

The role of inhaled anti-inflammatory pharmaceuticals in COVID-19 incidence, morbidity, and mortality

DK titel:

“Inhalerede anti-inflammatoriske lægemidler og sygelighed af COVID-19”

DANSK SYNOPSIS

De danske sundhedsregistre er på verdensplan enestående på grund af meget detaljeret information om bl.a. lægemiddelforbrug, indlæggelsesvarighed, respirator-behandling, og infektionstest-resultater for en hel befolkning. I forbindelse med COVID-19 pandemien har vi derfor i Danmark en unik mulighed for at bruge vores sundhedsdata til at pege på mulige medicinske behandlinger for sygdommen. Rent praktisk vil vi undersøge om eksisterende inhalerede anti-inflammatoriske lægemidler (f.eks. inhalationssteroid til patienter med astma og KOL) påvirker et individs sygelighed med COVID-19, da coronavirussen medvirker til kritisk sygdom ved at udløse et massivt inflammatorisk respons i kroppen. Studierne vil afdække om eksisterende lægemidler kan benyttes til behandling og forebyggelse af COVID-19 eller helt skal undlades at bruges.

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SYNOPSIS

The current COVID-19 pandemic, mediated by the novel coronavirus SARS-CoV-2, does not have any specific prophylaxis or treatment(1). However, evidence indicate that SARS-CoV-2 infection can results in severe COVID-19 by creating massive inflammation via a cytokine storm (REF). Nevertheless, the role of inhaled anti-inflammatory pharmaceuticals (e.g. inhaled glucocorticoids and inhaled beta-2-agonists) in incidence, morbidity, and mortality of COVID-19 is unknown. Anecdotal evidence and early reports suggest adverse effect of systemic glucocorticoids(2), while some guidelines suggests it for treatment of acute respiratory distress syndrome (ARDS) caused by COVID-19(3). Furthermore, adding to the uncertainty, a novel pre-clinical study suggests the inhaled anti-inflammatory pharmaceutical ciclesonide as a potent inhibitor of SARS-CoV-2 infection(4). Therefore, insights into anti-inflammatory pharmaceuticals in COVID-19 could prove essential to understand and treat adverse, and potentially fatal, effects of SARS-CoV-2 infection.

Utilizing the unique Danish nationwide registers on prescription drug use, laboratory confirmed SARS-CoV-2 status, and detailed hospital information, we will create a rapid assessment of the effect of anti-inflammatory pharmaceuticals on COVID-19 to guide future treatment efforts.

RESEARCH QUESTIONS

- a) Is prescription inhaled anti-inflammatory pharmaceuticals associated with incidence of symptomatic COVID-19?
- b) Is prescription inhaled anti-inflammatory pharmaceuticals associated with COVID-19 morbidity?
- c) Is prescription inhaled anti-inflammatory pharmaceuticals associated with COVID-19 mortality?

MATERIALS

The Danish Civil Registration System (CRS) will form the backbone of the studies by linking national health registers, in addition to providing demographic information on the study population. Information on SARS-CoV-2 status and other respiratory viruses (e.g. influenza) is available through MiBA, the Danish Microbiology Database, which includes all microbiological SARS-CoV-2 test results in Denmark. The Danish National Patient Register covers information on length of hospital stay, days in intensive care units (ICU), use of mechanical ventilation, and diagnostic codes to identify underlying chronic diseases. The National Prescription Registry, which contains information on all redeemed prescriptions in Denmark, will provide information on pharmaceutical exposures of interest.

METHODOLOGY

For sub-study a) on COVID-19 incidence, we will explore whether individuals prescribed inhaled anti-inflammatory pharmaceuticals have different COVID-19 incidence compared to the general population, and compared to patients hospitalized for influenza, based on a nationwide cohort, with adjustments for age, sex, and other confounders, such as underlying morbidity. For sub-study b) on COVID-19 morbidity, we will compare severity of COVID-19 disease among test-positive cases, by users and non-users of inhaled anti-inflammatory pharmaceuticals, and again compare to severity of patients hospitalized for influenza. Severity will be investigated by the following clinical endpoints; length of hospital stay, days in ICU, and use of mechanical ventilation while in-hospital. Our analysis will be a propensity-scored matched design using logistic regression. Cases will be matched on age, sex, and other confounders. For sub-study c) on COVID mortality, we will compare mortality of SARS-CoV-2 test positive cases by users and non-users of anti-inflammatory pharmaceuticals, also using a propensity-scored matched design.

FEASIBILITY

Although there are currently few hospitalized cases in Denmark (507 as of April 4, 2020) projections suggest further growth in number of diseased. Furthermore, as a result of our unique nationwide prescription registry we know that approximately to 500,000 individuals in Denmark (approx. 10%) are prescribed anti-inflammatory pharmaceuticals(5), which gives adequate statistical power for comparison of users versus non-users. Furthermore, due to the frequent updates of the Danish health registers, our project will provide the first clinically relevant results within 1-2 months. Lastly, our research group has both the extensive domain knowledge of Danish registries and the thorough statistical expertise needed to undertake the proposed studies.

RESEARCH GROUP

The research group consists of researchers from the Department of Epidemiology Research at Statens Serum Institut, in addition to the pharmacoepidemiology unit at Clinical Pharmacology and Pharmacy, University of Southern Denmark, and researchers from Department of Clinical Epidemiology at Aarhus University. The research project will be led by MD, PhD Anders Husby and dr.med. Anders Hviid. The group has substantial documented research experience in epidemiology and pharmacoepidemiology.

Conflicts of interest

None.

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