STUDY PROTOCOL

Risk of pneumonia and death in outpatients with chronic obstructive pulmonary disease treated with different lengths of corticosteroids

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INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) contribute to high morbidity and mortality. Similarly, admission with pneumonia is associated with high mortality(1). The treatment of an exacerbation of COPD involves the use of bronchodilators, oxygen treatment and systemic corticosteroids. Oral corticosteroids (OCS) are known to lead to a number of short-term and long-term adverse events, including hypertension, dyslipidemia, hyperglycaemia, myopathy, cataract, infection, and risk of bone fractures. It is also well-known that treatment with inhaled corticosteroids for the prevention of COPD exacerbations increases the risk of pneumonia (2). The incidence of pneumonia hospitalisation caused by the use of systemic corticosteroids in COPD patients is uncertain. However, prednisolone is an immunosuppressive agent, and therefore it is biologically plausible that it could lead to severe lung infections.

In 2013 the recommended treatment with oral OCS in patients with acute exacerbations of COPD changed from a 10-day regimen (total dose > 250 mg) to a 5-day regimen (total dose ≤ 250 mg), which we suppose has contributed to reducing the incidence of pneumonia.

METHODS

Study hypotheses

To investigate the risk of pneumonia hospitalisation and all-cause mortality in COPD users of short course of prednisolone (after June 2013) compared to COPD users with long course of prednisolone (before June 2013).

And to assess whether the effect varied by recent initiation of prednisolone therapy, dose, or duration of prednisolone use.

Study population

We performed a population based study in a cohort of Danish users of prednisolone with a diagnosis of COPD between 1 January 2008 and 31 October 2017. The outcome of interest was the effect of prednisolone length (short course versus long course) on risk of admission with first time pneumonia and all-cause mortality during three years of follow-up in the period 2008-2017. Pneumonia is identified by using discharge diagnoses from hospital.

We enrolled patients above 50 years of age with a clinical diagnosis of COPD and a discharged diagnosis of pneumonia from hospital. We excluded patients who had known asthma diagnosis or Tiffeneau index > 70. Patients were stratified into two groups: (i) OCS treatment below 250 mg (ii) OCS treatment above or equal to 250 mg.

Data sources

For this study, we used:

(1) The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD), which is a nationwide database that contains information on the quality of treatment of all patients with COPD in Denmark.

(2) The Danish National Patient Registry (DNRP), which holds information on all admissions to Danish hospitals since 1977 and hospital outpatient specialist clinic visit since 1995.

(3) The National Prescription Registry holds information on all prescriptions dispensed in Danish pharmacies since 2004 (coded according to the Anatomical Therapeutic Chemical (ATC) classification system).

STATISTICAL ANALYSIS

Main analyses:

Cox proportional hazards models will be used for the analysis of the primary endpoint. All analyses will be adjusted for age, sex, smoking status, inhaled corticosteroids, calendar-period, lung function (FEV1), body mass index and MRC dyspnea score.

Sensitivity analyses

These analyses will be followed by a conditional logistic regression model (matched on index date, age and gender) estimating risk of exposure (short course vs long course) 3 months before pneumonia hospitalisation and all-cause mortality (nested case control design). SAS Enterprise Guide 7.1 will be used for all statistical analyzes.

TIMETABLE

The study commences January 2018 and analyses will take place in the spring of 2018. The manuscript will be submitted early in the autumn of 2018.

ETHICS

The study was approved by the Danish Data Protection Agency (journal number: HGH-2017-091, with I-Suite no.: 05884) In Denmark, retrospective use of register data does not require ethical approval or patient consent.

FUNDING & PUBLICATION

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