Severe Asthma Management, Patient Pathway, and Disease Burden in Russia: Country Results From Multi-Country Retrospective Cross-Sectional Study

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Research Article

Keywords: severe asthma, eosinophil levels, Russia, Asthma Control Test (ACT), HRQoL questionnaire

Posted Date: November 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1027666/v1

Abstract

Background

Severe asthma is a poorly controlled disease in Russia which leads to significant healthcare resource use and costs. However, little is known about its burden and management in a real clinical practice in Russia. Here we report the results obtained in the Russian population during an international cross-sectional study.

Methods

The study comprised two phases: in Phase I data were collected retrospectively from medical records, while Phase II was a cross-sectional collection of patient-reported outcomes and up-to-date data. For Phase I, adult patients with severe asthma according to ERS/ATS criteria were enrolled. Phase I patients were enrolled into Phase II if they signed a written consent form. Data on demographics, history of asthma and comorbidities, treatment approach, and healthcare resource utilization were obtained in both phases. In Phase II, asthma control and health-related quality of life (HRQoL) were also evaluated.

Results

A total of 315 patients were included in Phase I of the study, 106 (33.6%) of them entered Phase II of the study. The study population included more female (n=211, 67.0%) than male patients (n=104, 33.0%). Majority of subjects were either obese (n=103, 39.8%) or overweight (n=94, 36.3%). The most common comorbidity was cardiovascular disease (n=217, 71.4%), followed by chronic respiratory disease (n=198, 68.8%), including COPD and allergies. Mean (SD) age at diagnosis of asthma and severe asthma were 42.9 (16.0) and 53.1 (13.2) years, respectively. There were 268 (85.1%) patients who had at least one exacerbation during last 12 months. Most subjects had only one blood eosinophil count in the last 12 months (n=143, 81.3%). Mean (SD) FEV1 was 56.9 (20.4) % predicted. The mean (SD) last serum IgE/(RAST) value was 254.3 (249.7) ng/mL. Asthma management was generally in line with guidelines. Most patients had poorly controlled asthma according to the ACT and impaired HRQoL.

Conclusions

In Russia, severe asthma patients had poor disease control, high hospital admission rates and multiple comorbidities. Eosinophil and IgE level measurements are not considered routine tests which might be a barrier for appropriate phenotyping and treatment selection, including prescription of biologics in course of disease management.

Background

Many patients with asthma can be adequately controlled by use of treatment recommendations as described by the Global Initiative for Asthma (GINA) guidelines (1). However, for some asthma patients, despite attempts to control their disease following these recommendations, asthma control is not achieved. Landmark studies have shown that uncontrolled asthma remains a worldwide problem (2). This group of subjects with frequent exacerbations, uncontrolled symptoms and impaired health-related quality of life (HRQoL) has been defined as severe asthma patients (3). Severe asthma has been defined by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) as “asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids [SCS]) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy” (4). Severe asthma patients experience considerable morbidity (5) and are responsible for approximately 50% of the total health costs associated with asthma (6, 7).

Evidence shows that patients with severe asthma are comprised of complex, overlapping phenotypes, including severe eosinophilic asthma (8, 9). Early identification of patients with eosinophilic asthma in clinical practice is important because these patients are at risk of poor asthma outcomes (10). For these reasons, there is a need to assess severe asthma management and the patient care depending on asthma phenotypes. However, little is known about the burden and management of severe asthma patients in real clinical practice in Russia, and it is unclear what asthma phenotypes are present in those with severe asthma in Russia. Thus, the primary objective of this study was to describe the patient care pathway, disease management and patient/disease characteristics, including patient demographics, clinical characteristics, and healthcare resource use in severe asthma patients.

Methods

Study design

This study was an observational, descriptive, retrospective cross-sectional conducted in Russia, Saudi Arabia, Kuwait, and the United Arab Emirates. This manuscript focuses on the Russian population. The study consisted of two phases. At Phase I retrospective data on severe asthma patients was collected. Investigators from 12 sites in Russia screened site medical records dated from 01 January 2016 until site initiation visit (SIV, start at 31 May 2018, finish on 10 August 2018). Any patients aged 21 years or older with severe asthma diagnosis according to ERS/ATS definition have been included in the registry. Known participants of a clinical or cohort study were ineligible. The number of patients to be enrolled was not limited. Medical records of eligible patients were reviewed by investigators for extraction of data including, but not limited to clinical data, disease and treatment history, laboratory tests, including eosinophil and immunoglobulin E (IgE) level measurements, spirometry results during 12 months prior to SIV, number of exacerbations, and number of hospital admissions.

Asthma exacerbation was defined as an event that required use of systemic corticosteroids (SCS) or led to hospital admission, emergency room (ER) visit, mechanical ventilation, or doubling the oral corticosteroids (OCS) dose for patients receiving maintenance OCS.

Eligible patients enrolled in Phase I of the study, and who presented at the site for a routine visit, were invited to participate in Phase II of the study. Patients who refused to sign informed consent, or who presented a severe mental illness or other disease that could, in an investigator's opinion, alter participation in the study, were ineligible. The recruitment period for Phase I and II lasted 14 weeks. Participants were asked to complete the Asthma Control Test (ACT) and the Five level EuroQol five-dimension (EQ-5D-5L) HRQoL questionnaires. Investigators also extracted relevant data from the medical records, as done during Phase I.

