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RESPIRATORY MEDICINE | RESEARCH ARTICLE

Exacerbations in COPD patients treated with Inhaled Corticosteroids/Long-acting β_2 agonists combinations, switching to another combination drugs or inhaler device: A "real – world" study

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Abstract: This study investigates the effects of switching to different devices of the same active substance or between different active substances, in patients with Chronic Obstructive Pulmonary Disease (COPD) treated with Inhaled Corticosteroids (ICS) plus Long-acting β_2-adrenergic agonists (LABAs) in terms of incidence of exacerbations. A retrospective cohort analysis, based on administrative databases of 3 Italian Local Health Units, was conducted. Patients with at least one prescription of a fixed dose combination of ICS/LABA from 1 January 2009 to 31 December 2011 were included. The *index-date* was defined as the earliest date within the inclusion period in which the patient had the first switch of drug or device (switchers) or the first prescription of ICS/LABA for patients continuing with the same treatment (non-switchers). Patients were observed until 31 December 2012. Propensity score matching was performed to check for cofounding effects. COPD exacerbations were defined as COPD-related hospitalization and prescription of corticosteroids and antibiotics. Number of: hospitalizations for COPD, oral corticosteroids and antibiotics prescriptions were analyzed using Poisson regression models. After matching, 1,759 patients per arm were analyzed. No statistically significant difference was found

ABOUT THE AUTHORS

CliCon is a company specialized in designing and developing retrospective observational studies in collaboration with General Practitioners, Specialist Centers and Local Health Authorities (Regional and Local Health Units), using administrative and clinical databases. Founded in 1996 on a combination of skills in clinical medicine, health economics and information technology, today we are a multi-functional, project oriented organization capable of developing the entire range of activities required for an observational study.

Our mission is to support health stakeholders involved in the continuous improvement of clinical practice providing the capture of data on processes and outcomes, the analysis of the gap between expected and achieved results, the assessment of health technologies and economics, the dissemination of evidence and training, the development of cooperation between different stakeholders.

PUBLIC INTEREST STATEMENT

This real-world study investigates the effects of switching to different devices of the same active substance or between different active substances, in patients with Chronic Obstructive Pulmonary Disease (COPD) treated with Inhaled Corticosteroids (ICS) plus Long-acting β_2-adrenergic agonists (LABAs) in terms of exacerbations.
A retrospective cohort analysis, based on administrative databases of 3 Italian Local Health Units, was performed. COPD exacerbations were defined as COPD-related hospitalization and prescription of corticosteroids and antibiotics. Our findings showed that switching to different devices of the same active substance or among different active substances in COPD patients treated with a fixed dose combination of ICS/LABA was associated with higher COPD related exacerbation rates than those who did not switch.

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between study groups'. Incidence Rate Ratio in favor of non-switcher patients, as compared to switcher patients, was 1.41 (95% CI: 1.10–1.80) for number of hospitalizations, 1.05 (95% CI: 1.11–1.09) and 1.02 (95% CI: 0.96–1.09) for number of oral corticosteroids and antibiotics prescriptions, respectively. Our findings showed that switching to different devices of the same active substance or among different active substances in COPD patients treated with a fixed dose combination of ICS/LABA can lead to an higher likelihood of exacerbation COPD related rates than those who did not switch. Considering the study's limitations, further studies are needed in order to confirm and enhance the generalizability of our findings.

Subjects: Health and Social Care; Health Conditions; Public Health Policy and Practice

Keywords: chronic obstructive pulmonary disease; exacerbations; inhaled corticosteroids; long-acting β_2-agonist; switching therapy

1. Introduction

Chronic obstructive pulmonary disease (COPD), is a major chronic obstructive lung disease characterized by persistent airflow limitation, chronic and progressive dyspnea and are often complicated by exacerbations (Global Strategy for the Diagnosis, Management & Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2016). Epidemiological data on COPD incidence and prevalence have shown a wide variation in estimates due to differences in survey methods, diagnostic criteria, and analytic approaches (Raluy-Callado, Lambrelli, MacLachlan, & Khalid, 2015). The currently available data published by World Health Organization (WHO) suggest that, the prevalence of COPD in Italy is 5.3%, for a total of approximately 3.3 million cases (World Health Organization (WHO), Global Health Observatory (GHO) data, Chronic respiratory diseases, 2016).

