STUDY PROTOCOL

Inhaled corticosteroids in patients with chronic obstructive lung disease: Assessing the risk of Non-Tuberculous Mycobacteria Infection

Emma Mørk Borremose[1], Victor Næstholt Dahl[2,3,4], Troels Lillebæk[3,5], Anna Kubel Vognsen[1], Barbara Bonnesen[1], Josefin Eklof[1], Pradeesh Sivapalan[1], Jens-Ulrik Stæhr Jensen[1,6]

[1]Section of Respiratory Medicine, Department of Medicine, Herlev and Gentofte Hospital, University of Copenhagen

[2] Department of infectious diseases, Aarhus University Hospital

[3] Department of Tuberculous and mycobacteria, The State's Serum Institute

[4] Center of Global Health (GloHAU), Department of Public Health, University of Aarhus

[5] Global Health Section, Department of Public Health, University of Copenhagen

[6] Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen

INTRODUCTION

Inhaled corticosteroid (ICS) is a widely used therapeutic drug prescribed on many indications, including asthma and chronic obstructive pulmonary disease (COPD). Treatment with ICS has many known and suspected side-effects, however it can also be very beneficial. Hence, the choice of treatment with ICS and especially choice of dosage may be of importance [1], [2]A limited number of studies have examined the correlation between ICS treatment and pulmonary infection caused by Non-Tuberculous Mycobacteria (NTM), often in the context of comorbid non-cystic fibrosis bronchiectasis in addition to the pulmonary disease indicating ICS treatment. One study pointed towards a dose-response increased risk of NTM infection among COPD patients treated with ICS[3]. Another study examined the correlation between NTM infection, ICS treatment and self-reported asthma and COPD[4]. Another examined risk factors for NTM, and found elevated risk associated to female gender, bronchiectasis, low BMI and long-term or high dose ICS treatment[5]. A case-control study found that increasing cumulative ICS doses, were associated with greater odds of NTM pulmonary infection[6]. A nested case-control study identified higher age, more severe airway obstruction and long-term ICS treatment as more prevalent among asthma patients with NTM pulmonary infection compared to controls, however ICS dose and oral corticosteroid treatment was not[7]. Finally, a meta-analysis found that ICS use within the preceding year increased the risk of NTM infection, with greater risk observed at higher ICS dose and longer cumulative duration of use. Discontinuation of ICS use for more than 120 days was associated with reduced risk of NTM infection to an insignificant level. The strongest association to ICS was with Mycobacterium Kansasii[8]. We aim to systematically investigate the association in a large national cohort study of COPD patients, as this has not been done previously. This would provide a deeper insight into the association between ICS use and NTM infections, particularly in the context of the specific patient group as well as the different NTM bacteria involved.

OBJECTIVE

The aim of our study will be to evaluate the associations between use of ICS and risk of NTM pulmonary infection among patients with COPD to investigate whether there is a dose-dependent association. Our hypothesis is that ICS increases the risk of NTM pulmonary infection in patients with COPD.

METHODS

Data sources: This study is a nationwide register-based observational cohort study with a retrospective design. Data will be obtained from the following Danish registers:

1. The Danish Database of Reimbursed Prescriptions (DNDRP) is a nationwide database, that holds information on all prescribed and redeemed medication dispensed by Danish pharmacies and hospital—based outpatient pharmacies since 2004. It includes date of dispensation, quantity dispensed, strength and formulation. Danish legislation require that all pharmacies report complete and accurate data[9].

2. The Danish National Patient Registry (DNPR) holds information on all admissions to Danish hospitals since 1977, and hospital outpatient clinic visits since 1995. Each visit is coded by physicians with one primary diagnosis and one or more secondary diagnoses, according to the International Classification of Diseases, ICD-8 until 1994 and ICD-10 thereafter[10].

3. The Danish Civil Registration System assigns a unique personal identification number to all Danish citizens at birth or immigration. This number links individual information for each resident to information on name, sex, date of birth and vital status[11].

4. The Danish Register of Cause of Death, established in 1973, contains information on civil registration number, cause of death and circumstances surrounding the death[12].

5. The State's Serum Institute will contribute with analysis of the pathogens found in in respiratory samples.

Cohort and inclusion criteria: The cohort includes all patients diagnosed with COPD. Patients with COPD only diagnosed in general practise won't appear in the DNPR. Therefore, COPD will be defined as age > 40, no diagnosis of asthma and a collected prescription of LAMA between 1st of January 2009 until 31st of December 2019.

Exclusion criteria: Patients with congenital lung malformations (DQ33), cystic fibrosis (DE84) or a diagnosis of immunodeficiency (DD80-DD89) or malignant neoplasm (DC00-DC99) within the last 5 years prior to cohort entry will be excluded. Patients with a collected prescription of immunosuppressive drugs (ATC: L04A) within 12 months of index day will be excluded as well.

Exposure: All prescriptions of ICS within the year before index day will be identified and converted to budesonide-equivalent doses. Budesonide equivalence conversion rates for all ICS are previously done by Heerfordt et al[13]. The control group will consist of patient with COPD, that are not using ICS.

