OBSERVATIONAL STUDY REPORT SYNOPSIS

BRAEOS (BRazilian Asthmatics patients EOSinophilic profile)

A National, Observational, Cross-Sectional, Multicenter Study to Estimate the Prevalence of an Eosinophilic Phenotype Among Severe Asthma Patients in Brazil.

Milestones:

Milestones	Date
Final Protocol	06-Sep-2018
Inclusion of First Study Subject (FSI)	24-Jan-2019
Inclusion of Last Study Subject (LSI)	15-Oct-2019
Database Lock & Data Extraction	23-Dec-2019
Final Report	06-Aug-2020

Phase of development: Not Applicable - Observational study

Sponsor: AstraZeneca

Authors:

Scientific Leader
AstraZeneca - Brazil

Operational Leader
AstraZeneca - Brazil

This study was performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice, including the archiving of essential documents.

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Study Centers:

The study was performed in ten research centers distributed in Brazil.

Background/Rationale:

Asthma is a complex and heterogeneous disease. Severe asthma is recognised as a major unmet need that poses a great burden on the healthcare system. While accounting for only a small proportion of the total asthmatic population, asthma-related costs are 1.7 to 4-fold higher than those observed in the mild-persistent asthma population and the associated personal and societal impact is significant.

Severe asthma is not considered to be a single disease, but can be divided into several phenotypes, owing to the variety of inflammatory, clinical and functional characteristics that it can present with. One of the proposed and most studied phenotypes is severe eosinophilic

asthma. Patients with severe asthma that is accompanied with a high concentration of eosinophils require greater healthcare resource use, overall greater disease management costs and have a much more impaired QoL than those who do not present with raised eosinophilia.

While the number of targeted treatments for asthma management has been growing in recent years, the heterogeneity of clinical presentations, treatment responses and inflammatory processes involved represents an added challenge for health care professionals. Thus, severe asthma management is a complex endeavour and a thorough and up to date understanding of the pathophysiologic characteristics of the patient population promotes effective therapeutic decision-making.

The purpose of this observational, cross-sectional, multicenter study was to determine the prevalence of an eosinophilic phenotype of blood eosinophil count > 300 cells/mm^3 among severe asthma patients followed at Brazilian sites specialized in the management of severe asthma. The prevalence of an atopic phenotype, asthma control, QoL and burden of disease was also studied.

Objectives:

The overall objectives of this study were to estimate the prevalence of eosinophilic phenotypes and of an atopic phenotype among severe asthma patients in Brazil. Asthma control, QoL and burden of disease among this patient population were also studied.

This study was descriptive in nature and did not attempt to test any specific a priori hypotheses. The following study objectives were assessed:

Primary Objective:

To determine the prevalence of an eosinophilic phenotype of blood eosinophil count >300 cells/mm^3 among severe asthma patients in Brazil.

Secondary Objectives:

• To determine the prevalence of an eosinophilic phenotype of blood eosinophil count >150 cells/mm^3 among severe asthma patients in Brazil;
• To determine the prevalence of an atopic phenotype, defined by a pre-existing history of atopy and total serum IgE > 100 UI/mL among severe asthma patients in Brazil;
• To determine the prevalence of atopy, as defined by a pre-existing history of atopy and total serum IgE > 100 UI/mL, among severe asthma patients in Brazil that present an eosinophilic phenotype of blood eosinophil count > 300 cells/mm^3;
• To determine the annual exacerbation rate among severe asthma patients in Brazil;
• To evaluate patient-reported QoL, as assessed by the St. George's Respiratory Questionnaire (SGRQ), among severe asthma patients in Brazil;
• To evaluate asthma control, as assessed by the Asthma Control Questionnaire 7 (ACQ 7), among severe asthma patients in Brazil;
• To describe the burden of disease, as assessed by asthma-attributed healthcare resource utilization, the Generalized Anxiety Disorder 7-item (GAD 7) scale, the Patient Health Questionnaire 9 (PHQ-9) and the Work Productivity and Activity Impairment: Asthma (WPAI: Asthma) questionnaire, among severe asthma patients in Brazil;
• To describe the socio-demographic, clinical, QoL and burden of disease profile of severe

asthma patients with chronic oral corticosteroid (OCS) use.

Study design:

This was a national, multicenter, observational, descriptive study with a cross-sectional design and retrospective data collection, to assess the prevalence of eosinophilic phenotypes and of an atopic phenotype among severe asthma patients in Brazil. Asthma control, QoL and burden of disease among this patient population were also studied.

The study was performed between January, 2019 and October, 2019, in ten Brazilian study sites.

Data Source(s):

The study was conducted in ten public or private centers specialized in the management of severe asthma in Brazil. The research sites were located throughout Brazil and investigators were Pneumology or Allergy specialists following subjects with severe asthma that could appropriately conduct this non-interventional study in accordance with the applicable regulatory and legal requirements. All investigators received training on the study protocol and other protocol-related procedures prior to study start.