Evidence-based clinical practice guidelines, recommend a multi-component approach for COPD management strategies (GOLD, 2016; Miravitlles et al., 2013; Qaseem et al., 2011). Inhaled corticosteroids (ICS) are frequently recommended for the treatment of COPD, often in combination with long-acting β_2-agonists (LABA), depending on the severity of the disease and/or on the specific clinical phenotype (GOLD, 2016). For patients with severe COPD and forced expiratory volume in one second (FEV_1) < 50%, who remain breathless or have history of repeated exacerbations despite maintenance therapy with a LABA, ICS/LABA combinations are recommended (GOLD, 2016).

One of the major therapeutic goals in COPD is the reduction of symptoms, including relief of immediate symptoms and improvements the overall health status (GOLD, 2016). An other major goal is to reduce the risk of exacerbations, which includes: prevention of developing COPD and stop its progression, prevention and treatment of exacerbations, and reduction in mortality (GOLD, 2016). Evidences from everyday clinical practice have shown that there are many different factors that play an important role in optimizing management of COPD (Braido, Baiardini, Sumberesi, Blasi, & Canonica, 2013; Bryant et al., 2013; Melani & Paleari, 2016). These factors are: identification of the appropriate drugs combination, compliance to treatment, choice among different available inhaler devices (e.g. metered-dose inhalers, dry powder inhalers, nebulizers) and consideration of patient-specific factors in device selection (Braido, Lavorini, Blasi, Baiardini, & Canonica, 2015; Braido et al., 2013; Bryant et al., 2013; Lavorini, Braido, Baiardini, Blasi, & Canonica, 2015; Yawn, 2011). Published studies suggest that medication adherence is often sub-optimal and that switching to different ICS/LABA device had a negative impact on optimizing to treatment (Braido et al., 2015; Bryant et al., 2013; Lavorini et al., 2015).

The objective of this real world study was to investigate the effects of switching to different devices of the same active substance or among different active substances in COPD patients treated with a fixed dose combination of ICSs/LABAs, in terms of the incidence of exacerbations (hospitalizations for COPD and the utilization of oral corticosteroids or antibiotics).

2. Methods

2.1. Data source

The study was conducted using administrative databases of three Italian Local Health Units (LHUs) geographically distributed throughout the national territory, representing approximately about 2 million health-assisted individuals.

In particular, the following databases were used: the Health-Assisted Subjects' Database, containing patients' demographic data; the Medications Prescription Database, providing information for each medication prescription; Hospital Discharge Database, including all hospitalization data, with the principal and secondary discharge diagnosis codes classified according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM); Ambulatory Care Specialist recording outpatient specialist services (visits, laboratory tests, diagnostic tests). The Italian Ministry of Health defines these archives as 100% complete and 95% accurate (Ministry of Labour, Health & Social Policies. Annual report on the hospitalization activity, 2005).

The patient code in each database permitted electronic linkage with all other databases. In order to guarantee patient privacy, an anonymous univocal numeric code was assigned for each subject. No identifiers related to patients were provided to the researchers. According to the Italian Medicines Agency (AIFA) (AIFA Guideline for the classification and conduction of the observational studies on medicines, 2010) Determination "Guidelines for classification and conduction observational studies on drugs" and AIFA circular "Procedures for launch of observational studies on drugs" analysis whereby it was notified to the LHU Committee of each participating LHUs.

