Study protocol – Updated

Inhaled Corticosteroids and Risk of Non-Tuberculous Mycobacteria in Bronchiectasis

Ismail Mohammad Lone[1], Emma Moerk Borremose[1], Anna Kubel Vognsen[1], Troels Lillebaek[3,4], Andres Fløe[5], Victor Naesthold Dahl[2,3], Jens-Ulrik Jensen[1,6], Pradeesh Sivapalan[1,6]

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

[2]Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark.

[3]International Reference Laboratory of Mycobacteriology, Statens Serum Institute, Copenhagen, Denmark.

[4]Global Health Section, Department of Public Health, University of Copenhagen, Copenhagen, Denmark.

[5]Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark.

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

Corresponding author:

Pradeesh Sivapalan, MD

E-mail: pradeesh.sivapalan.02@regionh.dk.

Telephone: 29880601

Introduction

Inhaled corticosteroids (ICS) are a cornerstone of therapy for a range of chronic inflammatory airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD). In patients with bronchiectasis, however, the role of ICS is generally limited to selected subgroups including those with coexisting asthma or significant eosinophic airway inflammation. While ICS may reduce airway inflammation and improve symptoms, their use is associated with both local and systemic adverse effects, including susceptibility to respiratory infections.[1] Previous studies examining the association between inhaled corticosteroids (ICS) use, and non-tuberculous mycobacterial pulmonary disease (NTM-PD) in patients with bronchiectasis are limited and have yielded conflicting results. Several observational studies and meta-analyses have reported an increased risk of NTM associated with ICS use, often demonstrating a dose-response relationship and identifying bronchiectasis as a major comorbid risk factor.[2,3,4] The association appears particularly pronounced among women, older individuals, patients with low body mass index, and those receiving high-dose or prolonged ICS therapy.[5,6] In contrast, at least one long-term cohort study found no increased risk after adjustment for confounders.[7] Overall, the existing evidence is inconclusive and limited by residual confounding and heterogenous study designs. Large, well-characterized population-based studies with detailed clinical data are therefore needed to clarify the relationship between ICS exposure and NTM risk in bronchiectasis.

Objective

The primary objective of this study is to quantify the association between inhaled corticosteroids (ICS) use and the risk of developing non-tuberculous mycobacterial (NTM) pulmonary infection among patients with bronchiectasis. Secondary objectives include evaluating whether a dose-response relationship exists between ICS exposure and NTM-risk, and exploring whether this association differs across clinically relevant subgroups (e.g., sex, age, smoking status, and lung function). We hypothesize that ICS use is associated with an increased risk of NTM pulmonary infection in patients with bronchiectasis, with higher doses conferring greater risk.

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 Civil Registration System: Upon birth or immigration, individuals in Denmark are assigned a unique personal identification number through **the Danish Civil Registration System**, which enables linkage of individual-level data across registers and provides information on name, gender, date of birth and vital status.[8]

2. The Danish Register of Cause of Death, established in 1973, includes data on civil registration numbers, causes of death and circumstances related to death.[9]

3. The Danish Database of Reimbursed Prescriptions (DNDRP) is a national registry covering all prescription medications that are prescribed and subsequently redeemed at Danish community pharmacies and hospital-based outpatient pharmacies since 2004. For each dispensation, the database records the dispensing date as well as details on the product, including the amount dispensed, strength and formulation. Under Danish law, pharmacies are required to report these data in full and with high accuracy.[10]

4. The Danish National Patient Registry (DNPR) contains nationwide records of all hospital admissions in Denmark since 1977 and of outpatient hospital contacts since 1995. For each hospital contact, physicians assign one primary diagnosis and may add one or more secondary diagnoses, coded according to the International Classification of Diseases using ICD-8 up to 1994 and ICD-10 from 1995 onward.[11]

5. The State Serum Institute will contribute by performing laboratory analyses of respiratory samples to identify and characterise detected pathogens, thereby providing detailed microbiological data for the study.