Statistical analysis

Data were analyzed using descriptive statistics. Categorical and ordinal variables are presented as frequency and counts. Continuous variables are presented as mean values with standard deviation (SD). Analyses conducted to meet the primary objective (to describe the patient pathway, in terms of disease management and patient/disease characteristics) were also stratified by the last available eosinophil count. Analyses conducted to meet the secondary objectives (to describe the burden of severe asthma in terms of healthcare resource utilisation, impact of disease on HRQoL for overall, controlled, and uncontrolled severe asthma patients in specialised sites) involved frequencies, and two-tailed 95% confidence intervals (CIs) were presented for selected variables.

Categorical variables were compared using chi-square test, Student's t-test or analysis of variance (ANOVA) were used for continuous variables. Two-sided significance level of 0.05 was accepted for all statistical tests.

All statistical analyses were performed using SAS 9.4 (SAS Institute, North Carolina, USA) software.

Results

Study population

Patient disposition is presented at Figure 1. A total of 392 patients screened for Phase I, 315 were enrolled, and 77 were excluded as ineligible. Of 315 patients, 106 visited sites during the enrollment period and gave consent for study participation.

Characteristics of patients included in the study are presented in Table 1. There were numerically more female (n=211, 67.0%) than male patients (n=104, 33.0%) in the study. Majority of patients were older than 50 years. Most enrolled patients were Caucasians (n=257, 84.3%) and were either obese with a body mass index (BMI) ≥30 kg/m^2 (n=103, 39.8%) or overweight with a BMI between 25 and < 30 kg/m^2 (n=94, 36.3%). More than half of the patients were non-smokers (n=193, 64.5%); the remaining patients were either past smokers (n=66, 22.1%), current smokers (n=38, 12.7%), or passive smokers (n=2, 0.7%). Among the current and past smokers, the mean (SD) number of cigarettes smoked per day was 17.7 (7.9), and the mean (SD) pack-years was 25.4 (17.7). The overall mean (SD) number of years as a smoker among past and current smokers was 27.7 (12.6) years.

Table 1
Summary sociodemographic data for patients who entered Phases I and II

Parameter	Study population from Russia (n=315)
Sex, n (%)	211 (67.0)
Female	104 (33.0)
Male	
Age at entry, median (range)	60.0 (24.0–83.0)
BMI, n (%)	2 (0.8)
Underweight (BMI < 18.5 kg/m^2)	60 (23.2)
Normal weight (18.5 ≤ BMI < 25 kg/m^2)	94 (36.3)
Overweight (25 ≤ BMI < 30 kg/m^2)	103 (39.8)
Obese (BMI ≥ 30 kg/m^2)	56
Missing	
Height, cm median (range)	164.0 (140.0–195.0)
Ethnicity, n (%)	257 (84.3)
Caucasian	5 (1.6)
Asian	43 (14.1)
Other	10
Unknown/missing	
Education, n (%)	12 (7.6)
Some high school	26 (16.5)
High school graduate	22 (13.9)
Technical postsecondary	66 (41.8)
Some college	29 (18.4)
College graduate	3 (1.9)
Post graduate degree	157
Unknown/missing	

Notes: BMI – body mass index; percentages in the table were calculated for available data (excluding unknown/missing).

Parameter	Study population from Russia (n=315)
Employment status, n (%)	83 (29.6)
Employed full or part time	9 (3.2)
Homemaker	145 (51.8)
Unemployed/Retired	43 (15.4)
Disabled or too ill to work	35
Unknown/missing	
Household income, n (%)	6 (5.7)
Less than minimum wage	59 (56.2)
Minimum wage	24 (22.9)
2 x minimum wage	16 (15.2)
More than 2 x minimum wage	210
Unknown/missing	
Smoking status, n (%)	38 (12.7)
Current smoker	66 (22.1)
Past-smoker	193 (64.5)
Non-smoker	2 (0.7)
Passive smoking at home/other	16
Unknown/missing	

Notes: BMI – body mass index; percentages in the table were calculated for available data (excluding unknown/missing).

Medical history

Among the 315 patients enrolled in Phase I, 303 (96.2%) patients had at least one comorbidity. Overall, the mean (SD) number of all comorbidities, disease comorbidities, allergic conditions, and other comorbidities were 3.0 (1.4), 2.2 (1.0), 1.8 (0.8), and 1.0 (1.0), respectively. The most common comorbidity was cardiovascular disease (n=217, 71.4%), followed by chronic respiratory disease (n=198, 68.8%) (including chronic obstructive pulmonary disease [COPD, n=99, 31.5%], allergic rhinitis [n=94, 30.4%], or other [n=62, 20.9%]), respiratory allergies (n=64, 22.6%), drug allergies (n=57, 21.3%), gastrointestinal disease (n=55, 19.3%), and other allergies (n=36, 12.7%). Renal disease, rheumatological disease, diabetes with/without end-organ damage, malignancy disease, immunological disease, and food allergies were each reported in less than 10% of the patients. There were nine other comorbidities also reported, including obesity, osteochondrosis, benign prostatic hyperplasia, iron deficiency anemia,

dyslipidemia, gout, hyperlipidemia, osteoarthritis, and sinusitis; 56 (57.1%) patients had other comorbidities.

Asthma history data is presented in Table 2. Among the 315 patients, the median (range) age at diagnosis of asthma or severe asthma was 45.0 (1.0–79.0) and 55.5 (15.0–82.0) years, respectively. The median (range) age at the first symptoms of asthma was 42.0 (1.0–76.0) years. The mean (SD) time between asthma diagnosis and severe asthma diagnosis was 10.1 (11.1) years. Most patients did not have a familial first-degree history of asthma (n=150, 62.0%).

