Emergence of novel coronavirus and progress toward treatment and vaccine

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Summary
In late December 2019, a group of patients was observed with pneumonia-like symptoms that were linked with a wet market in Wuhan, China. The patients were found to have a novel coronavirus genetically related to a bat coronavirus that was termed SARS-CoV-2. The virus gradually spread worldwide and was declared a pandemic by WHO. Scientists have started trials on potential preventive and treatment options. Currently, there is no specific approved treatment for SARS-CoV-2, and various clinical trials are underway to explore better treatments. Some previously approved antiviral and other drugs have shown some in vitro activity. Here we summarize the fight against this novel coronavirus with particular focus on the different treatment options and clinical trials exploring treatment as well as work done toward development of vaccines.

KEYWORDS
bat coronavirus, chloroquine, remdesivir, SARS-CoV-2, vaccine

1 | INTRODUCTION

Coronaviruses are a form of positive-strand non-segmented RNA viruses distributed among birds, mammals and humans that cause respiratory and neurological illnesses. There are six different types that can cause disease among humans. Four of these (HKU1, 229E, NL63 and OC43) cause only the common cold in patients, while two others cause severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV caused severe respiratory illness in China during its outbreak in 2002-2003, while the MERS-CoV outbreak started in the Middle East in 2012. Due to the broad genetic variation and diversity of coronaviruses and higher chances of animal to human spread they are likely to emerge periodically in future.

During December 2019, an outbreak of pneumonia-like symptoms occurred in patients that were linked to the seafood market in Wuhan China. Investigation identified a new strain of coronavirus called SARS-CoV-2.

The detection of this novel coronavirus is key to confirm the cases and proceed to treatment. In an early method for detecting SARS-CoV-2, the samples from bronchoalveolar-lavage fluids were collected, centrifuged to remove debris and inoculated onto human epithelial cells of airway origin. About 20,000 sequences from each sample were obtained and genome matches showed more than 85% identity with SARS-like betacoronavirus. Results were also obtained from real-time PCR, and isolated viruses were named SARS-CoV-2. To further characterize SARS-CoV-2, the de-novo sequence was obtained by using nanopore sequencing and Illumina methods. The airway epithelial cell cultures were suitable for visualization and identification of the novel coronavirus.

2 | TREATMENT OPTIONS FOR CORONAVIRUS

Currently, no treatment is approved for SARS-CoV-2, but various already approved drugs are being tried in different clinical trials to...
check efficacy against this virus. The possible options include nucleoside analogs, interferon that can act as immune modulators and approved antimalarials having antiviral activities such as chloroquine and hydroxychloroquine.

### 2.1 Antiviral drugs

The nucleoside analogs such as ribavirin, favipiravir, galidesivir and remdesivir target RNA polymerase and block the synthesis of viral RNA. Favoripiravir was effectively used against influenza and has the potential to inhibit viral RNA synthesis and a new study also supports its activity against SARS-CoV-2. Different clinical trials are underway where patients are being recruited to evaluate the efficacy of a combination of favipiravir and interferon-α and a combination of favipiravir and baloxavir marboxil is being evaluated. Ribavirin is a guanine derivative antiviral drug approved for the treatment of HCV and RSV, but it causes anemia at higher doses that limit its use and its efficacy against coronavirus is uncertain.

Remdesivir is an adenine derivative antiviral drug. It has activity against a variety of viral strains such as SARS and MERS and a recent study also supports its activity against SARS-CoV-2. A recent patient in US with SARS-CoV-2 has shown recovery with intravenous administration of remdesivir. Recently, Phase-III clinical trials have been started in USA to evaluate the efficacy of IV remdesivir as 200 mg OD or 100 mg OD for 9 days. A recent RCT apparently reported no significant efficacy, but we await the published findings.

