STUDY REPORT SYNOPSIS

REALizing and Improving Management of Stable COPD in China (REAL I): A Multi-centre, Prospective, Observational Study to Realize the Current Situation of COPD Patients in China

MILESTONES:	Proposal Approval	20 Jun 2016
	Final Clinical Study protocol	13 Oct 2016
	Study Start Up: contracts in place, regulatory submissions, initiation visits	13 Dec 2016
	First Patient In	30 Jun 2017
	Last Patient In	29 Jan 2019
	Database Lock	21 Dec 2020
	Final Clinical Study Report	23 Dec 2021
PHASE OF DEVELOPMENT:	**Non-interventional study**	
SPONSOR:	**AstraZeneca**	
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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) prevalence in China has been reported as 13.7% in general population aged 40 and older.[3] This figure is likely to be an underestimate as many patients with COPD remain undiagnosed.[4] COPD is still the third leading cause of death in China.[5] Its mortality and burden are predicted to increase in the coming decades. And the huge social and economic impact makes COPD a major health problem in China.

Although some studies conducted to understand the COPD status and patients' disease awareness, at present, there are still many unknown and unsolved problems with COPD in China, such as the yearly rate of all kinds of COPD exacerbations under conventional treatments, the compliance of COPD patients, the current clinical practice and outcome, the severity distribution of COPD patients and progression, patients' perception to disease, and the risk factors of COPD exacerbations.

This multi-centre, prospective, observational study can help to understand the current COPD situation and may provide some references for improving COPD evaluation and treatment strategies in China.

Objectives: 1. Primary objective: To describe the one year clinical outcome of COPD patients in current clinical practice in China.

2. Secondary objectives: (1) To describe the severity distribution of COPD patients in China. (2) To describe the treatment pattern among COPD patients in China. (3) To assess the treatment compliance of COPD patients in China.

3. Exploratory objective: To investigate the risk factors of COPD exacerbations, severity and compliance of COPDpatients.

Study design: Multi-centre, prospective, observational study.

Data source: 1**.** Case Report Form (CRF). 2. Medical records. 3. Patient-Reported Outcome (PRO) questionnaires: (1) mMRC (2) CAT. 4. COPD-Q.

Study population: This study was conducted in 50 medical institutions in 6 regions of China from June 2017 to Aug 2020.

Patients who met all the inclusion criteria and not met any of the exclusion criteria had been included in this study.

A total of 5097 patients were screened, 5013 patients were enrolled into the study. 4978 patients were included in the full analysis set (FAS) population, and 4241 patients had completed the study.

Inclusion criteria: 1. Outpatients, ≥ 40 years old.

2. Clinically diagnosed as COPD (the patients are clinically diagnosed as COPD based on chronic cough, sputum, wheeze and a history of exposure to harmful factors, and confirmed by spirometry (FEV_1/FVC < 0.7, post-bronchodilator) according to GOLD 2016).

3. Sign (or their legally-acceptable representatives must sign) and date the informed consent form indicating that they understand the purpose of and procedure required for the study and are willing to participate in the study.

Exclusion criteria: 1. Participated in any interventional clinical trial during the last 30 days.

2. With acute exacerbation within 4 weeks before enrolment.

3. Not suitable for study observation judged by investigators.

Statistical methods: All statistical procedures were completed using SAS version 9.4. Analysis for this study was mostly descriptive. Summary statistics was provided. For continuous variables, this included the number, mean, median, standard deviation, minimum and maximum. For categorical variables, this included frequency counts and percentages at each group. There was no pre-planned hypothesis testing for this study. Two-sided 95% confidence intervals were presented, where applicable.

Results: A total of 5097 patients were screened, 84 patients (1.6%) failed and 5013 patients were enrolled into the study. Among them, 4978 patients (99.3%) were included in the FAS population, 4241 patients (84.6%) had completed the study and 772 patients (15.4%) withdrew before study ending.

The patients in FAS had a mean age of 66.2 years old with the range of 40-98 and the median age of 66.0. 3959 (79.5%) patients were males and 1019 (20.5%) were females. 1280 (25.7%) of the patients had no smoking history, 2556 (51.3%) patients had quitted smoking and 1142 (22.9%) had not quitted yet.

1. Primary endpoints

1.1 COPD exacerbation

During the one year follow-up period, the overall mean rate of exacerbations (acute exacerbation number per patient per year) was 0.56, and the severe exacerbation rate (0.31) is almost twice as the moderate one (0.17), indicating the severe exacerbation as a heavy burden to the patients.

The study results also showed the annual exacerbation rate increased progressly with COPD severity, from 0.33 in mild patients to 0.90 in very severe patients. Likewise, annual exacerbation rates were 0.26, 0.36, 0.62 and 0.93 in GOLD 2017 A/B/C/D groups, respectively.

In terms of hospital level, the overall mean exacerbation rate in secondary hospitals (0.66) was higher than that of tertiary hospitals (0.47), especially severe exacerbation (0.44 for secondary vs. 0.18 for tertiary), indicating heavier burden in lower level of hospitals.

