Respiratory Medicine 130 (2017) 75–84

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Effects of inhaled corticosteroids /long-acting agonists in a single inhaler versus inhaled corticosteroids alone on all-cause mortality, pneumonia, and fracture in chronic obstructive pulmonary disease: A nationwide cohort study 2002–2013

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ARTICLE INFO

Article history:
Received 13 January 2017
Received in revised form
16 July 2017
Accepted 17 July 2017
Available online 19 July 2017

Keywords:
Inhaled corticosteroids
Long-acting β-agonists
ICS/LABA in a single inhaler
Chronic obstructive pulmonary disease
All-cause mortality
Adverse events

ABSTRACT

Background: Both inhaled corticosteroids (ICS) and long-acting β-agonists (LABA) have been recommended for the treatment of severe/moderate chronic obstructive pulmonary disease (COPD), but mild COPD has not been frequently studied.

Methods: We performed a prospective cohort study to compare the effect of inhaled corticosteroid (ICS) and ICS/long-acting β-agonist (LABA) in a single inhaler on all-cause mortality and adverse events, such as pneumonia and fracture, in patients with newly diagnosed chronic obstructive pulmonary disease (COPD). We used representative nationwide cohort data from the Korean National Health Insurance claims database (2002–2013). Patients who were at least 40-years-old, newly diagnosed with COPD, and prescribed ICS or ICS/LABA in a single inhaler (N = 1995). To analyze the data, we utilized a Cox's proportional hazard regression.

Results: Among the total of 1995 patients, 807 had severe COPD (FEV_1 < 50%) and 1188 had mild/moderate COPD ($FEV_1 \geq 50\%$). The cumulative incidence and 5-year cumulative incidence of all-cause mortality was 59.5% and 29.6% for ICS users, and 35.8% and 20.2% for single inhaler ICS/LABA users, respectively. The adjusted hazard ratio (HR) of all-cause mortality for new ICS/LABA users, compared with that in new ICS users, was 0.77 (95% CI: 0.62–0.95) for the total population. For the severe and non-severe COPD groups, the adjusted HRs of all-cause mortality for new ICS/LABA users were 1.07 (95% CI: 0.65–1.76) and 0.70 (95% CI: 0.55–0.89), respectively. There was no difference in the risk for the first hospitalization due to pneumonia between new ICS and ICS/LABA users among the total population (HR: 1.02; 95% CI: 0.79–1.34). The adjusted HR of the first hospitalization for fractures in new ICS/LABA users, compared with that in new ICS users, was 0.60 (95% CI: 0.39–0.92) for the total population.

Conclusions: Among newly diagnosed COPD patients and new users of ICS or ICS/LABA, use of ICS/LABA in a single inhaler was associated with lowered risk of all-cause mortality and delayed first hospitalization for fracture, as compared with use of ICS alone. However, there was no significant difference in terms of first hospitalization for pneumonia.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a condition associated with high morbidity, mortality, and national cost. In the

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http://dx.doi.org/10.1016/j.rmed.2017.07.012
0954-6111/

most recent global guidelines, COPD is defined as "a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases" [1]. Medications are the mainstay of COPD management, and knowing the most effective medication to use is necessary in real world practice [2].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 treatment guidelines recommend the use of inhaled corticosteroids (ICS) for symptomatic COPD patients with forced expiratory volume $(FEV)_1 < 50\%$ predicted and repeated exacerbations, as the start to controller medications [1]. Both ICS and long-acting beta-agonists (LABAs) have been shown to be effective in COPD [3]. ICS reduce the frequency and severity of exacerbations [4], but have not yet been shown to slow disease progression or improve mortality rates [5]. Compared with placebo or ICS alone, combination therapy consisting of LABAs and ICS might interact in a beneficial way, potentiating local anti-inflammatory actions [6], and may thereby decrease exacerbations and possibly decrease mortality [5,7,8]. However, recent studies have suggested contrasting ideas about ICS, including combinations of LABAs and ICS. A recent systematic review of randomized clinical trials found that co-administration of LABAs and ICS resulted in fewer exacerbations and better quality of life, and had a statistically significant effect on all-cause mortality, as compared to treatment with placebo [3]. In contrast, some previous studies have shown that the evidence of the benefits of ICS, or of ICS/LABA combinations in COPD, is compromised by major methodological problems such as an immortal time bias that does not consider the follow-up time elapsed before the start of medication use [9–11]. Another study has found that ICS/LABA did not affect mortality in patients with moderate COPD more than did placebo [12]. Moreover, there have been a few previous studies that have compared the effect of ICS/LABA in a single inhaler and ICS alone on the risk for all-cause mortality in mild or moderate COPD in an Asian population [13–15].