Table 2
Asthma medical history

Parameter	Study population from Russia (n=315)
Age at diagnosis, years median (range)	45.0 (1.0–79.0)
Age at first symptoms of asthma, years median (range)	42.0 (1.0–76.0)
Age at diagnosis of severe asthma, years median (range)	55.5 (15.0–82.0)
Years since diagnosis of severe asthma median (range)	3.0 (0.0–43.0)
Familial first-degree history of asthma, n (%)	92 (38.0%)
Yes	150 (62.0%)
No	73
Missing	
Number of physicians that were seen before being diagnosed with severe asthma median (range)	2.0 (1.0–10.0)
Medical specialty of the physician that has diagnosed severe asthma, n (%)	19 (6.7%)
General/Family Practice	189 (66.5%)
Respiratory specialist	75 (26.4%)
Allergist	1 (0.4%)
Cardiologist	31
Missing	
Medical specialty of the physician seen most often by patient for severe asthma follow-up, n (%)	98 (32.7%)
General/Family Practice	161 (53.7%)
Respiratory specialist	41 (13.7%)
Allergist	15
Missing	
Routine follow-up for severe asthma, n (%)	279 (94.9%)
Yes	15 (5.1%)
No	21
Missing	

The most reported frequencies of nighttime awakenings due to severe asthma in the last 12 months were once a week (n=55, 23.9%), twice a week (n=40, 17.4%), and once per fortnight (n=39, 17.0%) (Figure 2).

There were 268 (85.1%) patients who experienced at least one asthma exacerbation during the last 12 months, the majority of them had 1 exacerbation during the past 12 months (n=209, 66.3%) (Figure 3). Exacerbations were most common during spring (n=116, 36.8%), followed by winter (n=91, 28.9%), summer (n=70, 22.2%), and autumn (n=54, 17.1%). The mean (SD) duration of exacerbation was 8.5 (5.3) days. For most patients, flu or common cold was the trigger for exacerbation (n=135, 46.2%).

Laboratory data

A total of 176 patients had blood eosinophil counts data available in either Phase I or II, one measurement data was available for the majority of patients (n=159, 82.0%). Therefore, eosinophil count control is not frequently used in routine practice. The highest mean (SD) eosinophil level observed was 123.9 (173.2) cells/μL. Among the 106 patients enrolled in Phase II of the study, 4 (3.8%) patients had a blood eosinophil count recorded at visit. Mean (SD) blood eosinophil count was 46.5 (86.4) cells/μL.

Data on IgE measurements were available for 88 patients, nearly all patients had only one test performed in the 12 months prior to data entry in Phase I (n=82, 93.2%). The mean (SD) last serum IgE value was 254.3 (249.7) ng/mL. Therefore, most patients' last serum IgE value was ≤244 ng/mL, which is considered normal (n=52, 59.8%).

Retrospective spirometry data are shown in Figure 4.

Note FEV1 – forced expiratory volume in first second; last FVC – forced vital capacity; data represent mean for 279 patients.

Among the 279 patients with available data on lung function examinations in the last 12 months, the majority had only one lung function examination (n=202, 72.4%). The mean (SD) last forced expiratory volume in first second (FEV1), last forced vital capacity (FVC), and last FEV1/FVC value were 56.9 (20.4), 76.0 (21.1), and 76.0 (18.0) % of predicted, respectively. Overall, most patients had a last FEV1/FVC value between 50% and 70% (n=230, 93.9%).

No IgE evaluations were recorded in cross-sectional part of study. Spirometry data was available for 29 patients included in Phase II. The mean (SD) FEV1 value was 56.6 (21.7) % of predicted, and most patients had a FEV1 value of >50% (n=16, 55.2%). There were 15 patients with a FVC value recorded at the cross-sectional visit. The mean (SD) FVC value was 80.9 (18.3) % predicted, and most patients had a FVC value of >70% (n=10, 66.7%). The mean (SD) FEV-1/FVC ratio was 72.3 (19.4) % predicted (n=15).

Disease management

Asthma treatment related data are shown in Table 3. Among the 315 patients, the most common treatment prescribed in the last 12 months was controller/maintenance treatment (n=313, 99.4%), followed by reliever treatment (n=305, 96.8%), exacerbation treatments (short-acting β-agonists [SABA]

excluded) (n=249, 79.0%), and other medication (n=245, 77.8%). In terms of the distinct number of medications prescribed for each category, exacerbation treatments (SABA excluded) had the highest mean (SD) number during the last 12 months (4.3 [3.2]), followed by other drugs (3.2 [2.3]), controller/maintenance treatment (1.9 [0.9]), and reliever treatments (1.1 [0.4]). New or ongoing reliever treatments had the longest mean (SD) treatment duration (11.1 [2.6] months), followed by controller/maintenance treatments (9.9 [3.3] months), other medications (8.0 [4.2] months), and exacerbation treatments (SABA excluded) (1.0 [2.2] months).

Table 3
Treatments prescribed and average duration of treatment use for severe asthma

Parameter	Study population from Russia (n=315)
Number of distinct controller/maintenance treatments prescribed for severe asthma in the last 12 months median (range)	1.9 (0.9)
Number of distinct reliever treatments for severe asthma prescribed in the last 12 months, mean (SD)	1.1 (0.4)
Number of distinct exacerbation treatments for severe asthma prescribed in the last 12 months, mean (SD)*	4.3 (3.2)
Number of distinct other medications prescribed in the last 12 months, mean (SD)	3.2 (2.3)
Average duration of any new or ongoing controller/maintenance treatments for severe asthma in the last 12 months, months, mean (SD)	9.9 (3.3)
Average duration of any new or ongoing exacerbation treatments for severe asthma in the last 12 months, months, mean (SD) *	1.0 (2.2)
Average duration of any new or ongoing other medications in the last 12 months, months, mean (SD)	8.0 (4.2)
Note: SABA – short-acting β-agonist; * – excluding SABA; SD – standard deviation.	

