283), and 24.5% of all screened patients with severe asthma (n=339) were eligible for biological therapy per clinical judgment of the investigator. Eligible per label criteria were 0.65% of all screened patients with asthma, and 13.9% of all screened patients with severe asthma. 49.4% of patients considered eligible by investigators proved to be eligible (i.e. patients were eligible as per label criteria). Severe asthma was observed in 4.65% of all screened patients with asthma. A median of 10 sick days were recorded in the Bulgarian cohort, which was among the lowest in the RECOGNISE study.

DISCUSSION

Severe asthma is increasingly recognized as a heterogeneous condition of diverse etiologies and molecular pathophysiology with overlapping symptoms.[4-6,8-10] The stratification of patients with distinct subtypes based on clinicopathological and asthma-specific biological characteristics is therefore imperative for efficient disease management through the selection of personalized treatment, particularly biological therapy, in an attempt to reduce corticosteroid use and the associated side effects.[25-29] The RECOGNISE study provides insights into clinical and biological characteristics of patients considered eligible or non-eligible for biological therapy as per the judgment of clinicians from twelve countries and 140 sites across Europe. The Bulgarian RECOGNISE study provided unprecedented insight into the profile of patients deemed eligible/non-eligible for biological therapy and a basis for comparison with overall European data.

In the Bulgarian RECOGNISE cohort, over 90% of patients were considered eligible for biological therapy, while 9.8% were non-eligible. Eligible and non-eligible patients were diagnosed at a similar adult age (median age [Q1–Q3] at diagnosis was 40 [30–54] years in eligible vs. 41 [34–53] years in non-eligible patients). The proportion of female patients was comparable between eligibility-based subgroups (66% vs. 56%). Eosinophilia was more common among eligible patients (median total EOS [Q1–Q3]: 431 [330–540] vs. 360 [250–470] cells/μl; median blood EOS in % [Q1–Q3]: 6 [2.4–8.7] vs. 6 [2.3–10]). In general, differences between eligibility-based groups with regard to age at diagnosis, female patient proportion, and eosinophilia prevalence were in agreement for the Bulgarian and the overall RECOGNISE cohorts.

Of note, a history of atopy was more common among non-eligible patients (78% vs. 50.6%) of the Bulgarian cohort, while the opposite was observed for the overall RECOGNISE cohort (30% vs. 50%). In the Bulgarian cohort, IgE levels were only determined for eight patients, all of which were eligible. Thus, no comparison could be made based on eligibility. Pre-bronchodilator FEV1 was the same between subgroups (median FEV1 in the last 12 months [Q1–Q3]: 1,390 [1,090–1,930] vs. 1,390 [1,220–1,640] ml), suggestive

of a comparable exacerbation risk, in agreement with European cohort data. The proportion of patients with exacerbations in the last 12 months was indeed similar (95% vs. 89%) between the two subgroups in the Bulgarian cohort as opposed to the overall RECOGNISE cohort where exacerbations were more common in eligible patients (87% vs. 53%). Chronic OCS use was more common in Bulgarian eligible patients (30% vs. 0%) as was also observed for the overall cohort (28% vs. 18%). The proportion of patients having undergone short courses of systemic corticosteroids was similar between the eligibility-based subgroups (84% vs. 78%) in the Bulgarian cohort, which was different from the tendency observed for the overall cohort where short courses of systemic corticosteroids were more common in eligible patients (77% vs. 45%). Of note, the level of inhaled nitric oxide was not determined for the Bulgarian cohort. In the total European cohort of RECOGNISE, a tendency toward higher exhaled NO was observed in eligible compared to non-eligible patients.