2.2. Cohort definition

This retrospective cohort study included all patients with at least one prescription of a fixed dose combination of ICS/LABA [adrenergics in association with corticosteroids and other medicines for obstructive airway diseases - ATC code: R03AK- (fluticasone/salmeterol, budesonide/formoterol, beclomethasone/formoterol)] between 1 January 2009 and 31 December 2011 (*inclusion period*) (Figure 1). Two cohorts of patients were performed: "switchers" including those patients who switched between different devices of the same active substance or between different active substances, and "non-switchers" including patients continuing with the same medication. The *index-date* was considered: for switchers the date of the first switch of medication within the *inclusion period,* while for non-switchers the first prescription of ICS/LABA combinations. Patients were followed until 31 December 2012, death or end of treatment, whichever occurred first (*follow-up period*). Patients were required to be aged ≥40 years and have at least 6 months of follow-up from *index-date* and the last drug prescription. Patients who were transferred to another LHU during the follow-up period were excluded from analysis.

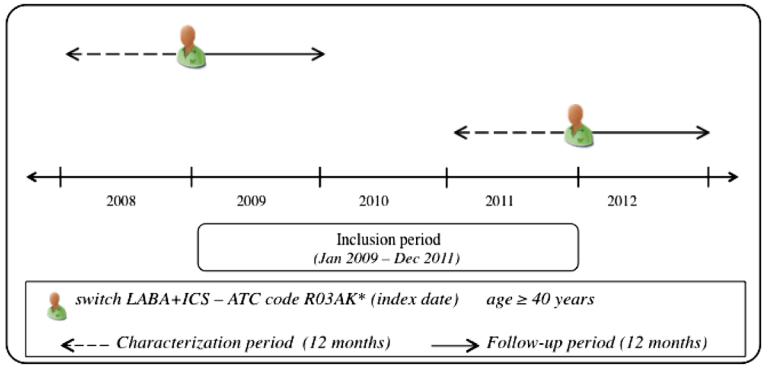

Figure 1. An overview of the study design.

Notes: Long-acting β_2-adrenergic agonists (LABAs); inhaled corticosteroid (ICS); Anatomical Therapeutic Chemical (ATC) code; Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics (ATC code R03AK).

2.3. Definitions and study outcomes

Baseline characteristics, including demographics, risk factors and medical history, were collected. Furthermore clinical characteristics of patients were investigated within 1 year before the *index-date* (*characterization period*). In particular, previous visits or hospitalizations COPD related were identified (ICD-9-CM codes for primary or accessory discharge: 490–496 excluding 493).

Previous use of antibiotics (ATC code: J01), oral corticosteroids (ATC code: H02), tiotropium (ATC code: R03BB04), ipratropium (ATC code: R01AX03), ICS (ATC code: R03BA), SABA (ATC code: R03AC), LABA (ATC codes: R03AC12, R03AC13), angiotensin receptor blockers (ATC codes: C09C, C09D), β-adrenergic blocking agents (ATC code: C07), statins (ATC code: C10AA), calcium channel blockers drugs (ATC code: C08) and thiazide (ATC code: C03A was also evaluated. Previous COPD exacerbations were also evaluated. The patients analyzed have been defined as patients with exacerbations in relation to the presence or absence of at least one of following conditions: Oxygen therapy, defined as at least one hospitalization with diagnosis for respirator dependence (ICD-9-CM code: V461), treatment with breathing exercises (ICD-9-CM code: V570), respiratory failure in other conditions (ICD-9-CM code: 518.81; 518.83; 518.84) or at least one hospitalization with breathing exercises (ICD-9-CM code: 9318), continuous positive airway pressure breathing (ICD-9-CM code: 9390), intermittent positive pressure breathing (ICD-9-CM code: 9391) or at least one prescription of oxygen (ATC code: V03AN01); antibiotics and/or corticosteroids therapy defined as at least two prescriptions of antibiotics (ATC code: J01) and/or oral corticosteroids (ATC code: H02); diagnosis of COPD, defined as at least one hospitalization with diagnosis for bronchitis, not specified as acute or chronic (ICD-9-CM code: 490), chronic bronchitis (ICD-9-CM code: 491), emphysema (ICD-9-CM code: 492), bronchiectasis (ICD-9-CM code: 494), extrinsic allergic alveolitis (ICD-9-CM code: 495), chronic airway obstruction, not elsewhere classified (ICD-9-CM code: 496); surgical reduction of the lung volume (ICD-9-CM code: 3222); lung transplantation, defined as at least one hospitalization with an intervention for lung transplantation, not otherwise specified (ICD-9-CM code: 3350), unilateral lung transplantation (ICD-9-CM code: 3351), bilateral lung transplantation (ICD-9-CM code: 3352).