Among the 315 patients, 199 (63.2%) patients received OCS treatment in the past 12 months. The mean (SD) overall daily dose of OCS in the last 12 months was 2.9 (5.1) mg (n=199). The mean (SD) daily dose of OCS for controller/maintenance treatment in the last 12 months was 6.1 (4.1) mg (n=16). The mean (SD) daily dose of OCS for exacerbation treatment in the last 12 months was 2.5 (4.9) mg (n=194).

Among the 313 (99.4%) patients who received controller/maintenance treatment, the most common treatments (i.e., prescribed in >5% of patients) were medium/high dose ICS/long-acting β-agonists (LABA) (n=291, 93.0%), tiotropium bromide (n=156, 49.8%), leukotriene receptor antagonist (LTRA) (n=28, 8.9%), other (n=19, 6.1%), medium/high dose ICS (n=18, 5.8%), and low dose OCS (n=16, 5.1%). The mean (SD) days of treatment among the most common treatments ranged from 239.9 (125.3) days in LTRA to 315.8 (100.0) days in medium/high dose ICS/LABA. In 12 months prior to inclusion, the most common (i.e., observed in >5% of patients) first prescribed controller/maintenance treatment started during the past 12

months was medium/high dose ICS/LABA (n=291, 92.4%), followed by tiotropium bromide (n=156, 49.5%), LTRA (n=28, 8.9%), medium/high dose ICS and other (n=19, 6.0%, for both).

Among the 305 (96.8%) patients who received reliever treatment, the most common treatments (i.e., prescribed in >5% of patients) were short-acting beta 2 agonists (n=224, 73.4%), followed by other treatments (n=70, 23.0%), and low dose ICS/formoterol (n=21, 6.9%). The mean (SD) treatment duration was 293.2 (133.7) days in low dose ICS/formoterol, 337.5 (78.0) days in other treatments, and 341.1 (75.1) days in SABA.

There were 250 (79.4%) patients with prescribed exacerbation treatment during the 12 months prior to study inclusion. The most common treatments (i.e., prescribed in >5% of patients) were systemic corticosteroid (OCS/parenteral) (n=198, 79.2%), other treatments (n=175, 70.0%), SABA (Salbutamol) (n=24, 9.6%), short-acting muscarinic antagonist (SAMA) (ipratropium) (n=22, 8.8%), and oxygen (n=16, 6.4%). Among the common exacerbation treatments for severe asthma, the mean (SD) treatment duration ranged from 22.6 (30.6) days for oxygen to 60.0 (92.0) days for SABA.

Among the 250 patients who experienced at least one exacerbation within the prior 12 months, physician consultation was the most frequent intervention (n=227, 75.4%). A total of 30 (10.6%) patients experienced at least one exacerbation which required an ER visit, and 200 (67.1%) were hospitalized with a mean (SD) of 12.3 (6.0) nights spent in hospital in the last 12 months.

Patient-Reported Outcomes

Questionnaires were completed by the patients who participated in Phase II (n=106). Most patients had an ACT score of ≤15 and fell in the category “asthma may not be under control” (n=79, 74.5%); there were 22 (20.8%) patients with an ACT score of ≥16 to ≤19 and fell in the category “asthma partially or not well controlled”; and 5 (4.7%) patients with an ACT score of ≥20 and fell in the category “asthma may be under control”. The mean (SD) ACT score was 11.4 (4.7).

The mean (SD) EQ-5D-5L utility score was 0.5 (0.3), and the mean (SD) EQ-5D visual analogue scale (VAS) score was 51.8 (20.2). The mean (SD) number of school or workdays patients reported missing due to severe asthma was 17.6 (21.8) days. The mean (SD) number of school or workdays with less productivity due to severe asthma was 44.6 (45.2) days. Overall, higher quality of life was associated with better asthma control.

Limitations

Most of the sites selected in this study were public hospitals (hence the results show that almost all patients were covered by public/social security healthcare), and thus the generalizability of the results is limited to patients treated in public healthcare settings. Physician participation in Phase I/II and patient participation in Phase II were on a voluntary basis; this may have resulted in selection bias, thereby impacting the representativeness of the final sample of participating physicians and patients. Missing data, which is a known disadvantage of observational studies, could reduce the statistical power of

analyses and may potentially bias estimates. There was very limited data captured on blood eosinophil measurements in this study. Finally, it is important to consider the reliability of certain variables, e.g., smoking status may be impacted by reporting bias, due to the reluctance of patients to report smoking behavior to their doctor.

Discussion

This retrospective cross-sectional study conducted in Russia collected and analysed real-world data on patients with severe asthma, including patient care pathway, disease management and patient/disease characteristics (demographics, clinical characteristics, healthcare resource utilisation and HRQoL).

In the Russian population included in the current study, most of the patients were female, which is in line with the previously reported data on asthma epidemiology (11, 12). The majority of patients were aged >50 years. Similar was reported by the International Severe Asthma Registry (ISAR), where 52.1% were aged 55 to 69 years (12).

