STUDY REPORT SYNOPSIS

Study Name

Exacerbation and their outcomes international (EXACOS international): Understanding the burden of severe exacerbations of COPD and the association between frequency of severe exacerbations and clinical and healthcare utilization outcomes in less well-resourced countries.

Study Description

Observational, cross-sectional study with retrospective data collection from medical records, in patients, treated by pulmonologists, with an investigator-confirmed diagnosis of COPD for at least five years from the index date (the date that signed informed consent) and who met all the inclusion and none of the exclusion criteria.

During the cross-sectional study visit, data was captured using electronic case report forms, and there was only one study visit, no prospective data collection took place.

Milestones:

Milestone	Planned date
Protocol approved	Q1 2021
First patient in	Q4 2021
Last patient in	Q4 2022
Statistical analysis plan approved	Q2 2022
Final study results tables	Q2 2023
The clinical study report approved	

The Phase of development: Not Applicable- Observational study

Sponsor AstraZeneca

Authors: [redacted]

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

Background/rationale

Chronic obstructive pulmonary disease (COPD) is a common, progressive disease characterized by airflow obstruction which is not fully reversible. Acute exacerbations of COPD (AECOPD) are worsening COPD symptoms (breathlessness, cough, and sputum volume and purulence) beyond the normal day-to-day variation. Between 30- 50% of patients with COPD experience at least one AECOPD per year [1]. Even a single moderate AECOPD increases the risk of future multiple AECOPD events, starting a spiral of excessive disease progression and leading to an increased risk of death [2]. AECOPDs have also been associated with other clinical outcomes such as accelerated lung function decline [3, 4].

Global Burden of Disease estimates that 90% of COPD deaths occur in low- and middle-income countries. There is a significant socioeconomic burden associated with these deaths for patients, their families, and societies. The best way to reduce premature COPD deaths around the world is to optimize COPD treatment in low- and middle-income countries. Dissemination and implementation of guidelines are effective ways to optimize treatment. Guidelines should provide standardized, evidence-based prevention, diagnosis, and management recommendations. In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Strategy Report has been established. As a result, several countries have adopted GOLD updates since then [5-8].

Studies have shown that AECOPDs are related to future AECOPDs, however, little is known about the clinical burden and healthcare utilization in the COPD population [2, 9]. To date, most of the published literature reports a combined category of moderate-severe exacerbations, typically stratifying patients as experiencing frequent (i.e., two or more events per patient-year vs. infrequent (none or one) exacerbations.

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This study aims to quantify the burden of severe AECOPD in countries in the international region of AstraZeneca, by investigating the association between the frequency of severe AECOPD and clinical healthcare care utilization outcomes.

This study will help to understand the relationship between severe AECOPD and clinical and healthcare utilization burden in less well-resourced countries with no established healthcare databases.

Objectives

1. To estimate the frequency of severe AECOPD, in a COPD population.
2. To describe any time trends in the frequency of severe exacerbations throughout the study period (over five years).
3. To describe lung function decline over time (FEV1)
4. To quantify healthcare resource utilization by the number of severe AECOPD over five years.
5. To measure the modified Medical Research Council (mMRC) dyspnea scale at the time of the visit

Study design

As in most of the countries in the international region of AstraZeneca, there were no established healthcare databases for secondary data collections. This was an observational, cross-sectional study with retrospective data collection from medical records. During this study, data was captured through electronic case report forms (eCRFs).

Data source

Medical records of participating sites

Study population:

In this study, investigator confirmed COPD population for at least five years from the index date (the date when informed consent was obtained) and who met the study inclusion criteria.

Inclusion criteria

Patients who met the following inclusion criteria:

1. Investigator confirmed diagnosis of COPD of at least five years and were over the age of 40 years.

2. Smokers or ex-smokers (quit smoking no more than 15 years before the study visit).
3. COPD-related data recorded in medical records for at least five years, including spirometry and medication data.
4. Signed a written informed consent form.