The Charlson comorbidity Index (CCI) was also calculated for each patient by summing the assigned weights for all comorbid conditions evaluated in the characterisation period: the CCI score reflects a patient's overall health status. This methodology has been widely used in order to compare disease severity in retrospective analyses when data are unavailable.

Hospitalizations related to COPD, oral corticosteroids and antibiotics prescriptions were analyzed during follow-up period.

COPD exacerbations were defined as COPD-related hospitalizations or visits and prescriptions of systemic corticosteroids or antibiotics.

3. Statistical analysis

Continuous variables were reported as mean and standard deviation (SD) (median and range as appropriate), whereas categorical variables were expressed as numbers and percentages.

In order to minimize selection bias, a second multivariable analysis was also performed using propensity score to match switchers and non-switchers. Propensity score was determined using a logistic regression model in order to calculate for each patient the probability to be switched or not. Propensity score matching was performed to check for cofounding effects such as: age, sex, number of previous visits/hospitalizations for COPD, number of previous prescriptions of antibiotics, oral corticosteroids, tiotropium, ipratropium, ICS, Short-Acting Beta Agonists (SABAs), LABA, angiotensin receptor blockers, β-adrenergic blocking agents, statins, calcium channel blockers drugs, thiazide, previous exacerbations and comorbidities. Hosmer-Lemeshow and C-statistic tests were used to

assess model calibration and model discrimination. Switcher and non-switcher groups were then matched inside each quintile of the propensity score. Number of hospitalizations for COPD, oral corticosteroids and antibiotics prescriptions during follow-up were analyzed using Poisson regression models. Since the groups considered were matched for all baseline characteristics, the 3 outcomes considered were compared by univariate Poisson models, which take into account not only the dependent variable expressed by a count but also the exposure time of patients in analysis.

P-values less than 0.05 were considered to be statistically significant, and all statistical analyses were conducted using SPSS statistical software for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

4. Results

A total of 21,375 patients met the inclusion criteria and were included in the analysis; about 52% of all subjects included were male and the mean (±SD) age was 67 ± 12 years. Of these patients, 1,759 (9%) switched to an alternative inhaler or another fixed dose combination of ICS/LABA during the inclusion period. Baseline demographic characteristics of the study population are shown in Table 1.

After matching, 1,759 patients per arm were analyzed; no relevant differences were observed with respect to demographic and clinical characteristics (Table 2). No statistically significant difference was found between study groups'. At the Poisson regression models, Incidence Rate Ratio (IRR) in favor of non-switcher patients, as compared to switcher patients, was 1.41 (95% confidence interval (CI): 1.10–1.80, $p = 0.006$) for number of hospitalizations, 1.05 (95% CI: 1.11–1.09, $p = 0.016$) for number of oral corticosteroids prescriptions, 1.02 (95% CI: 0.96–1.09, $p = 0.479$) for number of antibiotics prescriptions (Figure 2).

Table 1. Baseline demographic and clinical characteristics of the study population

	Non switchers	Switchers	*p*-value
N (%)	19,616 (91)	1,759 (9)	
Males (*n*, %)	10,220 (52)	892 (51)	0.275
Age (mean ± SD)	67.2 ± 12.8	66.7 ± 12.3	0.115
Exacerbations pre-index date (*n*, %)	12,712 (65)	1,402 (80)	<0.001
Charlson comorbidity index (mean ± SD)	2.00 ± 1.31	2.12 ± 1.32	<0.001

Note: SD: Standard deviation.

Table 2. Baseline demographic and clinical characteristics of the study population after matching

After matching	Non switchers	Switchers	*p*-value
N (%)	1,759	1,759	
Males (*n*, %)	883 (50)	892 (51)	0.787
Age (mean ± SD)	66.4 ± 12.6	66.7 ± 12.3	0.617
Exacerbations pre-index date (*n*, %)	1,389 (80)	1,402 (80)	0.617
Charlson comorbidity index (mean ± SD)	2.11 ± 1.49	2.12 ± 1.32	0.833

Note: SD: Standard deviation.