Previous studies have shown that other respiratory disease, such as cardiovascular disease, gastrointestinal disease, allergies and diabetes are prevalent in patients with asthma (13–15). In this study, on average, patients had approximately three comorbidities and the most common comorbidities were cardiovascular disease (71.4%) and chronic respiratory disease (68.8%). It is of interest to note the high proportion of patients with concomitant COPD (31.5%) observed in this study, it is known that asthma represents a significant risk factor for COPD (16). On the other hand, there might be a high proportion of COPD patients in Russia misdiagnosed with asthma due to difficulties in differential diagnosis and/or intention to receive better therapies refunded by healthcare system. Another possible explanation for this finding is the relatively high rate of smoking in patients with severe asthma.

Median age for asthma diagnosis was 45.0 years and 55.5 for severe asthma. In a US-based survey (n=12,216) the average age of asthma onset among adults was 38 years (17). Another study has shown that in asthma patients the risk of subsequent development of severe asthma increases by around 7% each year until age 45 years (18).

The majority of patients had at least one exacerbation in the last 12 months, highest exacerbation frequency was in spring, followed by winter, summer, and autumn. Seasonal peaks in asthma exacerbations are well described in the literature, with variations according to the geography and climate (19). In this study flu/cold was the major trigger for exacerbation (46.2%), which has also been identified by the other studies (20).

Mean blood eosinophil levels remained consistently elevated over consecutive measurements. It was observed in other study that elevated eosinophils are related to poorer asthma control (21). Sites that participated in this study did not routinely record eosinophil levels, despite blood eosinophil counts being part of the complete blood count (CBC) measurement. This may be because the clinical practice at the time of the study observation period (2016–2018) did not require routine measurement of blood

eosinophil counts to assess patients' eligibility for phenotype-guided biologic therapy. Previously published data from Russia (27) as well as the results of this study suggest that biologics were infrequently used to treat severe asthma in Russia, and so this may also partly explain the limited measurement of eosinophil counts observed in this study considering eosinophil counts are used to guide biologic therapy. Furthermore, approximately one-third of patients visited general/family practice physicians for the treatment of severe asthma. Since eosinophil counts are not routinely measured in general/family medicine, this may also explain the limited data on eosinophil counts.

Despite clinical significance implied by some authors, especially for uncontrolled asthma patients, IgE levels were not measured in most patients (22). FEV1 values in this study should be considered as moderately severe lung impairment (23). It was shown in one study that low FEV1 I may be a risk factor of future exacerbation of asthma (24).

The most common treatment prescribed in the last 12 months was controller/maintenance treatment (99.4%). This is to be expected considering the study inclusion criteria – for patients to be included in the study, they must have been treated with high dose ICS plus a second controller (and/or systemic corticosteroids). The next most frequently used treatments were reliever treatment (96.8%), and exacerbation treatment (SABA excluded) (79.0%), and other medication (77.8%). The use of SABA, corticosteroids, and oxygen as treatment for exacerbations complies with guidelines for the management of exacerbations (25). However, use of SAMA for treatment of exacerbations, as observed in this study, is unusual and does not follow management guidelines (26), but combinations of SABA and SAMA is recommended to use in severe asthma exacerbation by GINA. The high proportion of other unspecified exacerbation treatments is also of scientific interest; this warrants further investigation to elucidate the specific other exacerbation treatments used.

Use of anti-IgE was very low (2.9%), the same was also reported for severe asthma patients in Russian Severe Asthma Registry (RSAR) (27). Biologics are recommended when they are available/affordable in cases of severe asthma where patients are prescribed with high dose ICS treatment and fulfil the criteria for residual Type 2 airway inflammation (28). Therefore, drug availability/affordability may partly explain the low use of biologics in Russia during the study.

Most patients experienced at least one exacerbation in the last 12 months which required an intervention. Rates of hospital admission and duration of in-hospital stay were notably high, which can reflect standard of care in Russia during the study period (2016–2018). ISAR data indicated 12-month admission rates of 26.8% (12). Similarly, results from a study (n=3,619) conducted among asthmatic patients across five European countries (France, Germany, Italy, Spain, and UK, observation period: 2008) reported a hospitalization rate of 27.3% over a 6-month (29).

The mean (SD) ACT score was 11.4 (4.7) and is corresponded to uncontrolled asthma. This mean score is in line with findings from other research; one study conducted in Brazil among severe asthmatic patients (n=74) in an outpatient clinic reported a similar mean (SD) ACT score of 11.7 (4.5) (30). Moreover, disease course significantly affected patient's quality of life.

Overall, the findings of this study suggest an unmet medical need among severe asthmatic patients in Russia. The majority of patients in the study sample used medium/high dose ICS/LABA (along with a second therapy). However, most patients had uncontrolled asthma, according to the ACT; and experienced at least one exacerbation in the past 12-months. In addition, most patients reported a reduction in the quality of their life due to their severe asthma.

Conclusion

The results of this study showed that alongside elevated eosinophil levels, most patients in the study sample had uncontrolled asthma, and most patients experienced at least one severe exacerbation within the past year. Additionally, most patients reported at least moderate limitations in their usual activities due to asthma. In line with these findings, healthcare resource use among patients was high. Most patients experienced at least one severe exacerbation during the last 12 months which required an intervention, some patients experienced two; and most patients experienced at least one exacerbation in the last 12 months which required hospitalization. Overall, the findings of this study suggest an unmet medical need among severe asthmatic patients. Although most patients used medium/high dose ICS/LABA (along with a second therapy), which is the preferred treatment option for uncontrolled asthma, most patients remained uncontrolled. This highlights a need for alternative or additional treatment options for severe asthma.

In recent years, new biological agents that block eosinophil specific interleukins (IL) such as anti-IL5 have become available (31). Research has shown that treatment with these new biologics result in a marked reduction in exacerbations and a significant improvement in HRQoL (10, 32). To capitalize on the newly available biologics, it is important to diagnose severe eosinophilic asthma at an earliest convenience.