Exclusion criteria

Patients excluded who met any of the following exclusion criteria:

- Had been diagnosed with bronchiectasis, sarcoidosis, interstitial lung diseases, or idiopathic pulmonary fibrosis. This is because differentiating deteriorations in symptoms/exacerbations in these individuals at attributing them to COPD is impossible.

Statistical methods

Statistical analysis was performed using SAS (version 9.4 or higher) software (SAS Institute Inc USA). Categorical variables were summarized with the frequency and percentage of subjects in each category. Continuous variables were summarized descriptively with the number of subjects, mean, standard deviation, minimum, median and maximum values.

Primary outcome analysis based on the COPD population and summary statistics were also provided per country. Categorical variables were summarized with the frequency and percentage of subjects in each category. Continuous variables were summarized descriptively with the number of subjects, mean, standard deviation, minimum, median and maximum values.

1. Number of severe AECOPD events and interval between severe AECOPDs were summarized based on COPD population. Descriptive summaries were provided for the number of severe AECOPD events and interval between severe AECOPDs. All continuous variables were summarized descriptively with the number of subjects, mean, standard deviation, minimum, median and maximum values.

The interval between two hospitalizations, for two or more consecutive hospitalizations in severe AECOPD patients, were calculated and the average duration between two consecutive hospitalizations were presented.

2. To evaluate the clinical burden, the change in % FEV1 from baseline (Note: Spirometry data assessment first date was considered as baseline) to post-baseline (Note: Spirometry data assessment last date was considered as post-baseline) was analysed using Paired t –test/ Wilcoxon signed –Rank test at 5% level of significance.

Change from baseline was determined as:

[redacted]

Change from Baseline = (Post-baseline – Baseline)

3. Patients' comorbidities were summarized based on the enrolled population. Descriptive summaries were provided for the comorbidities. All categorical variables were summarized as counts and percentages.

4. Health care utilization burden was summarized based on COPD population. Descriptive summaries were provided for the Health care utilization burden.

Health care utilization burden characteristics such as the number of emergency department visits, number and length of hospitalisations, number and length of ICU episodes, number of COPD maintenance prescriptions over the past 5 years were summarized and tabulated for COPD population. All continuous variables were summarized descriptively with the number of subjects, mean, standard deviation, minimum, median and maximum values.

The length of hospitalisation between two consecutive hospitalisations in severe AECOPD patients, for two or more consecutive hospitalisations, were calculated and the average length of hospitalisations between two consecutive hospitalisations were presented.

5. Descriptive summaries were provided for SABA canisters, OCS prescriptions, and antibiotics.

Results

In our study, we found that 1 out of 5 patients (20.08%) had severe exacerbations per year. This could be because the study was conducted during the COVID pandemic. However, the overall 5-year data showed that 48% patients had at least one severe exacerbation, suggesting severe exacerbation remains a problem in Latin America and Asia. We also observed that the annual exacerbation frequency was 0.34. Among the COPD medications prescribed to the patients one year before enrolling in the study, it was observed that majority of the patients were prescribed SABA (45.53%), followed by ICS+LABA (41.72%), LAMA (37.9%) and LABA+LAMA (36.49%). The patients were maintained on OCS in 3.58% patients. The results of COPD medications (Systemic corticosteroids, OCS prescriptions and prescriptions for antibiotics) prescribed to the patients over 5 years showed that an overall 46.7% patients received OCS bursts and 56.2% patients received antibiotics over 2 courses (median), each course lasting 7 days (median). The mean FEV1 decreased significantly ($p<0.001$) from 1.348 (SD 0.687) to 1.127 (SD 0.516), showing a decline in lung function over time. It was noted that 97.55% and 96.27% patients who visited the emergency department and hospitalized respectively, had at least one severe exacerbation. The average length of stay was 10.2 and 8.5 days in the hospital and ICU respectively. In the overall study population, 76.15% COPD patients had comorbidities - hypertension

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(58.28%) was the most prevalent followed by diabetes mellitus (20.45%). Some patients also had more than one comorbidity. Diabetes and hypertension together were observed in 20.16% patients, suggesting 1 out of 5 COPD patients had both these cardiovascular risk factors.

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