In terms of patient proportion, a total of 1535 patients (30.8%) had at least one acute exacerbation during the one year follow-up. Among them, 960 (62.5%) patients experienced at least one severe exacerbation. The results also demonstrated that the proportion of patients with severe exacerbation increased along with the severity of the disease, from 47.9% in mild to 75.3% in very severe patients. Similarly, that proportion increased across GOLD 2017 A/B/C/D groups, from 35.8% to 71.7%. 57.0% of total 1535 patients were admitted to hospital at least once due to exacerbation during the follow-up period.

The results described above clearly demonstrated the enormous exacerbation burden to COPD patients.

1.2 Pulmonary function

At baseline, the number and proportion of patients were 458 (10.1%), 1886 (41.7%), 1558 (34.5%) and 616 (13.6%) in mild, moderate, severe, and very severe airflow limitation respectively. It can be concluded that Chinese outpatients with COPD were mainly with moderate to very severe airflow limitation, 89.9% of all FAS patients.

Both at baseline and after one year of follow-up, there were 792 patients participated in pulmonary function test. The total mean FEV_1 change after one year of follow-up from baseline is 0.027 L. The mean FEV_1 change after one year of follow-up from baseline is -0.120 L, -0.004 L, 0.079 L, and 0.141 L in the severity of mild, moderate, severe, and very severe, respectively. By GOLD A/B/C/D assessment, FEV_1 declined in group A and increased in group D.

1.3 PRO questionnaires

During the study among all 4978 patients, 4976 conducted CAT at V0 and 4184 at V1 respectively. The mean CAT score was 14.6 at V0 and 10.6 at V1 respectively. The mean change of CAT scores was -4.0 after one year follow-up from baseline. The mean CAT score from V0 to V1

were above 10 throughout the whole study. The mean mMRC score was 1.4 at V0 and 1.1 at V1 respectively. The mean change in mMRC was -0.3 after one year from baseline.

1.4 COPD-Q

In terms of disease awareness, 4973 patients took COPD-Q at V0 and 4142 at V1 respectively. The mean COPD-Q score was 5.9 at V0 and 6.7 at V1 respectively. The mean change in COPD-Q results was 0.7 after one year from baseline. The patients' COPD awareness needs to be further improved.

2. Secondary endpoints

2.1 Drug distribution

Among all 4978 patients, 4653 patients who took the pharmaceutical treatments of either mono or combination were recorded at baseline. The number and proportion of stable COPD medications at baseline by drug class were as below: ICS/LABA 1316 (28.3%), ICS/LABA+LAMA 871 (18.7%), LAMA 754 (16.2%), Methylxanthines 204 (4.4%), and SABA 102 (2.2%). The proportion of the patients using other treatment regimens, such as traditional Chinese medicine (TCM) , SAMA, SABA/SAMA, LABA, ICS, etc, were less than 2% repectively. Besides, the number and proportion of patients with neither ICS nor long-acting bronchodilator were 681 (14.6%).

Among all 4978 patients, 2358 patients who took the pharmaceutical treatments of either mono or combination were recorded by the end of one year of follow up period. The number and proportion of stable COPD medications by drug class are as below: ICS/LABA 848 (36.0%), ICS/LABA+LAMA 417 (17.7%), LAMA 361 (15.3%), TCM 53 (2.2%), and SABA 49 (2.1%). The proportion of the patients using other treatment regimens, such as methylxanthines, LABA, ICS, SAMA, SABA/SAMA, etc, were less than 2% repectively. And the number of patients with neither ICS nor long-acting bronchodilator was 273 (11.6%). It clearly indicated that ICS/LABA, ICS/LABA+LAMA and LAMA are the most common treatment regimens for patients with stable COPD.

At baseline, by the severity of airflow limitation, the number and proportion of patients prescribed with ICS/LABA were 117 (27.2%), 498 (28.1%), 393 (27.2%), 138 (24.0%) in mild, moderate, severe, and very severe respectively. The number and proportion of patients prescribed with ICS/LABA+LAMA were 47 (10.9%), 278 (15.7%), 313 (21.7%), 152 (26.4%) in mild,

moderate, severe, and very severe respectively. And the number and proportion of patients prescribed with LAMA were 110 (25.6%), 374 (21.1%), 166 (11.5%), 53 (9.2%) in mild, moderate, severe, and very severe respectively.

After one year of follow up, by the severity of airflow limitation, the number and proportion of patients prescribed with ICS/LABA were 76 (46.3%), 300 (36.3%), 257 (32.9%), 112 (30.5%) in mild, moderate, severe, and very severe respectively. The number and proportion of patients prescribed with ICS/LABA+LAMA were 18 (11.0%), 110 (13.3%), 162 (20.7%), 100 (27.2%) in mild, moderate, severe, and very severe respectively. And the number and proportion of patients prescribed with LAMA were 28 (17.1%), 166 (20.1%), 109 (14.0%), 25 (6.8%) in mild, moderate, severe, and very severe respectively. That is, with the increase of the severity of airflow limitation, the proportion of ICS/LABA+LAMA was obviously increasing and the proportion of LAMA decreased gradually.