Visits to the asthma specialist within the last 12 months were comparable between eligible and non-eligible patients in the Bulgarian cohort (97.6% vs. 100%), while considerably more common in the former subgroup for the overall RECOGNISE cohort (93% vs. 68%). GP visits were more common for non-eligible patients (44.6% vs. 55.6%), which was in agreement with the overall cohort results (65% vs. 74%). Hospitalizations were equally common between the eligibility-based subgroups of the Bulgarian cohort (55.4% vs. 55.6%), while more common for eligible patients in the overall cohort (21% vs. 13%). In contrast to the overall cohort (19% vs. 9%), emergency visits were more common for non-eligible patients in the Bulgarian cohort (19.3% vs. 44.4%). Sick leave was slightly more common for non-eligible patients in the Bulgarian cohort (18.1% vs. 22.2%), while the opposite was observed for the overall RECOGNISE population (15% vs. 12%). Somewhat lower Charlson scores were observed in eligible Bulgarian patients (ACCI 0–1: 42.2% vs. 33%), which was in agreement with the results for the overall cohort (ACCI 0–1: 44% vs. 37%). Based on the SGRQ, impairment seemed to be lesser in eligible patients, indicating a better HRQoL in this subgroup, while the opposite was observed for the overall cohort. Based on the ACQ-6, asthma was somewhat less well-controlled in eligible patients of the Bulgarian cohort, which was in agreement with data for the overall RECOGNISE cohort.

90.2% of Bulgarian patients were considered eligible for biological therapy by investigators compared to 81% for RECOGNISE Phase 1 countries (Bulgaria included) and 52% for Phase 2 countries (including Germany). Among Phase 1 countries, Bulgaria was second only to Slovenia (91.26%) with regard to the proportion of eligible patients. As per approved EU labels[25-29], 51% of Bulgarian patients were eligible for biological therapy, relative to 64% for all phase 1 countries and 55% for Phase 2 countries (not incl. Germany).

The major reasons for referral to biological therapy according to the investigator were 'high-risk patients', 'corticosteroid treatment (high dose, long-term use & side effects), and 'add-on specialist treatment', which was in line with overall Phase 1 results.

Approximately one-quarter of Bulgarian patients were dependent on chronic OCS use (maintenance OCS for ≥50% of the previous year), which was a similar proportion to that observed for the overall RECOGNISE cohort. These patients tended to have somewhat higher eosinophil levels. While the IgE count of patients with chronic OCS use was considerably lower than that of patients without, a history of atopy was more common in the former subgroup. Short courses of systemic corticosteroids were slightly less common in patients with chronic OCS use in the Bulgarian cohort, while the opposite was observed for the overall RECOGNISE cohort. Exacerbations were more frequent in those frequently using OCS, which was in agreement with overall RECOGNISE results. The same was observed for emergency visits in both the Bulgarian and overall cohorts. Charlson scores were similar between OCS use-based subgroups as were ACQ-6 scores. It should be noted that doctor's and emergency visits were lowest in Bulgaria out of the countries included in RECOGNISE (both phases). Days in hospital recorded for the Bulgarian cohort were also among the lowest.

All investigators in the Bulgarian RECOGNISE were pulmonologists, which was in agreement with other Phase 1 countries, whether the majority of investigators were of the same specialization. This prevalence of pulmonologists as investigators was associated with the considerably higher proportion of patients deemed eligible (81%) in Phase 1 countries, including Bulgaria (90.2%), as opposed to the proportion in Phase 2 countries (52%), where the majority of specialists involved were general practitioners. This difference highlights the importance of having an asthma specialist to evaluate patients. It should be noted that a lower proportion of Bulgarian participants (51%) were also eligible for biological therapy based on approved EU labels when compared to Phase 1 patients (64%). The heterogeneous nature of the disease may require greater consideration and flexibility upon assessment, which an asthma specialist is able to provide. The Lancet Commission previously suggested that 'arbitrary' disease labels should not be the point of focus as opposed to the determination of measurable and treatable disease features.[30] Further, having the patient's medical history at their disposal, the pulmonologist should be able to consider various relevant factors that are beyond the competence of the general practitioner.

As an observational real-world study, RECOGNISE has certain limitations inherent to its design. One example would be the relatively small number of inclusion/exclusion criteria as compared to criteria employed in randomized controlled trials. However, it should be noted that the employed criteria were sufficient for minimizing the enrolment of patients with a misdiagnosis of asthma. As the local study teams selected study sites, site selection bias also cannot be excluded as a possibility. Since patients were recruited at hospitals, a bias toward patients with more

frequent HRU is quite possible. This would also imply a bias toward patients suffering from more severe disease. It should be noted that source data verification was carried out only for two sites per country. For the Bulgarian RECOGNISE study, this would mean 50%, which was highest among the proportion across all countries from both study phases (21%). A limitation specific to the Bulgarian RECOGNISE study was the lack of data on FeNO, which, along with IgE and eosinophils, is considered an important factor for the characterization of patient inflammatory profiles.

