

Emerging prophylaxis strategies against COVID-19

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To the Editor

The Novel corona virus 2019 which started as an outbreak in China in December 2019 has rapidly spread all over the world, such that on 11th March 2020 WHO declared this disease as pandemic [1,2]. The emergency that the world faces today demands that we develop urgent and effective measures to protect people at high risk of transmission. WHO has accelerated research in diagnostics, vaccines and therapeutics for this novel coronavirus [3].

The various strategies for prevention of transmission and infection of this respiratory pathogen includes:

- 1) Health promotion - non pharmacological interventions [4]:
 - a. isolation at home,
 - b. voluntary quarantine at home,
 - c. social distancing of entire population especially of the elderly and
 - d. temporary closure of schools, universities and work places.
- 2) Specific protection through chemoprophylaxis or immunoprophylaxis which includes:

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1. Antiviral agents;
2. Chloroquine-HydroxyChloroquine (HCQS);
3. Vaccination.

This article is an overview of the emerging prophylaxis strategies under investigation against COVID-19.

Antiviral agents

Neuraminidase inhibitors are known to reduce viral shredding in respiratory secretions and is used for prophylaxis against influenza [5]. Jefferson *et al.* in a Cochrane systematic review found reduction in symptomatic influenza by 55% by Oseltamivir and 61% by Zanamavir [6]. Oseltamivir is currently being investigated as a treatment option (NCT04303299) but not specifically for prophylaxis against the corona virus disease. However, taking cue from its prophylaxis properties against influenza viruses, it may have a role in chemoprophylaxis in corona virus disease as well.

Protease inhibitors like Lopinavir have shown to be a strong inhibitor of the protease enzyme present in SARS-CoV which is important for the life cycle function of this virus [7]. Ritonavir has been used to boost this action of Lopinavir in HIV patients [8]. However, the largest study reported till date on use of Lopinavir plus Ritonavir for its efficacy in patients infected with COVID-19 conducted in China found no difference in the clinical outcome when compared to standard care alone [9].

There is currently a trial NCT04304053 ongoing to look into the efficacy of Darunavir/Cobicistat plus chloroquine treatment in all who are found to be infected. Currently, there is no recommendation for use of antiviral agents for prophylaxis of COVID-19.

Chloroquine-HydroxyChloroquine Sulphate

Chloroquine is a widely known for more than 70 years, is easily available and affordable antimalarial agent with proven chemoprophylaxis properties in malaria. Various mechanisms have shown it to have a role in SARS CoV infection, too. The SARS-CoV2 is known to bind to human cells *via* the Angiotensin Converting Enzyme 2 (ACE 2) receptor. *In vitro* studies have shown that the glycosylation process of ACE2 receptor gets affected thus causing the Vero cells pre-treated with chloroquine to be refractory to SARS-CoV infection, that may be the mechanism through which even human cells can become refractory to this infection [10]. It has also been seen that treatment with chloroquine prevents the spread of SARS-CoV infection in the postinfection period [11].

HCQS has the same mechanism of action but a better safety profile than chloroquine and hence makes it a more preferable drug. Both these drugs have also shown to have immunomodulatory effects and can suppress the increase immune factors [11], which may play a role in reducing the severity of coronavirus disease.

The first ever human trial of chloroquine against COVID-19 was conducted by Chinese investigators. The study conducted in more than 100 patients found chloroquine to be superior in reducing symptom duration, exacerbation of pneumonia, radiological improvement and lead to virus-negative seroconversion [12].

Hydroxychloroquine along with azithromycin was studied by the French group of investigators. It was an open label non-randomized control trial. They included 36 patients in the trial and 20 patients were given hydroxychloroquine at a dose of 600 mg daily along with azithromycin. The authors showed significant reduction in viral load on day 6 of the treatment and much lower average carrying duration of the virus as compared to the control group [13]. Currently many trials are underway to study the effect both for prophylaxis and treatment (Table 1).

Based on these studies, the Indian Council of Medical

Table 1. Summary of ongoing clinical trials for chemoprophylaxis.