After providing written informed consent, the subject's study information was collected from the subject's medical records (including retrospective data collection) and by subject interview. In addition, the subject was asked to complete the Saint George's Respiratory Questionnaire (SGRQ), the Asthma Control Questionnaire 7 (ACQ 7), the Work Productivity and Activity Impairment: Asthma questionnaire (WPAI: Asthma), the Generalized Anxiety Disorder 7 scale (GAD-7) and the Patient Health Questionnaire 9 (PHQ-9).

Additionally, and compliant with the subjects' routine assessment at the centers, total serum IgE levels and complete blood count values were collected in a blood sample.

The investigator was responsible for ensuring that all the required data was collected and entered into the study-specific electronic Case Report Form (eCRF). No subject identifiable information was captured.

Study Population:

The study population included adult patients with severe asthma, as per the definition of the BRAEOS Protocol v2.0. Subjects were identified and invited to participate in the study, as they attended their routine clinical appointment at the research centers.

To be included in the study, each patient should meet all the inclusion criteria and none of the exclusion criteria described below. Subjects provided written, informed consent prior to any study-specific procedures.

385 patients have been included in the analysis.

Inclusion criteria:

- Male or female subject, aged 18 years or older at the time of study entry;
- Subject followed at a participating center and attending a routine clinical appointment;
- Subjects with evidence of asthma of either:
    - Documented airway reversibility (forced expiratory volume in one second (FEV1)

≥12% and 200 mL) using the maximum post-bronchodilator procedure; OR
o Documented airway hyperresponsiveness (provocative concentration of methacholine causing a ≥20% fall in FEV1); OR
o Documented airflow variability in pre-bronchodilator FEV1 ≥20% between two consecutive lung function assessments prior to study entry (FEV1 values recorded during exacerbations should not be considered for this criterion).

- Subjects with a diagnosis of severe asthma for at least one year:
  - o Asthma which requires treatment with guidelines suggested medications for Global Initiative for Asthma (GINA) steps 4-5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year; OR
  - o Systemic CS for ≥50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.
- Subject with accurate and complete medical records at the center;
- Subject that voluntarily signed and dated the informed consent form prior to study entry.

Exclusion criteria:

- Subjects experiencing a moderate or severe asthma exacerbation, according to the Protocol v2.0, at the time of the study entry, or who had a moderate or severe asthma exacerbation less than 4 weeks prior to study entry;
- Subjects who have administered systemic corticosteroid less than 4 weeks prior to study entry;
- Subjects who have administered the biological medicines benralizumab and mepolizumab less than 16 weeks or 22 weeks, respectively, prior to study entry.
- Subjects whose pharmacological therapy for asthma was modified in the 3 months prior to study entry;
- Subjects diagnosed with at least one of the following:
  - o Lung cancer;
  - o Pulmonary fibrosis;
  - o Allergic bronchopulmonary aspergillosis;
  - o Eosinophilic granulomatosis with polyangiitis;
  - o Clinically relevant bronchiectasis or bronchiectasis associated with cystic fibrosis and/or allergic bronchopulmonary aspergillosis;
  - o Chronic obstructive pulmonary disease associated with a smoking history ≥10 pack-years and/or history of exposure to biomass fuel combustion.
- Subjects who are currently smokers or who have a history of smoking ≥10 pack-years.

Statistical Methods:

Descriptive statistics were obtained for numerical variables, including central tendency measures such as mean, median as well as the dispersion measures standard deviation, min-max and inter-quartile range. Descriptive statistics for categorical variables included frequencies' tabulation with counts and percentages. No missing values allocation were made. 95% confidence intervals (CI) were used if applicable. The significance tests were made at the 5% significance level and SAS package was used in all statistical analyses.

Primary objective:

The primary objective of this study was assessed by the proportion of subjects with a blood eosinophil count >300 cells/mm^3 among the severe asthma patients that were followed in the participating research centers in Brazil and are included in the study.

Secondary objectives:

• The prevalence of an eosinophilic phenotype of blood eosinophil count >150 cells/mm^3 was assessed by the proportion of subjects with a blood eosinophil count >150 cells/mm^3 among the severe asthma patients that were followed in the participating research centers in Brazil and were included in the study;

• The prevalence of an atopic phenotype of total serum IgE > 100 UI/mL and pre-existing history of atopy was assessed by the proportion of subjects with total serum IgE >100 UI/mL that had an history of atopy among the severe asthma patients that were followed in the participating research centers in Brazil and were included in the study;

• Three annual exacerbation rates were computed: overall annual exacerbation rate; annual moderate exacerbation rate; and annual severe exacerbation rate.

The prevalence of atopy among subjects with an eosinophilic phenotype of blood eosinophil count >300 cells/mm^3 was assessed by the proportion of subjects with atopy among the severe asthma patients with blood eosinophil count >300 cells/mm^3 followed in the participating research centers in Brazil and were included in the study. For this, atopy was considered to be present when there was a documented, pre-existing history of atopy.

Patient-reported QoL, asthma control and burden of disease was summarized using descriptive statistics. Likewise, the socio-demographic, clinical, QoL and burden of disease profile of severe asthma patients with chronic OCS use was summarized descriptively.

