Use of inhaled corticosteroids and risk of osteoporosis and osteoporosis-related fractures in COPD patients: A Nationwide study of n=100,000 COPD outpatients

Protocol

An observational study investigating the risk of osteoporotic fractures in COPD patients treated with different dosing regimens of inhaled corticosteroids.

Coordinator

Mette Johannsen Mandøe, MD, Department of Internal Medicine, Respiratory Medicine Section, Gentofte Hospital, Kildegårdsvej 28, 2900 Hellerup.

Supervisors

Jens-Ulrik Stæhr Jensen, PhD, Research Associate Professor
Department of Internal Medicine, Respiratory Medicine Section, Herlev and Gentofte University Hospital, Hellerup, Denmark
&
Institute for Clinical Medicine, Faculty of Health Sciences, University of Copenhagen

Pradeesh Sivapalan, MD, Research Fellow
Department of Internal Medicine, Respiratory Medicine Section, Herlev and Gentofte University Hospital, Hellerup, Denmark

Table of contents

Introduction

The burden of comorbidities among patients with Chronic obstructive pulmonary disease (COPD) is substantial (1).

Apart from treatment with long-acting β_2-agonist (LABA) and/or long-acting muscarinic antagonists (LAMA) (1), inhaled corticosteroids (ICS) in different dosages are given frequently, although the effect is somewhat disputed and additionally there is a growing concern regarding the potential side effects to this treatment.

One of the well-known side-effects for patients treated with *systemic* glucocorticoids is osteoporosis. Osteoporosis can be defined as a systemic skeletal disease characterized by low bone density and microarchitectural changes, leading to an increase in fragility and an attributed increase in the risk of fractures (2), especially in the vertebral spine, in which trabecular tissue is abundant. The risk of fractures is increased up to one year after the termination of treatment with systemic glucocorticoids.

It remains unclear whether increasing exposure to ICD in COPD patients leads to increasing risk of osteoporotic fractures (37).

Method and design

Hypothesis

Fractures are seen more frequently in COPD patients treated with ICD. The risk is increasing with increasing time of treatment and increasing dosage.

Aim of the study

To determine whether the risk of any fracture in COPD patients is related to the use of ICS and to assess whether the risk of fractures increases with increasing daily ICS dose.

Population

We will perform a Nationwide population-based cohort study among patients with a spirometry-verified and specialist diagnosed COPD from the period January 2010 to October 2017. The database covered all Danish patients followed in a specialist COPD outpatient clinic. This database was merged with data on all medical prescriptions on the same patients in this period as well as complete data on all admissions and vital status.

Inclusion

- COPD diagnosis (verified by spirometry)
- Age ≥ 40 years
- Types of ICS: all with the ATC code = R03BA

Exclusion

- Treatment with systemic corticosteroids > 450 mg accumulated within 12 months
- Immune-modulating therapy
- Cancer diagnosis except for basocellular carcinoma
- Known history of high energy trauma
- Never smoker

Data sources

1) The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD). A nationwide database that contains information on the quality of treatment of all patients with COPD in Denmark.
2) The Danish National Patient Registry. A database holding information on all admissions to Danish Hospitals since 1977 and hospital outpatient specialist clinic visits since 1995.
3) The National Prescription Registry. A database holding information on all prescriptions dispensed in Danish pharmacies since 2004 (coded according to the Anatomical Therapeutic Chemical (ATC) classification system.)

Statistical considerations and power calculations

Primary endpoint

Any fracture treated in a hospital (outpatient or during admission) within the study period

Secondary endpoint

Prescription of any anti-osteoporotic medicine in the study period including the ATC-codes M05BA, M05BB (bisphosphonates), M05BX04 (denosumab), M05BX03 (strontiumranelate), G03XC (SERM) and H05AA02 (teriparatide)

Analysis

Cox proportional hazard regression models will be used to calculate the adjusted hazard ratio (aHR) and 95% confidence interval (CI) for the analysis of the primary endpoint.

All analyses will be adjusted for age, sex, smoking status, body mass index and pre-existing fractures.

SAS Enterprise Guide 7.1 will be used for all statistical analyzes.

Sensitivity analyses

(Propensity score matching with ICS users vs. non-ICS users)

Publication of results

The study findings will be published regardless of whether they are positive, negative or in-conclusive.

Ethical statement

In Denmark, retrospective use of register data does not require ethical approval or patient consent.

References

(1) Global strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Obstructive Lung Disease. 2019 report. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf
(2) Anon. Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. Am J Med. 1993;94:646-50.
(3) National guidelines for the treatment of osteoporosis, Danish Bone Society.