Some protease inhibitors like lopinavir and ritonavir have shown activity against SARS and MERS coronaviruses. Clinical trials have been started to test the efficacy of lopinavir and ritonavir combination against SARS-CoV-2. These drugs are known to inhibit the chymotrypsin-like protease of MERS and SARS coronaviruses. A study in vitro using Vero E6 cells infected with SARS-CoV-2 assessed efficacy of different therapies by quantitative analysis using PCR (qRT-PCR). Remdesivir and chloroquine showed promising results. Remdesivir has previously shown efficacy against MERS coronavirus and Ebola virus and is currently under clinical trial for treatment of Ebola. The results showed that EC90 value of remdesivir against SARS-CoV-2 was 1.76 μM.

Neuraminidase inhibitors are recognized antiviral agents for the treatment of influenza. The treatment with oral oseltamivir has been given to suspected patients in China. In past, oseltamivir has shown efficacy against MERS-COV.

### 2.2 Chloroquine and hydroxychloroquine

Small molecular weight drugs such as chloroquine have shown inhibitory effects against SARS-CoV-2 (EC50 = 1.14 μM in Vero E6 cells) and is under evaluation in open-label trials. Chloroquine (CQ) is a recognized anti-malarial drug but also has antiviral activity. The antiviral activity of chloroquine was first noticed in the late 1960s. Chloroquine and its analog hydroxychloroquine both have inhibitory effects against various viruses including SARS, enterovirus and Zika virus. Chloroquine inhibits the virus by increasing endosomal pH and so reducing viral cell fusion and also interferes with cellular receptor glycosylation. The EC90 value of chloroquine against SARS-CoV-2 is 6.90 μM that can be achieved with administration of 500 mg dose. Remdesivir and chloroquine have shown activity in in vitro studies and can easily be tested in patients with SARS-CoV-2.

In another recent study, Gao et al found that chloroquine phosphate reduced the symptoms of pneumonia in SARS-CoV-2 patients and shortening the duration of disease. The guidelines for the treatment of SARS-CoV-2 were revised six times since its issuance on 15 January 2020. The recent guidelines also include IFN-α, remdesivir, ribavirin, ritonavir and chloroquine. The mode of administration of IFN-α is through inhalation at a dose of 5 million units diluted with water for injection. The dose of ritonavir is 100 mg BD for adults. Ribavirin may be given in combination with IFN-α or ritonavir at a dose of 500 mg BD or TDS. Chloroquine phosphate should be administered at a dose of 500 mg BD. Arbidol can be given three times a day at 200 mg.

Hydroxychloroquine (HCQ) is an approved disease-modifying antirheumatic drug that also has immunomodulatory effects and prevents organ damage. HCQ alters endosomal pH and interrupts the binding between RNA/DNA and toll-like receptors that leads to suppression of TLR signaling. Inside the cytoplasm, HCQ also interferes with the interaction between nucleic acid sensor cyclic GMP and cytosolic DNA. These two mechanisms lead to increase production of IL-1, TNF and type-1 interferon. Such mechanism supports the idea that HCQ suppress the cytokine release storm (CRS) which is due to SARS-CoV-2 triggered overreaction of immune system. In a recent study, HCQ was found to be more effective than chloroquine; a loading dose of 400 mg twice daily and maintenance dose of 200 mg twice a day is recommended for SARS-CoV2 infection.

The mechanism involves in antiviral role of HCQ and CQ is inhibition of receptor binding and fusion of cell membrane. These two are crucial steps that are required for cell entry of SARS-CoV-2. Chloroquine interferes with the glycosylation of ACE-2 (angiotensin-converting enzyme receptors) receptors that are considered as cellular receptors for SARS-CoV-2 and block the fusion of SARS-CoV-2 with host cell. Thus, the binding of virus is blocked and infection is prevented. The HCQ and CQ after entry into the cell tend to concentrate in lysosomes and endosomes. The SARS-CoV-2 use endosome as a tool for cellular entry. HCQ and CQ increase the pH of endosomes and create a negative influence on the binding of SARS-CoV-2 with endosomes. Lysosomal protease helps in viral fusion with cell membrane. Increase lysosomal pH prevents the action of protease and fusion and replication of virus is blocked. The mechanism of action of chloroquine and hydroxychloroquine is represented as (Figure 1).