The distribution of patients prescribed with the top three treatment regimens in GOLD 2017 A/B/C/D groups was as follows. At baseline, the number and proportion of patients prescribed with ICS/LABA were 198 (26.2%), 497 (25.4%), 119 (36.0%), 502 (31.3%) in group A/B/C/D respectively. The number and proportion of patients prescribed with ICS/LABA+LAMA were 150 (19.9%), 354 (18.1%), 57 (17.2%), 309 (19.3%) in group A/B/C/D respectively. The number and proportion of patients prescribed with LAMA were 185 (24.5%), 322 (16.4%), 58 (17.5%), 188 (11.7%) in group A/B/C/D respectively.

After one year of follow up, the number and proportion of patients prescribed with ICS/LABA were 112 (35.4%), 322 (35.2%), 73 (38.6%), 341 (36.4%) in group A/B/C/D respectively. The number and proportion of patients prescribed with ICS/LABA+LAMA were 57 (18.0%), 154 (16.8%), 27 (14.3%), 178 (19.0%) in group A/B/C/D respectively. The number and proportion of patients prescribed with LAMA were 68 (21.5%), 152 (16.6%), 33 (17.5%), 108 (11.5%) in group A/B/C/D respectively.

At baseline, the number of patients with at least one exacerbation during the previous 12 months was 2459 (49.4%) in the FAS population, while the number of patients who were administered with ICS containing therapy was 1521 (61.9%) and the number of patients with ICS/LABA+LAMA was 543 (22.1%) in these 2459 patients. During the one year follow-up period,

the number of patients who had at least one acute exacerbation was 1535 (30.8%) in the FAS population. Among them, 954 patients (62.1%) were administered ICS containing therapy and 353 patients (23%) used ICS/LABA+LAMA.

The number and proportion of medications for COPD exacerbations by drug class were as below: antibiotics 1058 (21.3%), ICS 510 (10.2%), short-acting bronchodilators 488 (9.8%), systemic corticosteroids 425 (8.5%), and others 1050 (21.1%).

The distribution of non-drug treatments (health education, smoking cessation, exercise of respiratory function and vaccine injection) during the study is that, at V0, 3342 patients participated in non-drug treatments as 2976 (89.0%), 1298 (38.8%), 1567 (46.9%) and 391 (11.7%) for health education, smoking cessation, exercise of respiratory function and vaccine injection, respectively. At V1, 2441 patients participated in non-drug treatments as 2334 (95.6%), 453 (18.6%), 1358 (55.6%) and 196 (8.0%) for health education, smoking cessation, exercise of respiratory function and vaccine injection, respectively.

2.2 Compliance

The overall medication compliance of the COPD treatment drugs (ICS/LABA, LAMA, LABA), which was defined as the actual fraction of drug taken days in the entire follow-up period, stayed consistently below 60% (59.0%, 59.4%, 59.8% by the assessments of airflow limitation, GOLD 2016, and GOLD 2017, respectively).

For the visit compliance, the mean usual care visit times per patient per year was 0.3, the dropout numbers of patients for each of the four visits (TC1, TC2, TC3, V1) accumulatively were 308 (6.2%), 423 (8.5%), 505 (10.1%) and 739 (14.8%) among all the 4978 patients.

2.3 Cost

During the follow-up period, the mean total direct COPD cost per year per patient was 4488 RMB. By the severity of airflow limitation, the mean direct COPD costs were 2712, 3477, 5043, and 7742 RMB in mild, moderate, severe, and very severe, respectively. It can be observed that the more severe the disease severity, the higher patients cost. The mean cost of patients with at least one exacerbation was 6797 RMB, much higher than that of all patients in FAS. Therefore, the prevention of acute exacerbation is very important in the management of stable COPD.

3. Exploratory endpoints

The result of multivariate Poisson regression model indicated that heart rate, mMRC score, mucus purulence, treatment by mucolytic drug, and exacerbation in previous 12 months were the popsitively related risk factors for COPD exacerbation. The exacerbation history during the previous year was noticed the relatively strong correlation (relative risk 2.7) with future exacerbation.

The result of multivariate Poisson regression model also indicated that heart rate, CAT score, mMRC score, mucus purulence, treatment by the drugs of ICS/LABA and Methylxanthines were the potential risk factors for COPD severity. Conversely, body mass index was negatively related with COPD severity.

The result of multivariate Poisson regression model indicated that only shortness of breath was the significant positively related risk factor to COPD patient compliance with LAMA exposure.

Conclusion:

This study indicated that a vast majority of Chinese outpatients with COPD had moderate to very severe airflow limitation. The high rate and proportion of severe exacerbations and mean CAT score constantly above 10 during the whole study period led to heavy exacerbation and symptom burden. COPD patients' exposure to ICS containing therapy seemed not follow the guideline properly, under exposure for higher severity patients, especially in patients with high risk of exacerbation. Moreover, patients' medication compliance and disease awareness was still suboptimal. In general, the standardization of COPD outpatient management in China needs to be enhanced further.