ICS type	**Equivalence conversion ratio**
Beclomethasone	1:1
Momethasone	1:1

Beclomethasone HFA	1:2
Fluticasone propionate	1:2
Ciclesonide	1:2.5
Fluticasone furoate	1:10

Outcome: We will assess the following primary outcome: NTM disease and investigation of the specific pathogen and secondary outcomes 1) pneumonia requiring hospital admission and 2) all-cause mortality.

Statistical analysis: The risk of NTM infection associated with ICS treatment will be estimated using an unadjusted cox proportional hazard regression model, with death as a competing risk. An adjusted cox proportional hazard regression model will be adjusted for possible confounders: age, sex, and Charlson Comorbidity index. Patients will be split into 4 groups according to their ICS dosage: no ICS, low, medium, and high dose. Results will be presented as hazard ratios (HR) with 95% confidence intervals (CI). A sensitivity analysis will be conducted as an IPTW weighted cox proportional hazard regression model. Statistical analysis will be performed using R. Assuming 30% of patient who doesn't get ICS treatment meet the primary outcome within the 2-year follow up and hypothesizing a 20% relative (corresponding to 6%) risk reduction or increase (2-sided comparison) While accepting a risk of a type 1 error limit (α) of 5% and a risk of a type 2 error of maximum 20% (corresponding to a power of at least 80%). The aim of this study is to have a sample size of 996 per group.

PUBLICATION OF RESULTS

The results of the study will be published whether they are positive, negative or inconclusive. Publication is planned in international peer-reviewed scientific journals in the coming year. If publication in a peer-reviewed scientific journal is not possible, the results of the study will be published in report format, which will be made available via the Internet.

ETHICAL APPROVAL

For this study, the authors were granted access to data in nationwide registries in accordance with current Danish laws (Data Protection Agency: P-2022-28). According to these laws, informed consent is not required for registry-based studies. The linkage between registries was done by using unique personal identification numbers, which allows an exact linkage on patient level and ensures complete follow-up.

REFERENCES

[1] Global Initiative for Asthma, “Global strategy for asthma mangement and prevention,” May 2024.

[2] Global Initiative for Chronic Obstructive Lung Disease, “Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease,” 2024.

[3] C. Andréjak, R. Nielsen, V. Thomsen, P. Duhaut, H. T. Sørensen, and R. W. Thomsen, “Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis,” *Thorax*, vol. 68, no. 3, pp. 256–262, 2013, doi: 10.1136/thoraxjnl-2012-201772.

[4] E. Henkle *et al.*, “Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry,” in *Chest*, Elsevier Inc, Dec. 2017, pp. 1120–1127. doi: 10.1016/j.chest.2017.04.167.

[5] G. Glodić *et al.*, “Risk factors for non-tuberculous mycobacterial pulmonary disease (NTM-PD) in Croatia 2,” *Wien Klin Wochenschr*, pp. 1195–1200, Aug. 2021.

[6] V. X. Liu, K. L. Winthrop, Y. Lu, H. Sharifi, H. U. Nasiri, and S. J. Ruoss, “Association between inhaled corticosteroid use and pulmonary nontuberculous mycobacterial infection,” *Ann Am Thorac Soc*, vol. 15, no. 10, pp. 1169–1176, Oct. 2018, doi: 10.1513/AnnalsATS.201804-245OC.

[7] L. G. Fritscher, T. K. Marras, A. C. Bradi, C. C. Fritscher, M. S. Balter, and K. R. Chapman, “Nontuberculous mycobacterial infection as a cause of difficult-to-control asthma: A case-control study,” *Chest*, vol. 139, no. 1, pp. 23–27, Jan. 2011, doi: 10.1378/chest.10-0186.

[8] C. C. Shu *et al.*, “Inhaled Corticosteroids Increase Risk of Nontuberculous Mycobacterial Lung Disease: A Nested Case-Control Study and Meta-analysis,” *Journal of Infectious Diseases*, vol. 225, no. 4, pp. 627–636, Feb. 2022, doi: 10.1093/infdis/jiab428.

[9] S. A. Johannesdottir, E. Horváth-Puhó, V. Ehrenstein, M. Schmidt, L. Pedersen, and H. T. Sørensen, “Existing data sources for clinical epidemiology: The Danish National database of reimbursed prescriptions,” *Clin Epidemiol*, vol. 4, no. 1, pp. 303–313, Nov. 2012, doi: 10.2147/clep.s37587.

[10] M. Schmidt, S. A. J. Schmidt, J. L. Sandegaard, V. Ehrenstein, L. Pedersen, and H. T. Sørensen, “The Danish National patient registry: A review of content, data quality, and research potential,” Nov. 17, 2015, *Dove Medical Press Ltd*. doi: 10.2147/CLEP.S91125.

[11] M. Schmidt, L. Pedersen, and H. T. Sørensen, “The Danish Civil Registration System as a tool in epidemiology,” 2014. doi: 10.1007/s10654-014-9930-3.

[12] K. Helweg-Larsen, “The Danish register of causes of death,” *Scand J Public Health*, vol. 39, no. 7, pp. 26–29, Jul. 2011, doi: 10.1177/1403494811399958.

[13] C. K. Heerfordt *et al.*, “Inhalation devices and inhaled corticosteroids particle size influence on severe pneumonia in patients with chronic obstructive pulmonary disease: A nationwide cohort study,” *BMJ Open Respir Res*, vol. 10, no. 1, Sep. 2023, doi: 10.1136/bmjresp-2023-001814.