### 2.3 Chymotrypsin-like inhibitors

Cinanserin is an antagonist of serotonin receptors. It can inhibit chymotrypsin-like (3C-like) protease and has shown promising results
against SARS coronavirus.37 The 3C-protease was also investigated to be encoded in SARS-CoV-2.38

Flavonoids such as chalcones, flavones and isoflavones produce antioxidant effects but they also have antiviral effects.39 A study has found that flavonoids can inhibit the entry of hepatitis-C virus.40 Some flavonoids have activity against MERS coronavirus, presumably due to inhibition of 3C-like protease.41

2.4 | Other treatment options

Pirfenidone is under clinical trial for the treatment of idiopathic pulmonary fibrosis resulting from SARS-CoV-2 infection. It also has an anti-inflammatory effect and serves as an anti-oxidant. The results obtained during SARS 2003 were promising and now beneficial effects could be obtained in patients with severe pneumonia from SARS-CoV-2.42

Nitric oxide (NO) is a biological gas produced from arginine. NO after reaction with superoxide forms peroxynitrite which has cytotoxic bactericidal action.43 Nitric oxide is also known to regulate airway function and reduce inflammation of airways.44 The beneficial effect of NO in SARS patients was observed in some studies.45 NO can also inhibit the synthesis of RNA and viral protein.46 A study has found that organic nitric oxide could inhibit the replication cycle of SARS-CoV-2.47

Mucroporin-M1 is a peptide derived from scorpion venom with broad spectrum antiviral activity against various infections like influenza H5N1 and SARS-CoV.51

The use of convalescent plasma for the treatment of SARS-CoV-2 is also under consideration with varying hope regarding efficacy. The pros of using plasma from recovered patients include easy availability and it can also be used as prophylactically in healthcare professionals who are at high risk of exposure to SARS-CoV-2 infection. The cons include that not all recovered patients have enough antibodies. Lack of availability of validated SARS-CoV-2 assay for detection of neutralizing antibodies may cause hindrance in identification of suitable donor.52 A large scale randomized clinical trials are needed to establish the efficacy of convalescent plasma.53

Some studies support the role of angiotensin-converting enzyme (ACE) inhibitors. This is based on the hypothesis that ACE-2 serves as receptor for SARS-CoV-2.54,55 So, ACE inhibitor could potentially compete for site binding and reduce the mortality and morbidity associated with SARS-CoV-2.56

The various ongoing clinical trials are summarized in Table 1.

3 | POTENTIAL VACCINES

Vaccine provides immunity against a particular pathogen before exposure of that infectious agent. Several types of vaccines exist that can be nucleic acid based, live attenuated vaccine, subunit proteins or nanoparticle vaccines.67 Different technologies are being utilized to
develop potential vaccine for SARS-CoV-2 including DNA and mRNA-based nanoparticles. Phase-I trials of potential vaccines focus on safety and immunogenicity, for example, against MERS. Two of the clinical trials on MERS vaccine are expected to be complete by the end of 2020 in Russia and one in Germany by December 2021. The Inovo pharmaceutical company has tested its vaccine against MERS coronavirus funded by coalition for epidemic preparedness innovation (CEPI) using DNA-based technology and named as INO-4700. The University of Oxford recombinant chimpanzee adenovirus has also begun Phase 1 randomized multicenter trials for intramuscular injection of vaccine ChAdOx1 against SARS-CoV-2. The 1100 participants have been divided into four groups and they will be observed for any serious adverse event for 6 months.

The ongoing clinical trials for development of vaccines have been summarized in Table 2 and completed vaccine trials for SARS and MERS viruses have been summarized in Table 3.