Abbreviations

Abbreviation	Definition
ACT	Asthma Control Test
ANOVA	Analysis of variance
ATS	American Thoracic Society
CBC	Complete blood count
COPD	Chronic obstructive pulmonary disease
EQ-5D-5L	Five level EuroQol five-dimension
ER	Emergency room
ERS	European Respiratory Society
FEV1	Forced expiratory volume in first second
FVC	Forced vital capacity
GCP	Good clinical practice
GINA	Global Initiative for Asthma
GPP	Good pharmacoepidemiology practices
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
ISAR	International Severe Asthma Registry
LABA	Long-acting β-agonists
LEC	Local Ethic Committee
LTRA	Leukotriene receptor agonist
OCS	Oral corticosteroid
RSAR	Russian Severe Asthma Registry
SABA	Short-acting β-agonists
SAMA	Short-acting muscarinic antagonist
SCS	Systemic corticosteroid
SD	Standard deviation

SIV	Site initiation visit
VAS	Visual analogue scale

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Local Ethics Committee. The study was conducted in accordance with good pharmacoepidemiology practice (GPP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) good clinical practice (GCP). Data protection and privacy regulations were strictly observed in collecting, forwarding, processing, and storing patient data. All applicable patient privacy requirements, and ethical principles outlined in the Declaration of Helsinki 2008 were followed.

Informed consent form (ICF) was signed by patients included in Phase II. Medical record data collected during Phase I was considered secondary and did not require an ICF signature.

The study was reviewed and approved by Local Ethic Committees in Russia (LEC at State Budgetary Health Institution "Regional Clinical Hospital #3" Chelyabinsk, LEC at Regional State Budgetary Institution of Healthcare "City Hospital #5" Barnaul, LEC at State Budgetary Institution of higher Professional Education "Krasnoyarsk State Medical University n.a. professor Voyno-Yasenetskogo", LEC at Irkutsk State Medical Academy of Postgraduate Education - branch of Federal State Budgetary Educational Institution of additional professional education "Russian Medical Academy of Continuously Professional Education", LEC at State Budgetary Healthcare Institution of Novosibirsk region "State Regional Clinical Hospital of Novosibirsk", LEC at "Outpatient clinic #2" Yaroslalv, LEC at State Autonomous Healthcare Institution "Clinical Hospital #2"Yaroslavl, LEC at State Autonomous Healthcare Institution of Yaroslavl Region "Clinical Hospital of Emergency Care named after N.V. Solovyev" Yaroslavl, LEC at State Budgetary Clinical Institution of Healthcare of Yaroslavl Region "City Clinical Hospital n.a. Semashko N.A" Yaroslavl, LEC at Regional State Budgetary Healthcare Institution "Clinical Hospital #1" Smolensk, LEC at Federal State Budgetary Educational Institution of Higher Professional Education "North-Western State Medical University n.a. Mechnikov I.I." St. Petersburg.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

A. E., G. I. report grants from GlaxoSmithKline, during the conduct of the study.

L. T., J. M., S. F., R. A., T. E. are GSK employees and shareholders.

Funding

The study was funded by GlaxoSmithKline (GSK Study Number 207102). GSK was involved in the study design, collection, analysis, and interpretation of the data, in the writing of the report, and in the decision to submit the article for publication.

Author's contributions

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

Z. A., O. K., T. E. provided support in the study concept and protocol development and data analysis and interpretation.

A. E., G. I. provided support in the study concept and acquisition of data.

L. T., J. M., S. F., R. A. provided support in data analysis and interpretation.

All authors took active part in this study design, acquisition of data, analysis, and interpretation of the study data. The authors contributed to manuscript review, applying their clinical, epidemiology, and study design expertise and take responsibility for the integrity of the data and the accuracy of the data analysis.

All authors participated in critical revisions of the manuscript and have approved the article for publication.

Acknowledgements

We thank all investigators for their contribution to the study, allowing the clinical epidemiology research to happen with a high level of integrity and the contract research organisation, IQVIA, which was funded by GSK, performing the study organisation and conduct.

Editorial support in the form of draft outline, editorial suggestions to draft versions of this paper, collating author comments, assembling tables and figures, referencing, and copyediting was provided by Aleksander Solodovnikov at Statandocs and was funded by GSK.

