Hydroxychloroquine sulfate early administration in symptomatic out of hospital COVID-19 positive patients
Hydro-Stop-COVID19 Trial

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BACKGROUND

In late December 2019, an outbreak of an emerging disease (COVID-19) due to a novel coronavirus (named SARS-CoV-2 latter) started in Wuhan, China and rapidly spread in China[1] and outside and has been declared pandemic by WHO on March 12th 2020. It has been shown that an excessive immune response to the SARS-CoV-2 virus would results in hyper-inflammation, with excessive increase of cytokines IL6 and IL10. This may progress to a cytokine storm, followed by multi organ failure and potentially death[2].

Italy is now facing the COVID-19 wave with more than 86.000 cases and over 9.100 deaths as of March 27th 2020. Notably most of the COVID19 positive subjects are out of Hospital patients even if they have moderate to severe symptoms because of hospitals overcrowding.

Generally, they are only under symptomatic therapy and they cloud have very rapid clinic deterioration with following hospitalization in very sick state. At least in part this could explain the higher relative lethality of COVID 19 disease in our Country.

There is an urgent need for an effective treatment to treat symptomatic patients in order to limit the number of patients who would need hospitalization because of severe organ damage, but also to decrease the duration of virus carriage in order to limit the transmission in the community.

In critically ill SARS-CoV-2 infected patients, the use of corticosteroids may be harmful[3]. Among candidate drugs to treat COVID-19, repositioning of old drugs such as Cloroquine and Hydroxychloroquine (HCQ) for use as antiviral treatment sounds as an interesting strategy because knowledge on safety profile, side effects, posology and drug interactions are well known[4].

Previous studies suggest that chloroquine and HCQ may inhibit the coronavirus through a series of steps. Firstly, the drugs can change the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane. It can also inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, virus release and other process to achieve its antiviral effects[5]. HCQ clinical safety profile is better than chloroquine ones (during long-term use) and allows higher daily dose[6] and has fewer concerns about drug-drug interactions[7].

Moreover HCQ was more effective than chloroquine to inhibit SARS-CoV-2 in vitro. According to physiologically based pharmacokinetic models, a loading dose of 400 mg twice daily of HCQ sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance[8].

Gautret et al. have recently completed an observational uncontrolled non-randomized open-label study[9] in which twenty hospitalized patients with confirmed COVID-19 were given HCQ sulfate 200 mg three times per day for 10 days. The primary end-point was virological clearance 6 days after inclusion. Six additional HCQ patients were lost to follow-up for early cessation of treatment for several reasons (death, admission to intensive care unit, adverse effects, decision of patients, etc). A group of 16 COVID-19 patients not treated with HCQ served as control group. At day 6 after inclusion, 70% of HCQ patients were virologically cured, versus 12.5% in the control group (p=0.001).

HCQ have also immunomodulatory effects and can suppress the increase of immune factors[10, 11]. In this setting, HCQ may be an ideal drug to use in early treatment of SARS-CoV-2 infection as it can inhibit the virus via its antiviral effects and may also mediate the cytokine storm via its immunomodulatory effects preventing the progression of the disease to a critical, life-threatening state. According to previous background AIFA has recently recognized and authorized HCQ off-label treatment in SARS-CoV-2 infected patients in Italy (March 19th 2020).

OBJECTIVE

To evaluate the efficacy of out-of-hospital treatment with HCQ in the reducing viral loads and need for hospitalization in symptomatic SARS-CoV-2 infected patient who are confined at home.

METHODS

Out-of-Hospital symptomatic confirmed SARS-CoV-2 patients will be included in a pragmatic, randomized, open-label, between-patient trial.

Inclusion criteria. All the following criteria are required:

1. Patients with SARS-CoV-2 infection in a nasopharyngeal sample, with diagnosis carried out in a centralized core-lab.
2. Patients confined at home because their clinical picture was judged by the local Health authorities not severe enough to require hospitalization.
3. Patients with 1 or more of the following symptoms/signs on the day of nasopharyngeal sample: 1) Fever (>37.0° Celsius); 2) Dyspnea; 3) Cough.

Exclusion criteria. One or more of the following*:*

1. Age <18 years.
2. Allergy to HCQ or chloroquine.
3. Contraindication to treatment with the study drug for one or more of the following conditions: retinopathy, G6PD deficiency, Long-QT syndrome or treatment with drugs associated with QTc prolongation (unless these drugs can be safely discontinued during HCQ treatment). Appendix 1 shows a table, derived from AIFA, which lists these drugs.
4. Breastfeeding and pregnant patients will be excluded based on their declaration and pregnancy test results when required.

Procedures. See also Appendix 2.

Trial Day -2. All the subjects with COVID19 suspected symptoms in which nasopharyngeal sample is executed will be asked to give their **written informed consent** to participate to the study the same day of the test (at patient home) by a trained COVID-team with personal protective equipment according to WHO recommendations (day -2). An information document that clearly indicates the risks and the benefits associated with the participation to the study will be given to each patient. Patients will receive information about their clinical status during care regardless of whether they participate to the study.

Trial day -1. The results of test are available. Patients with positive test will be registered as screened.