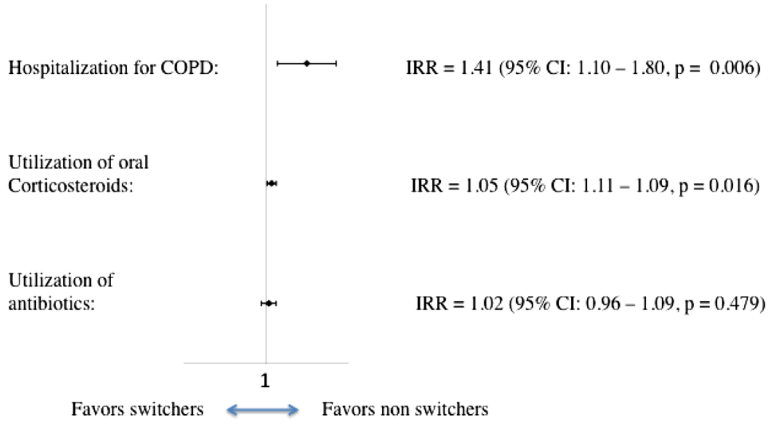

Figure 2. Propensity score-matched populations of Chronic Obstructive Pulmonary Disease patients treated with fixed-dose combination of Inhaled Corticosteroids/Long-acting β_2-adrenergic agonists, switchers to another medication device versus non switchers.

Notes: Chronic Obstructive Pulmonary Disease (COPD); Long-acting β_2-adrenergic agonists (LABAs); inhaled corticosteroid (ICS); Incidence Rate Ratio (IRR) 95% confidence intervals (CI); p-value (p).

5. Discussion

The present study showed that switching to different inhalers or to different drugs in patients with COPD treated with a fixed dose combination of ICS/LABA was associated with higher COPD related exacerbation rates than those who did not switch.

Our findings are consistent with data of previous studies that demonstrated how switching drugs and/or inhalers could be associated with mistakes in drug utilization and a decrease in treatment adherence and could generate a range of negative outcomes (Braido et al., 2013, 2015; Larsson et al., 2013; Lavorini et al., 2015; Melani & Paleari, 2016).

COPD represents a considerable economic and social burden and requires regular and ongoing treatment to keep symptoms under control (European Respiratory Society, 2013; Gibson, Loddenkemper, Lundbäck, & Sibille, 2013; Herse, Kiljander, & Lehtimäki, 2015). Inhalers play a crucial role in the optimal management of patients with COPD and their choice is as important as that of the drug molecule (Bonini & Usmani, 2015). Several fixed-dose ICS/LABA combinations are available as well as a variety of delivery systems are used to target ICS/LABA to the airways, including pressurized metered-dose inhalers (pMDIs), dry-powder inhalers (DPIs), and nebulizers (Lavorini et al., 2015).

The literature showed that there are many potential reasons for witch patients may change or discontinue medication (Braido et al., 2015; Laube et al., 2011; Lavorini et al., 2015; Melani & Paleari, 2016). When disease control is suboptimal, a switch to a more appropriate inhaled therapy may be appropriate (Laube et al., 2011; Melani & Paleari, 2016; Wurst, St Laurent, Muellerova, & Davis, 2014). At this point, the inherent characteristics of inhalers are concerned, it should always be kept in mind that in the most severe stages of the disease, the inhaler may fail to activate due to an inappropriate peak inspiratory flow, which would prevent an effective dose of drug from reaching the lungs (Sanduzzi et al., 2016).

Therefore, it is clear that the selection of the most appropriate drug and inhaler for a switch is critical. Published studies (Björnsdóttir, Gizurarson, & Sabale, 2013; Bonini & Usmani, 2015; Melani & Paleari, 2016) suggest that the decision to switch to an alternative drug or inhaler device should be carried out in agreement with the patient, in order to find the best solution. Furthermore, several parameters should be taken into account before switching, such as: drug availability and administration time, patient age and ability to use device correctly, easier-to-use, costs, as well as physician and patient preference.