Number	Title	Interventions	Age	Allocation	Masking	Start Date	Expected Completion Date	Locations
1. NCT04304053	Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention	Antiviral treatment and prophylaxis <i>vs</i> Standard Public Health measures	≥ 18 years	Randomized	Open Label	March 18, 2020	June 15, 2020	Barcelona, Spain
2. NCT04318444	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	Hydroxychloroquine <i>vs</i> Placebo	≥ 18 years	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Mar-20	Mar-22	New York, United States
3. NCT04318015	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)	Hydroxychloroquine <i>vs</i> Placebo	≥ 18 years	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 1, 2020	March 31, 2021	
4. NCT04251871	Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection	Oxygen therapy, alfa interferon via aerosol inhalation, and lopinavir/ritonavir and Traditional Chinese Medicines (TCMs) granules	14 Years to 80 Years	Randomized	Open Label	January 22, 2020	January 22, 2021	Beijing, China
5. NCT04303507	Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Chloroquine <i>vs</i> Placebo	≥ 16 years	Randomized	Double (Participant, Investigator)	May-20	May-22	Oxford, United Kingdom
6. NCT04321174	COVID-19 Ring-based Prevention Trial With Lopinavir/Ritonavir	Drug: Lopinavir/ritonavir	≥ 18 years	Randomized	Masking: Single (Outcomes Assessor)	March 30, 2020	March 31, 2022	Ontario, Canada
7. NCT04312243	NO Prevention of COVID-19 for Healthcare Providers	Drug: Inhaled nitric oxide gas	18 to 99 Years	Non-Randomized	Masking: None (Open Label)	March 20, 2020	March 20, 2022	Boston, United States
8. NCT04308668	Post-exposure Prophylaxis for SARS-Coronavirus-2	Hydroxychloroquine <i>vs</i> Placebo	≥ 18 years	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	March 17, 2020	May-21	Minnesota, United States

Table 2. Summary of ongoing clinical trials for immunoprophylaxis.

Number	Title	Interventions	Age	Intervention model	Masking	Start date	Completion date	Locations
1. NCT04299724	Safety and Immunity of Covid-19 aAPC vaccine	Biological: pathogen-specific aAPC	6 months to 80 years	Single arm clinical trial	Open label	February 15, 2020	December 31, 2024	Guangdong, China
2. NCT04276896	Immunity and safety of Covid-19 synthetic minigene vaccine	Biological: injection and infusion of LV-SMENP-DC vaccine and antigen-specific CTLs	6 months to 80 years	Single arm clinical trial	Open label	March 24, 2020	December 31, 2024	Guangdong, China
3. NCT04283461	Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) to prevent SARS-CoV-2 infection	Biological: mRNA-1273	18 years to 55 years	Non-randomized trial	Open label	March 3, 2020	June 1, 2021	United States
4. ChiCTR2000030906	A phase I clinical trial for recombinant novel coronavirus (2019-COV) vaccine (adenoviral vector)	Recombinant novel coronavirus vaccine (adenoviral vector)	18 and 60 years	Non-randomized trial	Open label	March 16, 2020	December 31, 2020	Hubei, China

Research (ICMR) [14] has recommended the use of HCQS for prophylaxis of:

- All health care workers those who are involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals.
- Asymptomatic household contacts of laboratory confirmed cases may be prescribed 400 mg twice a day on day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals.

Currently, clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection is lacking from CDC due to absence of randomized clinical trials (RCTs).

Similarly, JHMI clinical guidance do not recommend pre or post exposure prophylaxis in individuals with suspected exposure to SARS-CoV-2 [15].

Precautions

Patients taking these drugs should be frequently monitored for hematological parameters, serum electrolytes, blood glucose, hepatic and renal functions. As these drugs are known to cause QTc prolongation, routine ECG is essential prior to starting these drugs. Co-administration of other drugs known to cause QTc prolongation should be avoided.

Vaccines

There is considerable global investment and effort towards development of a vaccine (Table 2). The US (NIAID) collaborated with Moderna to develop an RNA vaccine. A safety clinical trial of the candidate vaccine mRNA-1273 is underway with sample size of 45 volunteers [16]. Another, Phase I safety trial of a recombinant adenovirus vaccine candidate (CanSino Biologics Inc.

(Tianjin, China)), Ad5-nCoV, recruiting 108 healthy adults in Wuhan, China in March [17]. However, a possible vaccine in development may or may not be safe or effective in future.

We hope that the results of the ongoing trials give us more insight on prophylaxis and help in better prevention and thus decreasing the transmission of this widely spreading disease.

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