Trial Day 0. On day 0, patients with positive test will be contacted by telephone to announce the results of test and provide them all the necessary support. During the phone call, carried out by a clinical investigator, patients with be asked whether they confirm their willingness to continue the study. In case of positive answer, patients will be randomized to receive, in addition to standard therapy, the following treatments:

1. **HCQ arm**

   Therapy. In addition to standard medications currently received by patients, patients will receive **hydroxychloroquine** 400 mg bid loading dose the first day of treatment, followed by 200 mg bid for the subsequent 6 days (total duration of treatment: 7 consecutive days). Patients aged 70 years or more, with known renal or liver impairment, or known heart disease (coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy) will not receive the 400 mg b.i.d. loading, but a 200 mg b.i.d. regimen for 7 consecutive days.

2. **No-HCQ arm**

   Therapy: standard medications according to current guidelines (SIMIT 2.0, 13/03/2020)

Trial day 1. HCQ treatment will be supplied at patient's home (patients randomized to HCQ arm).

Trial day 2. HCQ treatment is started in patients randomized to HCQ arm.

Trial day 8. Second nasopharyngeal sample.

Trial day 15. Third nasopharyngeal sample.

Clinical follow-up in both arms (body temperature, respiratory rate, peripheral capillary oxygen saturation, hospitalization and mortality) will be performed by phone contact or at patient home when needed.

Primary endpoint: virological clearance (nasopharyngeal sample negative for SARS-CoV-2 virus) at the sample taken on days 8. **Co-primary end-point**: Hospital admission over the time-interval between day 0 (randomization) and day 15.

Secondary endpoints:

a) Need for intubation during the interval between day 0 (randomization) and day 15;

b) All-cause death during the interval between day 0 (randomization) and day 15.

c) Virological clearance in all samples (both day 8 and day 15)

d) Composite of a), b), c). The first-occurring component will be considered for analysis.

Extended follow-up: phone call at day 28.

Sample size determination.

For the primary end-point 'virological clearance', we assume a type 1 error (α) of 0.05, a type 2 error (β) of 0.10 (Power 90%; i.e. likelihood of detecting the hypothesized difference between the two groups if it really exists), a proportion of patients with primary outcome (virologic clearance) of 15% in the control group and 60% in the HCQ group and a drop-out rate (nasopharyngeal sample at day 7 not executed) of 10% (1 out of 10 patients).

For the co-primary 'hospitalization at 2 weeks', we assume a type 1 error (α) of 0.05, a type 2 error (β) of 0.10 (Power 90%), a proportion of patients with hospitalization at 2 weeks of 35% in the control group and 15% in the HCQ group and a drop-out rate (lost to follow-up) of 10% (1 out of 10 patients).

Based on the above assumptions, the total number of patients to randomize would be 52 (26 in each group) to demonstrate a significant difference between the groups in the virological clearance, and 216 (108 in each group) to demonstrate a significant difference between the groups in the frequency of hospitalization over the time-interval day 0-day 15.

Thus, **216 patients will be ultimately randomized**.

The STATA software has been used to estimate the sample size (comparison between independent proportions).

Appendix 1

Table: Drugs capable to prolong the QT-interval. Patients who cannot discontinue one or more of these drugs during the study period will be excluded.

1. Farmaci associati a rischio di TdP	2. Farmaci potenzialmente associati a rischio di TdP	3. Farmaci da evitare in pazienti affetti da LQTS
Famaci che, di solito, sono riconosciuti capaci, dalle autorità regolatorie, di aumentare il rischio di TdP.	Farmaci che, secondo alcune segnalazioni, sono associati a TdP ma per i quali mancano chiare evidenze di correlazione ad un aumento del rischio di TdP.	Farmaci da evitare nei pazienti con sospetta diagnosi o a cui sia stata diagnosticata LQTS congenita (i farmaci delle liste 1 e 2 sono compresi anche nella lista 3)
Aloperidolo	Amantadina	Albuterolo
Amiodarone*	Azitromicina	Chinidina*
Arsenico triossido	Cloralio idrato	Cocaina
Chinidina*	Dolasetron	Dobutamina
Clorpromazina	Felbamato	Dopamina
Claritromicina	Flecainide	Droperidolo
Disopiramide*	Foscarnet	Efedrina
Domperidone	Granisetron	Epinefrina
Droperidolo	Indapamide	Fenilefrina
Eritromicina*	Isradipina	Fenilpropanolamina
Ibutilide*	Levofloxacina	Midodrina
Metadone*	Litio	Pseudoefedrina
Pentamidina*	Moexipril + idroclorotiazide	Ritodrina
Pimozide*	Moxifloxacina	Sibutramina
Procainamide	Nicarpidina	Terbutalina
Sotalolo*	Ocreotide	
Tioridazina	Ondansetron	
	Quetiapina	
	Risperidone	
	Salmeterolo	
	Tacrolimus	
	Tamoxifene	
	Telitromicina	
	Tizanidina	
	Venlafaxina	
	Voriconazolo	

Appendix 2. Flow-chart of the study.

Trial Days	-2	-1	0	1	2	3	4	5	6	7	8	....	15
Actions													
First nasopharyngeal sample taken at patient' home. Explanation of protocol to patients	*												
Informed Consent	*												
Results of samples available		*											
Telephone contact with patients. The patient confirms his/her participation to the study, then he/she is randomized and the CRF is filled.			*										
Patients randomized to HCQ receive HCQ supply at home				*									
Treatment with HCQ					*	*	*	*	*	*	*		
Second nasopharyngeal sample taken at patient' home.											*		
Phone interview			*			*		*			*		*
Third nasopharyngeal sample taken at patient' home.													*

An extended follow-up through telephone calls will be undertaken on day 28

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