CONCLUSIONS

Taken together, the findings of the Bulgarian RECOGNISE study indicate that a considerable proportion of severe asthma patients may benefit from biological therapy (e.g., mepolizumab, reslizumab, benralizumab, omalizumab, and dupilumab) to improve disease management, allowing for a lower need for systemic corticosteroids and less associated side effects. The current study also highlights the importance of observation by a specialist, who is able to consider the intricacies of asthma as a condition that is considered ever more heterogeneous and complex.

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Характеристики пациентов с тяжёлой астмой в учреждениях первичной и вторичной медико-санитарной помощи, считающихся подходящими для биологической терапии – болгарское исследование RECOGNISE

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Резюме

Введение: Бронхиальная астма является серьёзным неинфекционным заболеванием. Оно поражает как детей, так и взрослых, но является наиболее распространённым хроническим заболеванием среди первых. В то время как ингаляционные контролирующие препараты стабилизируют заболевание у большинства пациентов с астмой, есть определённое количество людей, страдающих тяжёлой астмой, которая требует эскалации лечения. Обычно добавляют пероральные кортикостероиды, но они связаны с различными побочными эффектами, которые могут ограничивать их применение. Внедрение биологических препаратов, нацеленных на медиаторы воспаления, открыло новую эру в лечении астмы, подчеркнув важность характеристики пациента.

Цель: Исследование RECOGNISE было направлено на то, чтобы дать реальное представление о характеристиках пациентов, которые считаются подходящими для биологической терапии, на основе суждения клинического исследователя в учреждениях первичной и вторичной помощи.

Folia Medica

Материалы и методы: Исследование RECOGNISE представляло собой многоцентровое обсервационное перекрёстное исследование с одним посещением для характеристики тех пациентов с тяжёлой астмой, которые считаются подходящими для биологической терапии среди пациентов с астмой в учреждениях первичной и вторичной помощи в Болгарии. Пациенты с астмой женского и мужского пола старше 18 лет были зарегистрированы в четырёх центрах по всей стране. Диагноз тяжёлой астмы должен был соответствовать рекомендациям Американского торакального общества/Европейского респираторного общества (ATS/ERS). Пациенты сообщали о результатах контроля астмы и качества жизни, связанного со здоровьем (HRQoL). Исследователи заполнили специально разработанные электронные формы отчётов о случаях заболевания (eCRF), которые включали демографические данные и историю болезни. Медицинский анамнез включал функцию лёгких, биомаркеры, сопутствующие заболевания, обострения, использование ресурсов здравоохранения (HRU) и назначенные лекарства от астмы за последние 12 месяцев, а также приверженность к лечению.

Результаты: 92 пациента с тяжёлой астмой были включены в болгарское исследование RECOGNISE (преобладание женщин – 65.22%). Средний возраст (диапазон) при постановке диагноза составлял 40 (18, 74) лет. Большинство пациентов никогда не курили (n=72, 78.26%). Для подходящих пациентов медиана общего анализа крови EOS составила 431.0 клеток/ μl (n=19), а процент EOS в крови составил 5.95% (n=64). Хроническое использование OCS (поддерживающее лечение с помощью OCS в течение ≥ 50% предыдущего года) было задокументировано у 30.1% подходящих пациентов. Результаты болгарской когорты RECOGNIZE показывают, что 90.2% пациентов с тяжёлой астмой в учреждениях первичной и вторичной медико-санитарной помощи имеют право на лечение утверждёнными биологическими препаратами.

Заключение: Текущие результаты подчёркивают, насколько важно для пациентов с тяжёлой астмой находиться под наблюдением специалиста по астме, который может определить, когда наступает время перехода на биологические препараты.

Ключевые слова

специалист по астме, биологическая терапия, соответствие требованиям, тяжёлая астма