CURE: Copenhagen Unit for Respiratory Epidemiology

COP:TRIN (www.coptrin.dk)

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Risk of increased mortality and cardiovascular events in patients with chronic obstructive pulmonary disease treated with clarithromycin

Introduction

More than 14% of adults in Denmark is estimated to have chronic obstructive pulmonary disease (COPD) (1). COPD is associated with both non-infectious and infectious exacerbations and thereby increased risk of hospital admissions and death (2). Patients with COPD have a higher risk of contracting community acquired pneumonia (CAP) compared to healthy individuals (3, 4). In the health care system, pneumonia is treated with antibiotics, e.g. β-lactam, macrolide or tetracycline (2, 5). Compared to healthy individuals, COPD-patients are more often treated with antibiotics because of pneumonia and exacerbations. Macrolides are a common choice to treat COPD-patients having atypical pneumonia, moderate to severe pneumonia or penicillin-allergy (6).

Early 2018, U. S. Food and Drug Administration (FDA) published a warning against treating patients with cardiac illnesses with the macrolide clarithromycin because the CLARICOR-study group had shown an increased cardiovascular 3-year mortality (HR=1.42) in patients treated with clarithromycin compared to placebo (7, 8). The patients included in the randomized, clinical trial were in a stable period of their cardiac illness (stable angina pectoris or more than 90 days since acute cardiac event).

In a retrospective cohort study including patients treated by family doctors with the macrolide clarithromycin, it was shown that treatment with clarithromycin was independently associated with a higher mortality and risk of cardiovascular events (apoplexia and acute myocardial infarction) when compared to patients treated with the macrolide erythromycin and the tetracycline doxycycline (9). The macrolide azithromycin has been shown to increase the risk of cardiovascular death as well (10).

In 2013 an analysis of two smaller prospective cohort studies including 1343 patients with acute exacerbations of COPD and 1631 patients with CAP, respectively, was published. The analysis

indicated that treatment with clarithromycin gave an increased risk of cardiovascular events (HR =1.50) and acute coronary syndrome (HR = 1.67) among the COPD-patients, whereas the patients with pneumonia only had an increased risk of cardiovascular events (HR = 1.68). However, the follow-up period was only one year, which has been shown in other studies, is not enough to see the full side effects of clarithromycin (7, 11).

Patients with COPD have an increased risk of cardiovascular events, chronic cardiovascular illnesses and death compared to healthy individuals (2, 4, 12). The hypothesis of this study is that clarithromycin and azithromycin further increases the risk of death and cardiovascular events within COPD-patients, which already have an increased risk due to their COPD.

Objective

The aim of the study is to investigate within a large population of Danish COPD-patients, if the risk of death (3-year mortality), cardiovascular events or cardiovascular death (within 3 years) is increased in the patients who have received treatment with clarithromycin or azithromycin.

Method

Study design:

- Retrospective cohort study
- 3 years follow-up from the first relevant treatment with antibiotics
- Groups:
  Patients who received:
- One treatment with clarithromycin vs azithromycin vs amoxicillin/clavulanic acid
- Two treatments with clarithromycin vs azithromycin vs amoxicillin/clavulanic acid
- Three treatments or more with clarithromycin vs azithromycin vs amoxicillin/clavulanic acid

Period:

January 1, 2010 – January 1, 2018

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Inclusion criteria:

- Tiffeneaus index (FEV1/FVC) < 70% (verified with spirometry)
- Age ≥ 40 years

Exclusion criteria:

- Cardiovascular event within the last 90 days (acute myocardial infarction, acute coronary syndrome, serious arrhythmia, stroke)

Exposure variable:

- Treatment with clarithromycin, azithromycin or amoxicillin/clavulanic acid

Primary endpoint

- Death within 3 years

Secondary endpoints

- Cardiovascular events within 3 years (acute myocardial infarction, acute coronary syndrome, serious arrhythmia, stroke)
- Cardiovascular death within 3 years (acute myocardial infarction, acute coronary syndrome, serious arrhythmia, stroke)

Data resources

Data from the Danish Register of COPD-patients (Dansk Register for KOL: http://www.kcks-vest.dk/kliniske-kvalitetsdatabase), data from the national agency of health (Sundhedsdatastyrelsen) (landspatientregistret, dødsårsagsregistret) and the agency of national statistics (Danmarks statistik) (lægemiddelstatistikregistret).

Statistical analysis of data

Regression analysis (Cox proportional hazard model) will be used to investigate the relationship between exposure (antibiotics) and endpoint (risk of death, cardiovascular event or cardiovascular

death). Log-rank test will be used to investigate if the difference in risk is significantly different between the groups.

The analysis will be adjusted for confounder variables gender (male/female), age (per year), smoking status (never smoker, former smoker, smoker), lung function (FEV1, percent of expected), Tiffeneaus index (FEV1/FVC, ratio), BMI (kg/m^2), diagnosed hypertension (yes/no) and Charlson comorbidity index (per unit).

Statistical analysis is carried out in SAS Enterprise Guide 7.1 windows version and IBM SPSS Statistics version 22.

Approval

We have applied for and are awaiting approval from The Capital Region of Denmark (Region Hovedstadens paraplyanmeldelse) and (herunder datatilsynet) and Clinical Quality Development Program of the Regions (Regionernes Kliniske Kvalitetsudviklingsprogram, RKKP) before we initiate analysis of data.

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