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Use of oral corticosteroids and the risk of venous thromboembolism and mortality in patients with Chronic Obstructive Pulmonary Disease

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Background:

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airway obstruction caused by a number of inflammatory changes in the airways and lungs. When a patient is hospitalized with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), the treatment is systemic corticosteroids, beta-adrenergic receptor agonists and muscarinergic-receptor antagonists, followed by a 5 day oral corticosteroid therapy(OCS), prednisolone 37.5mg per day(1).
During AECOPD an acute worsening of the patient's symptoms occur supposedly as a result of aggravation in inflammation in the respiratory track. OCS has a beneficial effect on the airway inflammation. However long term use of OCS is avoided since the treatment may cause major adverse effects: osteoporosis, risk of diabetes, fractures, hypertension, hypercholesterolemia and infection(2). Venous thromboembolism (VTE) is a side effect to OCS treatment as well, but according to the Danish Drug Information A/S (DLI) it is a very rare adverse event that affects 1 per 1000 or 1 per 10000 patients(3). However meta – analyses observing COPD patients with exacerbation admitted to hospital have shown a 25% prevalence of pulmonary embolism(PE)(4, 5). Increased air way inflammation could be one cause, but since these patients receive OCS as standard treatment, adverse event to the medication cannot be ruled out.
A large study(6) investigated the risk of adverse events in non-elderly adults in the US with short term OCS treatment compared to a non-steroid control group. The study showed significantly higher incidence rates of VTE in the case group. Another nationwide Danish study showed similar results(7). Multiple other European and American studies have illustrated that short term prednisolone treatment increases the risk of VTE(6-14).

However, research about the association between OCS and VTE in patients with COPD is very limited. Since OCS is a standard treatment in AECOPD a bigger awareness of adverse events in these patients is relevant. In 2014 there was a change in OCS duration from 7-10 days to 5-7 days, based on a robust randomized controlled trial(1, 2). The

Ema Rastoder MD
01.10.2020

change of OCS duration recommendation in 2014 made it possible for us to compare the treatments short course versus long course in the periods before (2010-2013) versus after (2014-2017). Both treatments were given in first line treatment of AECOPD thereby preventing the risk of more severe COPD in the second group.

Aim:

To investigate the risk of VTE hospitalization and all-cause mortality in COPD patients with short course prednisolone treatment (after June 2014) compared to COPD patients with a long course prednisolone treatment (before June 2014) for their AECOPD.

Endpoints:

Primary Endpoint: DVT or PE within 6 months.

Secondary Endpoint: All-cause mortality within 6 months.

Method:

Study design: A National epidemiologic study with 100% follow-up

This is a nationwide observational cohort study using patients with a specialist and spirometry verified diagnosis of COPD between 1 January 2010 and 31 October 2018. The individuals were linked with prednisolone prescriptions for the treatment of AECOPD. The change in OCS duration in 2014 has made is possible for us to compare long course (2010-2014) versus short course (2015-2018) prednisolon treatment. Both treatments were given in first line treatment of AECOPD thereby preventing the risk of more severe COPD in the first group.

Inclusion criteria:

Spirometry and specialist verified COPD patients.
Age > 30
Patients with prednisolone prescriptions below, and 250mg.
Patients with prednisolone prescriptions above 250mg.

Exclusion criteria:

Patients with asthma
Patients who did not receive Prednisolone (H02AB06) prescription.
Patients with Factor V Leiden syndrome (D68.51)

Ema Rastoder MD
01.10.2020

Data sources:

The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD)
The Danish National Patient Registry (DNPR)
The Danish National Health Service Prescription Database (DNHSPD)
The Danish Civil Registration System (CRS)

ICD-10:

Pulmonary embolism I26, I26.0, I26.9.
Venous thrombosis I80.1 – I80.5 and I80.8 – I80.9.
Venous thromboembolism I82.2 - I82.9

ATC code:

Prednisolone (systemic use) = H02AB06
Depo-Medrol (H02B)

Statistical analyses:

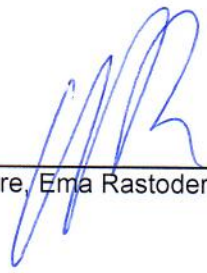
Demographic variables will be reported with median (IQR). The difference in continuous variables among the exposure groups will be analyzed with non-parametric tests.

Cox-regression will be used to assess the risk of DVT, PE or all-cause mortality at 6 months in COPD patients after short term OCS therapy compared to long term therapy. The results will be presented as HRs with 95% confidence limits (CI).

Competing risk model will be made between VTE and all – cause mortality.

All analyses will be adjusted for sex, age, Inflammatory Bowl disease, recent surgery or trauma, smoking status, FEV1 and heart failure.

Statistical analyses are carried out in SAS Enterprise Guide 9.1.



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