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Figures

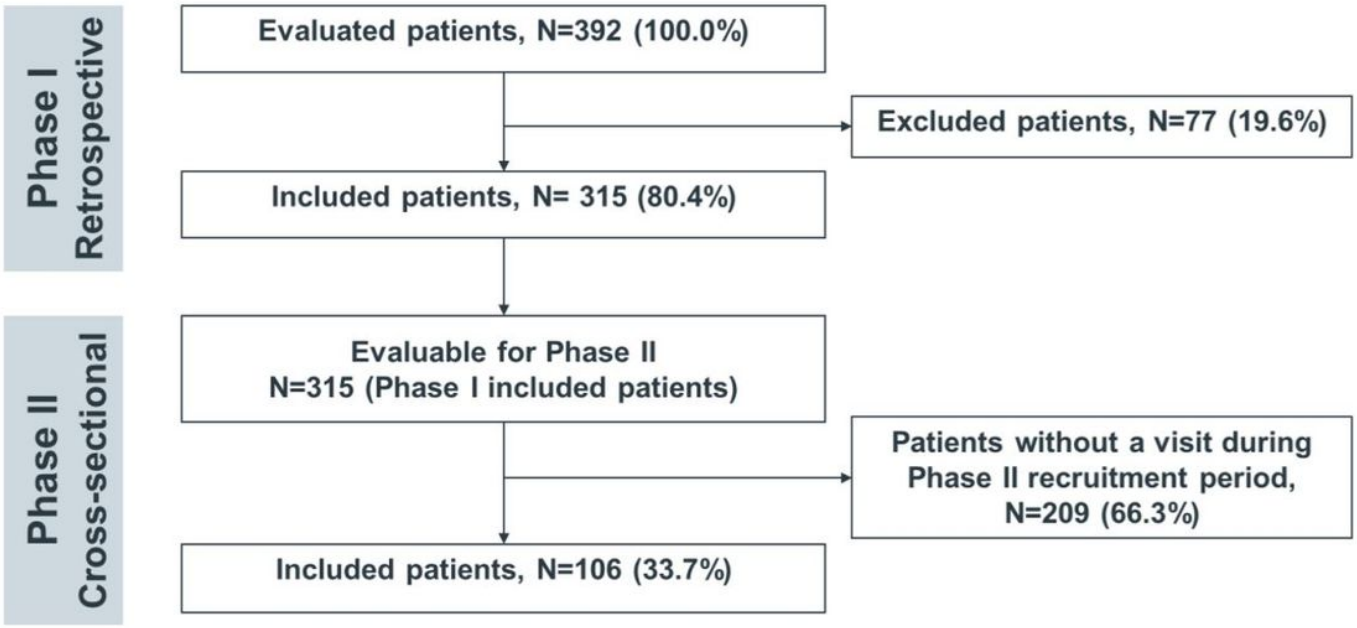

Figure 1

Patient flow chart

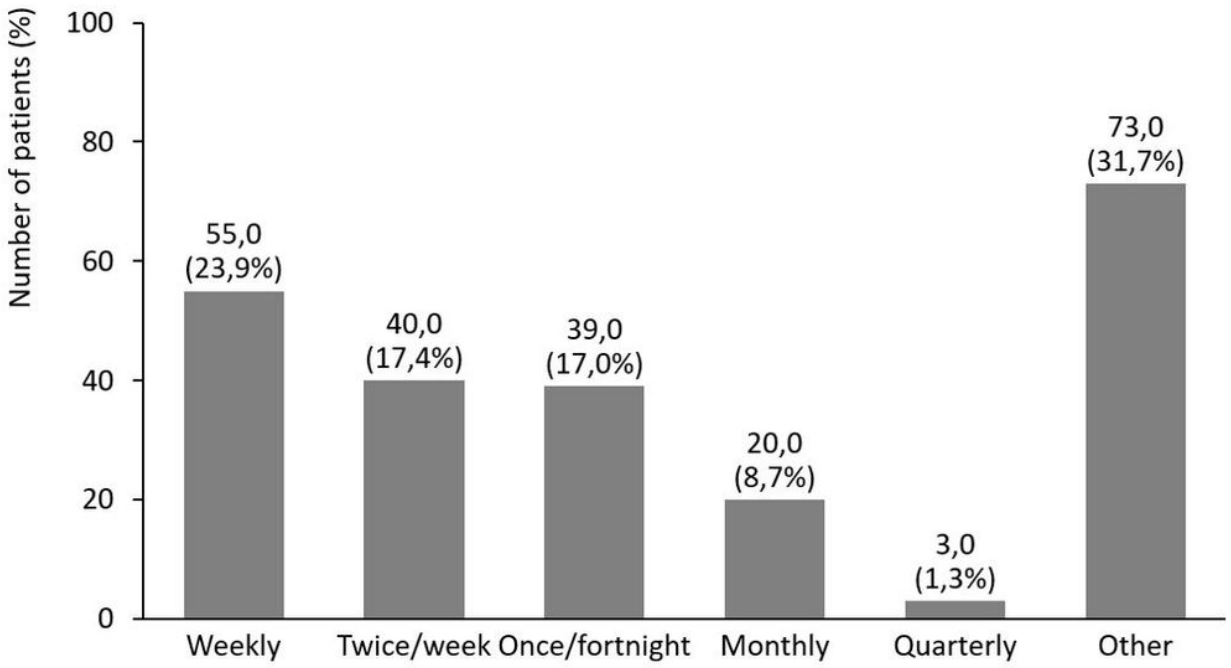

Figure 2

Frequency of nighttime awakenings due to severe asthma during 12 months prior to data entry