Cohort: The study cohort will comprise all adult patients in Denmark with a hospital-based diagnosis of bronchiectasis (ICD-10 J47) who are registered during the study period from 1 January 2004 to 31 December 2022. Patients will be classified according to inhaled corticosteroid (ICS) exposure, defined by redeemed prescriptions recorded in the Danish National Database of Reimbursed Prescriptions. The exposed group will consist of patients who redeem at least one prescription for ICS during follow-up, whereas the control group will comprise patients with bronchiectasis who do not redeem any ICS prescriptions during the

study period. The index date will be defined as the date of the first registered hospital outpatient visit or hospital admission for bronchiectasis, whichever occurs first.

Inclusion criteria: Patients will be included if they are aged 18 years or older, are registered in the Danish National Patient Registry (DNPR) with a diagnosis of bronchiectasis (ICD-10: J47), and have had at least one recorded hospital outpatient contact or hospital admission between 1 January 2008 and 31 December 2021.

Exclusion criteria: Patients were excluded if they had a diagnosis of cystic fibrosis (ICD-10: E84), congenital lung malformation (ICD-10: Q33), immunodeficiency (ICD-10. D80-D89), or a malignant neoplasm (ICD-10: C00-C43, C45-C99) within 5 years prior to cohort entry. Patients with non-melanoma skin cancer (ICD-10: C44) were not excluded. In addition, patients were excluded if they had used immunosuppressive medication (ATC codes beginning with L04A) within one year prior to cohort entry based on prescription data, or if they had a positive nontuberculous mycobacteria (NTM) microbiological sample prior to the index date.

Exposure: ICS exposure will be assessed using redeemed prescriptions recorded in the Danish Database of Reimbursed Prescriptions (DNDRP). All ICS doses will be standardised to budesonide-equivalent dosis using previously established conversion factors,[12] and ICS exposure will be modelled as a time-varying variable to minimise immortal time bias. Patients will be categorised into four exposure groups: no ICS use; low dose (<400 µg budesonide-equivalent/day); moderate dose (400-800 µg budesonide-equivalent/day); and high dose (>800 µg budesonide-equivalent/day).

ICS type	**Equivalence conversion ratio**
Momethasone	1:1
Beclomethasone	1:1
Fluticasone propionate	1:2
Beclomethasone HFA	1:2
Ciclesonide	1:2.5
Fluticasone furoate	1:10

Outcome: Incident NTM pulmonary infection, defined as the occurrence of at least one positive respiratory culture for non-tuberculous mycobacteria (NTM) recorded after cohort entry.

Statistical analysis: Time-to-event analyses will be performed to estimate the association between ICS use and the risk of incident NTM-PD. Follow-up will commence at the index date and continue until the first occurrence of NTM-PD, death, emigration, or the end of the study period, whichever occurs first. The primary analysis will use Cox proportional hazards regression, with death treated as a competing event. An initial unadjusted model will be fitted, followed by a multivariable model adjusting for potential confounders and markers of disease severity, including age at cohort entry, sex, smoking status, body mass index (BMI), lung function (FEV_1% predicted), Medical Research Council (MRC) dyspnoea score, calendar year of cohort entry, and ICS exposure. ICS exposure will be modelled as a time-varying covariate and categorized according to the daily budesonide-equivalent dose into four groups: no ICS use, low dose (<400 µg/day), moderate dose (400-800 µg/day), and high dose (>800 µg/day).This approach reduces immortal time bias and allows patients to contribute person-time to different exposure categories during follow-up. Results will be reported as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazards assumption will be assessed using Schoenfeld residuals. As a sensitivity analysis, inverse probability of treatment weighting (IPTW) based on propensity scores will be applied to balance baseline covariates between exposure groups. Weighting Cox proportional hazards models will be fitted to assess the robustness of the primary findings. All statistical analyses will be conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

Publication of results

The study findings will be published regardless of whether they are positive, negative or inconclusive. We plan to submit the results to international peer-reviewed scientific journals within the next year. If publication in a peer-reviewed journal is not feasible, the results will be released as a publicly accessible report made available online.

Ethical approval

The project has received authorization from the Danish Data Protection Agency. Under Danish regulations, retrospective analyses based solely on registry data do not require ethics committee approval or informed consent from patients.

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