3.1 | Development of neutralizing antibodies against coronaviruses

The fusion of coronavirus with a cell occurs after biding of S protein to a target receptor delivers viral nucleocapsid and initiates replication. The S protein causes syncytial formation at the receptor site. A neutralizing antibody that can target the S protein on the surface of

| Clinical Trial Registration Number | Clinical trial information | Date | Type | References |
|-----------------------------------|---------------------------|------|------|------------|
| ChiCTR2000030897                   | The efficacy of Newgen beta-gluten probiotic powder in patient with 2019-nCOV. | 16 March 2020 | Interventional | 57 |
| ChiCTR2000030894                   | The efficacy of combination of Favipiravir + Tocilizumab in patient with pneumonia (COVID-19). | 16 March 2020 | Interventional | 58 |
| ChiCTR2000030892                   | A prospective study on Pirfenidine in the treatment of Coronavirus Pneumonia (COVID-19) Fibrosis. | 16 March 2020 | Interventional | 59 |
| ChiCTR2000030883                   | The efficacy of traditional Chinese qingfei detoxification decoction (mixture) in coronavirus pneumonia (COVID-19). | 16 March 2020 | Observational | 60 |
| ChiCTR2000030857                   | A study for bronchoscopic alveolar lavage in patients undergoing trachea intubation with new coronavirus pneumonia (COVID-19). | 16 March 2020 | Observational | 61 |
| ChiCTR2000030853                   | The study of protective effect of dexmedetomidine in severe novel coronavirus pneumonia (COVID-19) patients. | 16 March 2020 | Interventional | 62 |
| NCT04252885                        | The combination of Lopinavir + Ritonavir and Arbidol against 2019-nCOV. | 28 January 2020 | Interventional | 63 |
| NCT04273763                        | The study of bromhexine hydrochloride along with standard treatment in patients with novel coronavirus pneumonia (COVID-19). | 18 February 2020 | Interventional | 64 |
| NCT04280588                        | The use of Fingolimod in patient with COVID-19. | 21 February 2020 | Interventional | 65 |
| NCT04288713                        | The efficacy of Eculizumab (Soliris) in Covid-19 Infected Patients (SOLID-C19). | 28 February 2020 | Interventional | 66 |

| Company                            | Technology | Stage | Expected timeline | References |
|------------------------------------|------------|-------|-------------------|------------|
| Inovo pharmaceuticals              | INO-4800 DNA based | Pre-clinical studies funded by Coalition for Epidemic Preparedness Innovations (CEPI) | Human testing in few months | 73 |
| Vir Biotechnology                  | anti-coronavirus monoclonal antibodies (mAbs), CRISPR- based screening | Pre-clinical | No decided timeline | 74 |
| The university of oxford           | Adenovirus vector and SARS-CoV-2 spike protein | Phase-1 started on 23rd April in 1100 peoples | Upto 6 mo | 75 |
| University of Queensland           | Molecular clamp technology | Pre-clinical | 6 mo-1 y | 76 |
| Johnson & Johnson                  | Adenovirus based technology | Pre-clinical | 1 y | 77 |
| The University of Saskatchewan’s   | Not known | Pre-clinical | 3-4 mo | 78 |
| GeoVax and BravoVax                | Modified Vaccinia Ankara (MVA) platform technology | Pre-clinical | Not known | 79 |
| Chinese clinical trial center      | Clinical trial for recombinant novel coronavirus (2019-CoV) vaccine based on adenoviral vector | Phase-1 clinical trial | Not known | 80 |
SARS-CoV-2 could also be an option to produce passive immunity in patients. Recent research on the genome of SARS-CoV-2 (MN908947.3) allows scientists to express the S protein as immunogen on the surface and explore options such as yeast libraries for generating antibodies that neutralize the virus.

CONFLICT OF INTEREST
The authors have no conflict of interest in this manuscript.

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