Effect of hydroxychloroquine treatment on the general immunocompetence

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22387

Source
Nationaal Trial Register

Brief title
CHDR2014

Health condition

COVID19

Sponsors and support

Primary sponsor: CHDR
Source(s) of monetary or material Support: CHDR

Intervention

Outcome measures

Primary outcome

Pharmacokinetic endpoints
- Hydroxychloroquine plasma concentration
- Hydroxychloroquine whole blood concentration

Pharmacodynamic endpoints

- Endosomal TLR responses
o TLR3-driven cytokine production
o TLR7-driven cytokine production
o TLR8-driven cytokine production
o TLR9-driven cytokine production
- T cell responses
o Proliferation
o Activation marker expression
o Cytokine production
- B cell responses
o Activation marker expression
o Proliferation
- Leukocyte differentiation
- Flow cytometry phenotyping of dendritic cells, monocytes, T cells and B cells

Secondary outcome

N.A.

Study description

Background summary

In December 2019, a novel coronavirus (SARS-CoV-2) emerged in Wuhan, China causing a disease named COVID-19. The rapid global outbreak of SARS-CoV-2 led the World Health Organization to characterize it as a pandemic. There are currently no approved drugs to treat COVID-19. Consequently, there is a very urgent need for effective prophylactic and therapeutic treatment options. Hydroxychloroquine (HCQ) sulfate is a less toxic derivative of a known antimalarial drug chloroquine (CQ), widely available and mostly used as malaria prophylaxis and as treatment in autoimmune conditions. Because of its known antiviral and immunomodulatory properties, HCQ has been proposed as a potential candidate drug for treatment and prophylaxis of COVID-19. The in vitro effect of HCQ on inhibition of SARS-CoV-2 replication has been investigated with promising results both in a pre-treatment and treatment setting. Additionally, the antiviral activity has also been studied in the context of previous outbreaks, such as in the severe acute respiratory syndrome (SARS) caused by the related SARS-CoV. Early clinical trials evaluating the effect of HCQ/CQ in COVID-19 patients are currently scarce, and available data from Chinese and French researchers show a beneficial effect on viral elimination, while other researches cannot reproduce this beneficial effect.
In addition to their antiviral properties, HCQ/CQ have a wide range of immunomodulating and metabolic effects, mainly by inhibiting activation of endosomal Toll-like receptors (TLRs) and T cell activation. Upon lysosomal entry, HCQ increases lysosomal pH and directly interacts with endosomal TLR ligands, making them unavailable to bind their receptor. This affects the innate immune response by reducing IFN-α and TNF production by plasmacytoid dendritic

cells (pDC), but also affects the adaptive immune response by suppressing B cell differentiation and IL-6, IL-1β and TNF production. Moreover, in T cells HCQ significantly reduces CD4+ T cell proliferation and IL-2, IFN-γ, IL-4, IL-13 production. Since the induction of an interferon (IFN) response by endosomal TLRs and subsequent T and B cell activation are essential steps in the antiviral response, HCQ treatment could theoretically increase susceptibility to viral infections. This is especially relevant in SARS-CoV-2 infection, since corona viruses actively suppress IFN responses. In addition, in the elderly, the population with the highest COVID-19 death rate, impaired endosomal TLR responses have been reported. Further impairment of the innate antiviral response may therefore not be desired in a prophylactic setting. On the other hand, the IFN-mediated immune response is also known to cause immunopathological damage in the lung tissue, which is one of the proposed mechanism for the development of the severe form of COVID-19. The net effect of HCQ on prophylaxis and treatment of COVID-19 is therefore still elusive and should be further investigated.

Study objective

Although the immunomodulatory effects of HCQ and CQ have been well described in isolated cell subsets in vitro, there is a lack of clinical studies describing the immune response after HCQ treatment in humans. In this clinical study we therefore aim to provide mechanistic insight into the effects of HCQ on general immunocompetence in young and elderly healthy volunteers. The mechanistic information generated in this study, together with currently ongoing clinical trials evaluating the prophylactic and therapeutic effect of HCQ on COVID-19 incidence, should guide future use of HCQ for SARS-CoV-19 infections or other viral infections.

Study design

Day 1, Day 2, Day 5, Day 10

Intervention

6 x 400 mg Hydroxychloroquine sulphate or placebo

Contacts

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Eligibility criteria

Inclusion criteria

1. Healthy male subjects, 18 to 30 years or 65 to 70 years of age, inclusive at screening.
2. Body mass index (BMI) between 18 and 28 kg/m2, inclusive, and with a minimum weight of 50 kg.
3. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions

Exclusion criteria

1. Known hypersensitivity reaction to chloroquine, hydroxychloroquine or 4-aminoquinolines;
2. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator, following a detailed medical history (including a known history of long QT syndrome, known history of retinal disease, G6PD deficiency, porphyria, psoriasis, myasthenia gravis, liver disease, diabetes mellitus type I and II, existing hearing loss, and current or revious history of a relevant psychiatric disorder ie. major depressive disorder, bipolar disorder, schizophrenia or another psychotic disorder or current of previous suicidality irrespective of an associated psychiatric disorder);
3. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects;
4. Signs or symptoms of any active infection within two weeks prior to first dosing.
5. Positive SARS-CoV-2 qPCR test pre-dose.
6. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;
7. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg and considered to be of clinical relevance by the investigator;
8. Abnormal findings in the resting ECG, including but not limited to QTcF> 450 msec.
9. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator;
10. Participation in an investigational drug study (last dosing of previous study was within 90 days prior to first dosing of this study);

11. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 14 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent and unable to abstain from alcohol use from at least 24 hours before every visit;
12. Positive test for drugs of abuse at screening or pre-dose. Drugs test may be repeated;
13. Smoker of more than 10 cigarettes per week prior to screening or who use tobacco products equivalent to more than 10 cigarettes per week and unable to abstain from smoking from at least 7 days before first dosing until the last return visit (day 10);
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable);
15. Loss or donation of blood over 500 mL within three months prior to screening or intention to donate blood or blood products during the study;
16. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2020
Enrollment:	40
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Plan description
All IPD that underlie results in a publication and study report can be shared. This IPD will always be fully anonymized and may include individual PK/PD relationships and individual

correlations between different effect measures.

Ethics review

Positive opinion

Date:	23-06-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 49980
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8726
CCMO	NL73816.056.20
OMON	NL-OMON49980

Study results

Summary results
N.A.