Data on healthcare resource utilization in the year preceding study entry was also summarized using descriptive statistics.

Results:

In approximately ten months of recruitment period in 10 research centers, the first-patient was included on the 24th of January 2019 and last-patient on the 15th of October 2019.

There was a total of 414 patients screened in this study. From those, 26 (6.3%) were screening failures and one was not eligible per Protocol v2.0 (0.2%). A total of 387 patients were included in the chronic oral corticosteroids (OCS) use analysis dataset (14 patients with chronic OCS use and 373 without chronic OCS use), which was initially considered in the study protocol. However, due to missing data regarding the blood eosinophil count for two eligible participants a second analysis dataset was created, and 385 patients were considered for analysis (154 patients with eosinophils >300 cells/mm^3 and 231 with eosinophils ≤300 cells/mm^3).

Having said that, results by eosinophilic phenotype considered 385 patients, as described above, being 154 patients with eosinophils >300 cells/mm^3 (40.0%; 95% CI: 35.1% to 44.9%) and 281 with eosinophils >150 cells/mm^3 (73.0%; 95% CI: 68.6% to 77.4%)), with median age 54.00 years old, mainly female (78.4%) and white (57.4%).

A total of 311 patients (81.6%) reported history of atopy (95% CI: 77.7% to 85.5%) and 286 (74.3%) reported levels of total serum IgE above 100 UI/mL (95% CI: 69.9% to 78.7%). The

prevalence of patients with total serum IgE above 100 UI/mL and history of atopy, among those with severe asthma, was 62.6% (241/385) (95% CI: 57.8% to 67.4%). The prevalence of patients with blood eosinophil count >300/mm^3 and history of atopy was 31.9% (123/385) (95% CI: 27.3% to 36.6%). Among the subjects with severe asthma and with blood eosinophil count >300 cells/mm^3 (n=154), the prevalence of history of atopy was 79.9%, (123/154), (95% CI: 73.5% to 86.2%).

For the patients with eosinophils >300 cells/mm^3, the overall annual exacerbation rate was 3.195 patient-years, the annual moderate exacerbation rate was 3.130 patient-years and the annual severe exacerbation rate was 0.065 patient-years. For the 385 patients, the most frequent comorbidities reported were rhinitis (84.9%), gastroesophageal reflux (51.4%) and obesity (44.4%). However, the comorbidities that were statistically different between the phenotype eosinophil groups were rhinitis, gastroesophageal reflux, other, type 2 diabetes mellitus and nasal polyps. The median Charlson comorbidity index score was lower on patients with eosinophils >300 cells/mm^3 (1.00 versus 2.00; p=0.0125). Patients with eosinophils >300 cells/mm^3 showed a higher median FEV1 predicted (2.76L) compared to those with eosinophils ≤300 cells/mm^3 (2.56L), (p=0.0433).

The variables that have shown statistically significant differences between the groups of patients with eosinophils >300 cells/mm^3 and patients with eosinophils ≤300 cells/mm^3 were the following: age; employment status; BMI; time since onset of asthma symptoms; annual moderate exacerbation rate; annual severe exacerbation rate; hemoglobin, total white blood cell count, monocytes absolute count, platelet count, total serum IgE, and neutrophils relative count; number of corticosteroid bursts; rhinitis, gastroesophageal reflux, other comorbidities, type 2 diabetes mellitus and nasal polyps; Charlson comorbidity index score; FEV1 predicted; percentage of activity impairment due to asthma; unscheduled medical appointments.

Results by chronic oral corticosteroids use include 387 patients (14 patients with OCS use and 373 patients without OCS use), with mean age 52.25±14.00 years, mainly female (78.6%) and white (57.4%).

The variables that have shown statistically significant differences between groups were: medical retirement due to severe asthma; weight; number of patients with orotracheal intubation due to asthma; moderate and severe asthma exacerbations; number of patients with severe asthma exacerbations in the 12 months prior to study; number of corticosteroids bursts; history of stroke and heart failure; Sgrq: activity score, impact score and total score; WPAI: asthma: percentage of work time missed due to asthma, percentage of impairment while working due to asthma, percentage of overall work impairment due to asthma and percentage of activity impairment due to asthma; Phq-9: severe depression; number of scheduled and unscheduled medical appointments related to asthma; patients hospitalized due to asthma exacerbations; physician-prescribed treatment plan for the management of asthma exacerbation; number of corticosteroid courses administered by the patient in the scope of the self-management plan.

Conclusion:

The population studied is a severe group of patients as a whole, that has been well characterized for the eosinophilic phenotype, which corresponds to 40% of the sample. The eosinophilic group has shown to be younger, with lower BMI, less comorbidities and with higher number of

corticosteroid bursts than the non-eosinophilic group (patients with eosinophils ≤300 cells/mm^3).

The results observed in the group of patients with OCS use were as expected more severe, with more exacerbations, with more healthcare resource utilization, worse quality of life and more cardiovascular comorbidities (heart failure and stroke).

These findings are extremely important to understand the national setting of severe asthma and its phenotypes allowing the physicians and decision makers to be more effective in the management of patients and disease and to implement better public health strategies.