The position paper issued by European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM) (Laube et al., 2011) recommends that patients with stable disease

should remain on their current inhaler rather than switching to a new one. Indeed, switching between drugs/devices for patients that have stable COPD without exacerbation may have a negative impact on disease control (Braido et al., 2015). Healthcare providers recommend (Laube et al., 2011) a number of questions to be asked the patient before changing the treatment protocol, in order to confirm that the cause of failure of inhalation treatment is related to the drug or inhaler device. When all conditions are satisfied, switching may be useful and could improve disease control.

Several studies have clearly shown that switching between inhaler devices can have an impact on disease control and the patient's well-being (Bonini & Usmani, 2015; Braido et al., 2015; Doyle et al., 2010; Lavorini et al., 2015; Melani & Paleari, 2016; Virchow et al., 2015). Patients' training and education in use of inhalers is often neglected, although clinical evidences have shown that suboptimal education is directly related to low efficacy of therapy and could negatively impact disease control increasing also healthcare resources utilization and costs (Braido et al., 2013; Doyle et al., 2010; Lavorini et al., 2015; Melani & Paleari, 2016). However, in daily clinical practice, too little consideration is given to the features of the different inhalers and to the ability of patients to properly handle the device. Specific recommendations are needed in order to help healthcare professionals to prescribe the most "appropriate" inhaled drug and inhaler device (Bonini & Usmani, 2015; Braido et al., 2013; Lavorini et al., 2015). Another factor that should be taken into due consideration is that an increased rate of inhalation mistakes could be caused by device switches (Braido et al., 2015). Indeed, multiple-inhaler use has been associated with higher rates of non-adherence than single-inhaler use in both asthma and COPD patients – potentially because of the increased complexity introduced by the switching of inhaler(s) (Braido et al., 2013; Mäkelä, Backer, Hedegaard, & Larsson, 2013; Sanduzzi et al., 2016). Furthermore, the occurrence of critical inhaler errors also led to a significant increase in risk of hospitalization, accesses to emergency department, use of antibiotics and systemic corticosteroids (Virchow et al., 2015).

Our findings should be considered in light of several limitations. Our cohort of patients reflected real clinical-practice, and the results must be interpreted, taking into account limitations related to the observational nature of the study, based on data collected through administrative databases. In order to reduce selection bias and create more comparable cohorts, propensity score matching was used to adjust for confounders measured and to mitigate the effect of potential switching of the index ICS/LABA on rate of COPD exacerbations. Nevertheless limitations include, first, the absence of relevant clinical information in the data setting (i.e. the severity of the diagnoses of COPD could not be verified by spirometry). Second, we had no information on inhaler errors. Third, the reasons for switch to an alternative device of the patients are not retrievable from the data-set. Fourth, we defined switchers as those patients who switched between different devices of the same active substance or among different active substances, for this reason we cannot document a switching among another active substance or an alternative device, separately. Fifth, medication use is based on prescription data, which do not fully reflect how patients actually use drugs. Consequently, we couldn't be excluded that the natural course of disease could be played a role on rate of COPD exacerbations. Although the included patients have been matched pairwise with respect to a number of variables, there may still be potential unknown confounding factors.

Despite these limitations, our study suggests that in a "real-world" setting, switching to different inhaler devices or among different drugs in COPD patients treated with a fixed dose combination of ICS/LABA can lead to an increase the likelihood of exacerbation COPD-related than those who did not switch The choice of the appropriate drugs combination and inhaler is an important determinant of treatment outcomes. Nevertheless, further studies are needed in order to confirm and enhance the generalizability of our findings.

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Author contributions
All authors contributed toward data analysis, drafting, and revising the paper and agree to be accountable for all aspects of the work.

Ethical Approval
For this type of study formal consent is not required. However, to guarantee patient privacy, no personal identifiers were provided to the researchers. According to the Italian law for confidentiality of data the study was notified to the Ethic Committees of each Local Health Unit.

Competing Interests
The authors declare no competing interest.

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