In terms of a comparison of the adverse effects between ICS and ICS/LABA, the TORCH trial found that patients receiving the combined medication did not have an increased risk of pneumonia as compared with patients receiving ICS alone. Yet, another systematic review of observational studies [16] and a randomized trial [17] have suggested that use of ICS increases the risk of pneumonia. A further systematic review of randomized trials has also shown that the use of ICS (including ICS/LABA) is consistently associated with a modest, but a statistically significantly increased likelihood of fractures as compared to placebo or LABA alone [18]. There has been no report that evaluated the risk for fracture between the use of ICS alone and the use of ICS/LABA in a single inhaler.

Therefore, the aim of this study was to compare the effect of ICS and ICS/LABA in a single inhaler on all-cause mortality, avoiding the methodological issues that have affected previous studies, and to identify whether there was a difference in adverse effects, including pneumonia and fractures, of these medications in patients who had been newly diagnosed with COPD.

2. Methods

2.1. Data source

The Institutional Review Board of the Graduate School of Public Health, Yonsei University granted ethical approval for this study.

This study used cohort data from the Korean National Health Insurance (KNHI) claims database released by the National Health Insurance Services (NHIS) for the period 2002 to 2013. Korea has a unique health care security system composed of a single insurer that is managed and supervised by the government and that covers almost all of the Korean population and medical facilities. The KNHI, in which all Koreans are mandatorily registered, covers nearly all medical expenses. In 2002, the NHIS established cohort data representative of the Korean population, which included information on 1,025,340 subjects who represented a stratified random sampling according to age, sex, region, type of health insurance, income quintile, and total individual medical costs. These cohort data also included information on reimbursement for each medical service, basic patient information, an identifier for the clinic or hospital, the disease code, costs incurred, results of health screening, patient/family health history, health behaviours, and information related to death.

2.2. Study population

We only included new users of ICS or ICS/LABA among COPD patients who had been newly diagnosed between 2004 and 2013. We confirmed that the diagnoses were new by verifying a lack of COPD claims from 2002 to 2012, and then by verifying an initial COPD claim in the period 2003–2013. For example, in case of patients who were newly diagnosed in 2004, an initial COPD claim of the patient emerged in 2004, and there were not claims of COPD until 2003. If we defined that a patient was newly diagnosed in 2009, in initial claim of COPD of the patient emerged in 2009, there were no claims of COPD for 7 years from 2002 to 2008. We defined every new case of COPD in this way. And we considered several things to identify true COPD patients, because we used claims data based on KNHI not medical record. The accuracy of diagnosis of our claim data is about 70% [19]. The Korean healthcare delivery system is classified into three steps based on fee-for-service as the reimbursement mechanism: clinics function as primary care institutions; hospitals function as secondary care institutions; general hospitals and tertiary general hospitals function as third tier care institutions. In Korea, patients should undergo some type of process for diagnosis of COPD. In primary care, if the physician suspects a patient has COPD, the physician refers the patient to a superior institution where a pulmonologist exists that can perform pulmonary function test with/without prescribing COPD medicine. The patient should take physical exams, interview and clinical tests (such as pulmonary function test), and then the physician can diagnose the patients with COPD and categorize COPD severity according to Global Initiative for Obstructive Lung Disease (GOLD) guidelines. Throughout this process, the code of COPD can be coded whether or not the patient is a real COPD patient. If anyone was a real patient with COPD, he/she would take a PFT and prescription for COPD medicine. Therefore, we used the International Classification of Diseases, 10th Revision (ICD-10) codes, medication information, clinical test information, and demographic characteristics among the recorded data. We selected only patients who met the following criteria. We selected only patients who met the following criteria according to previous studies [20–22]. Individuals were defined as COPD patients if they met all of the following criteria: 1) age $\geq$40 years, 2) ICD-10 codes for COPD (J42-J44, except J430), 3) use of one or more COPD medications at least once per year, and 4) undergoing a pulmonary function test before and at 6 months after an initial COPD claim. COPD medications included 1) inhaled long-acting muscarinic antagonists (LAMA), 2) inhaled and long-acting β2 agonists (LABA), 3) ICS, 4) ICS plus LABA, 5) inhaled short-acting muscarinic antagonists (SAMA), 6) inhaled short-acting β2 agonists (SABA), 7) methylxanthines, 8) oral corticosteroids, and 9) systemic β agonists. Of those patients who were newly diagnosed with COPD, we only included new users of ICS or ICS/LABA in a single inhaler for the period 2004–2013. ICS/LABA in a single inhaler included the following agents: fluticasone/salmeterol,