COVID-19: Prophylactic Properties of Hydroxychloroquine.

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Introduction

In November 2019 a new coronavirus called SARS-CoV2 emerged. With its pandemic potential it spread around the world and affected most countries on the planet. Until now there has been approx. 5 mio confirmed cases, of which about 300,000 have died.(1) There is a lack of specific treatment for this novel virus. Against SARS-corona virus chloroquine and hydroxychloroquine showed an in-vitro ability to inhibit the virus.(2) In-vitro studies on SARS-CoV-2 infected vero-cells have shown the ability of chloroquine to block infection by SARS-CoV-2.(3) Based on *in vitro* data, hydroxychloroquine may be more potent than chloroquine.(4)

Hydroxychloroquine as a prophylactic treatment against COVID-19 has not yet been investigated systematically. A systematic review concludes pre-clinical results to be promising but underlines the lack of evidence and warrants the examination through observational studies or randomized trials. (5)

In our country (Denmark), hydroxychloroquine is accepted by the authorities for treatment of rheumatoid arthritis, for discoid and systemic lupus erythematosus, for juvenile arthritis, for polymorph photosensitivity and for prophylaxis and treatment of malaria. (6)

Methods

Aim:

Primary:

The purpose of this study is to determine whether hydroxychloroquine reduces the risk of RT-PCR-confirmed COVID-19 in persons who receive this drug, and who started using the drug before the first confirmed case of COVID-19 in Denmark.

Hypothesis

Among patients who use hydroxychloroquine on a regular basis, this drug reduces the risk of RT-PCR confirmed COVID-19 disease.

Data sources:

1) The Danish National Patient Registry (Landspatientregistret): Holds information on all admissions to Danish hospitals since 1977 and hospital outpatient specialist clinic visit since 1995.

2) The National Prescription Registry (*Receptregistret*): Holds information on all prescriptions dispensed in Danish pharmacies since 2004 (coded according to the Anatomical Therapeutic Chemical (ATC) classification system)
3) The Danish Central Personal Registry (*CPR registret*): Holds information on citizens of Denmark e.g. weather the citizen is dead or alive.
4) The Danish Cause of Death registry (*Dødsårsagsregistret*): Holds information about cause of death, date, place, age etc.
5) Microbiological data from relevant departments of clinical microbiology in Denmark.

Study population:

Population study based on the entire Danish population.

The period of the study will be defined from 1st of January 2020 to 1st of June 2020.

Treatment with either of these drugs should be initiated before the 1st of January 2020.

Endpoints

Primary:

Positive test for COVID-19 either from either a nasopharyngeal swap, sputum or tracheal secretion in the study period.

Secondary: Only among COVID-19 positive patients:

Admission to a hospital within 4 weeks before or after test positivity

Statistical analysis

Sample size:

In Denmark 1,2% of the population have been infected with COVID-19. To be clinically relevant, the protective effect of hydroxychloroquine should be high, we suggest a relative risk reduction of 50%, and so, the absolute risk among patients who receive hydroxychloroquine should be lower than 0,6% for the drug to be effective.

Using conventional limits for α of 0.05 and β of 0.2 (corresponding to a power of 0.8), and the above absolute risk estimates, the study will have to include 217000 patients or more to be correctly powered.

For analysis a cox regression adjusted for relevant comorbidities, immunotherapies and age will be used to examine the effect of hydroxychloroquine.

Ethical statement

Approved by the Danish Data Protection Agency: File number P-2020-537. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

References

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