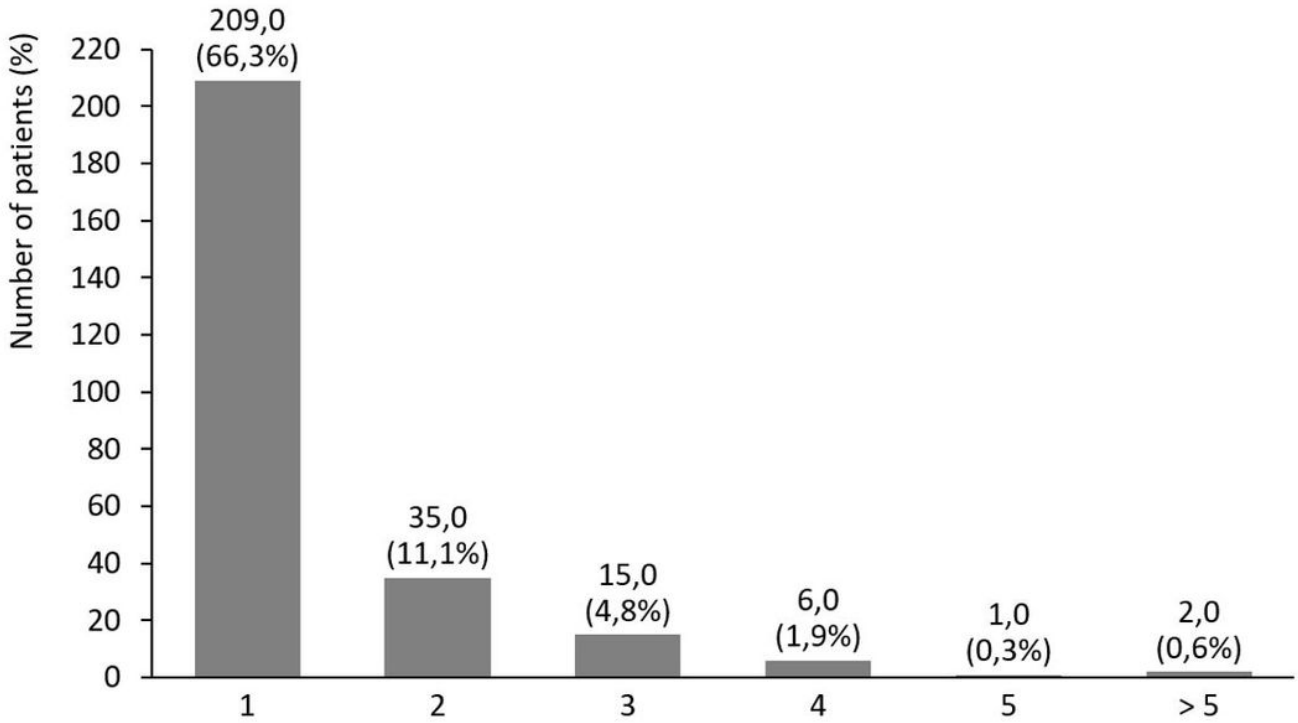

Figure 3

Frequency of exacerbations during the 12 months prior to data entry

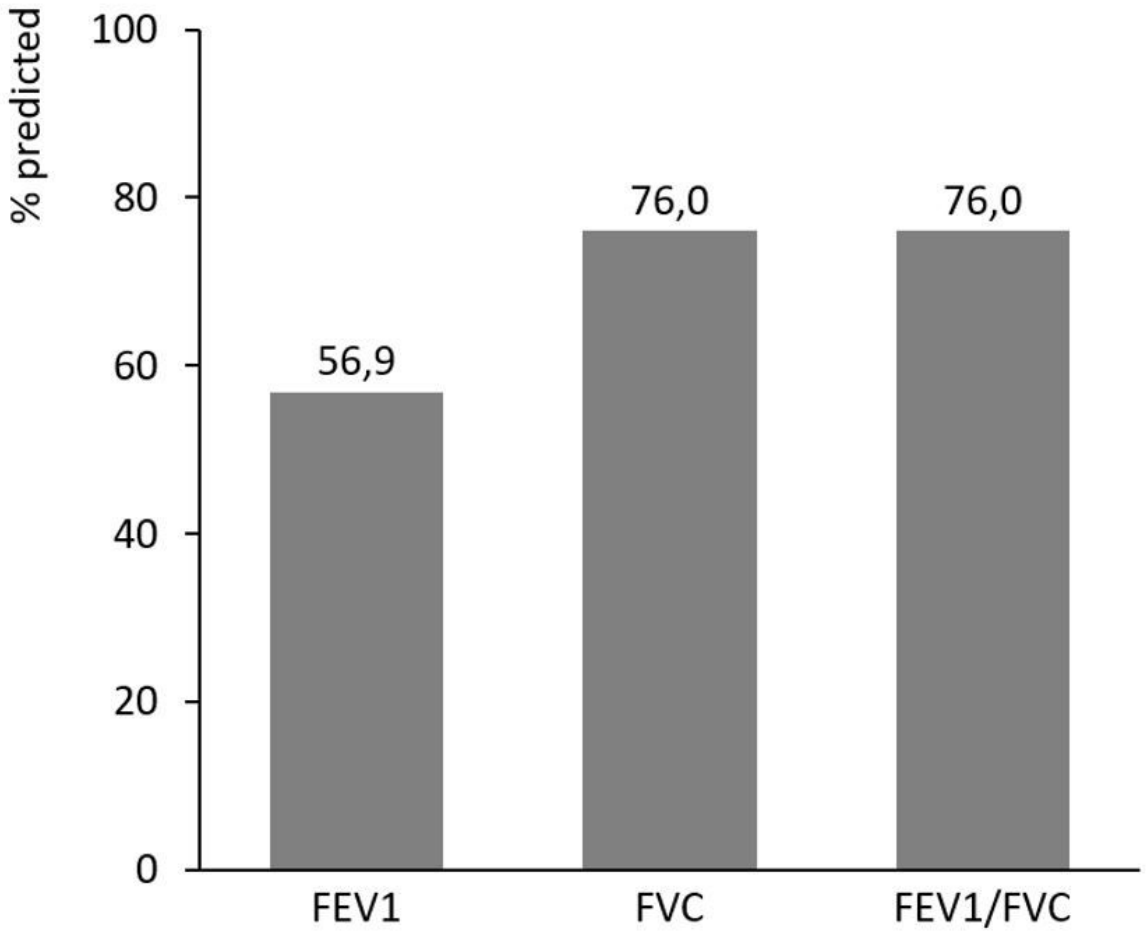

Figure 4

Last available spirometry measurement