Protocol

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Lopinavir/ritonavir combination therapy amongst symptomatic coronavirus disease 2019 patients in India: Protocol for restricted public health emergency use

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As of February 29, 2020, more than 85,000 cases of coronavirus disease 2019 (COVID-19) have been reported from China and 53 other countries with 2,924 deaths. On January 30, 2020, the first laboratory-confirmed case of COVID was reported from Kerala, India. In view of the earlier evidence about effectiveness of repurposed lopinavir/ritonavir against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus (CoV), as well as preliminary docking studies conducted by the ICMR-National Institute of Virology, Pune, the Central Drugs Standard Control Organization approved the restricted public health use of lopinavir/ritonavir combination amongst symptomatic COVID-19 patients detected in the country. Hospitalized adult patients with laboratory-confirmed SARS-CoV-2 infection with any one of the following criteria will be eligible to receive lopinavir/ritonavir for 14 days after obtaining written informed consent: (*i*) respiratory distress with respiratory rate ≥22/min or SpO_2 of <94 per cent; (*ii*) lung parenchymal infiltrates on chest X-ray; (*iii*) hypotension defined as systolic blood pressure <90 mmHg or need for vasopressor/inotropic medication; (*iv*) new-onset organ dysfunction; and (*v*) high-risk groups - age >60 yr, diabetes mellitus, renal failure, chronic lung disease and immunocompromised persons. Patients will be monitored to document clinical (hospital length of stay and mortality at 14, 28 and 90 days), laboratory (presence of viral RNA in serial throat swab samples) and safety (adverse events and serious adverse events) outcomes. Treatment outcomes amongst initial cases would be useful in providing guidance about the clinical management of patients with COVID-19. If found useful in managing initial SARS-CoV-2-infected patients, further evaluation using a randomized control trial design is warranted to guide future therapeutic use of this combination.

Key words Coronavirus disease 2019 - COVID-19 - lopinavir/ritonavir - severe acute respiratory syndrome coronavirus 2 - treatment outcome

Coronaviruses (CoVs) are enveloped non-segmented positive-sense RNA viruses, belonging to the family *Coronaviridae* and the order *Nidovirales*, and are broadly distributed in humans and other mammals[1]. In December 2019, a series of cases of pneumonia of unknown aetiology emerged in

Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia. Deep-sequencing analysis from lower respiratory tract samples indicated a novel CoV (nCoV)[2], which was named severe acute respiratory syndrome (SARS)-CoV-2[3]. Since December 31, 2019 and as of February 29, 2020, a total of 85,403 cases of CoV disease 2019 (COVID-19) have been reported, including 2,924 deaths. Of the total deaths reported, 2,838 were in People's Republic of China (PRC). Other than China, confirmed cases have been reported from 53 countries[4]. As per the statement of the WHO Emergency Committee, COVID-19 had a case-fatality ratio (CFR) of four per cent; however, recent reports suggested it to be between 1 and 2 per cent[5-7].

The published studies from China indicated that most cases with SARS-CoV-2-infected pneumonia were aged above 50 yr (median age: 55-59 yr), predominantly men (54-68%) and had chronic medical conditions (46.4-51%). The common symptoms included fever, fatigue, dry cough, myalgia, dyspnoea, expectoration and diarrhoea[8-11]. The common laboratory abnormalities amongst 138 patients were lymphopenia [lymphocyte count, 0.8×10^9/l (interquartile range IQR, 0.6-1.1), 70.3%], prolonged prothrombin time [PT, 13.0 sec (IQR, 12.3-13.7), 58%] and elevated lactate dehydrogenase [261 U/l (IQR, 182-403), 39.9%][10]. Unilateral (25%) or bilateral (75%) pneumonia and multiple mottling and ground-glass opacities (14%) were the common findings on chest X-ray/computed tomography (CT) scan[9,10]. Patients were treated with antivirals including oseltamivir, ganciclovir and lopinavir and ritonavir, antibiotics and glucocorticosteroids[8,10].

No antiviral treatment for SARS-CoV-2 infection has been proven to be effective. A few historical control studies or case reports indicate the effectiveness of combination of lopinavir/ritonavir against SARS-CoV and MERS-CoV infections. Ritonavir-boosted lopinavir was approved for use amongst HIV-infected individuals in September 2000 by the U.S. Food and Drugs Administration[12]. The drug has been used for over 15 years in India. Heat stable version of the medicine that is based on malt-extrusion technology Meltrex™ Technology was launched in India in 2007[13]. Lopinavir is metabolized by cytochrome P4503A (CYP3A) isoenzyme in the liver. Lopinavir is always used with ritonavir to reduce the dose of lopinavir and increase the plasma levels of lopinavir as ritonavir inhibits CYP3A isoenzyme. Lopinavir and ritonavir are antiretroviral protease inhibitors used in combination as a second-line drug for the treatment of HIV-1 infection in children and adults and have limited side effects[14,15]. As per the NACO (National AIDS Control Organization) guidelines, lopinavir/ritonavir is used as a second-line drug in the treatment of HIV in combination with nucleoside reverse transcriptase inhibitors (NRTIs). It is also recommended by NACO in post-exposure prophylaxis in HIV for 28 days. It is also part of the first-line regimen for patients with HIV-2 infection[16]. The drug has been used extensively in the management of paediatric HIV infection, especially amongst infants. Thus, there is a long period of experience of its use in India. A systematic review suggested no safety or efficacy concerns for use of standard-dose lopinavir/ritonavir amongst pregnant women[17]. Boosted lopinavir has been used to prevent mother-to-child transmission of HIV-1 and HIV-2 infection[16]. The main viral protease has been regarded as a suitable target for drug design against CoV infection due to its vital role in polyproteins processing necessary for CoV reproduction. Lopinavir/ritonavir has been shown to have the highest inhibitory potency against CoV amongst several anti-HIV-1 protease inhibitors[18].

In a historical control study, lopinavir/ritonavir with ribavirin amongst SARS-CoV patients was associated with substantial clinical benefit. The adverse clinical outcome (ARDS or death) was significantly lower in the treatment group than in the controls who received only ribavirin (2.4 vs. 28.8%, $P<0.001$) at day 21 after the onset of symptoms. A reduction in steroid usage and nosocomial infections was seen in patients initially treated with lopinavir/ritonavir, and these patients had a decreasing viral load and rising peripheral lymphocyte count[19]. Findings from *in vitro* and clinical studies, together with the availability and safety profiles of lopinavir/ritonavir and interferon beta-1b (IFN-β1b) suggest that the combination of these agents has potential efficacy for the treatment of patients with MERS-CoV. Oral treatment with lopinavir/ritonavir in the marmoset model of MERS-CoV infection resulted in modest improvements in MERS disease signs, including decreased pulmonary infiltrates identified by chest X-ray, decreased interstitial pneumonia and decreased weight loss[20]. Studies on MERS patients with treatment regimens including lopinavir-ritonavir reported positive disease outcomes including defervescence, viral clearance from serum and sputum and survival[21-24]. Arabi *et al*[25] initiated a

placebo-controlled trial of IFN-β1b, lopinavir and ritonavir amongst patients with MERS-CoV infection in Saudi Arabia.

In India, the first laboratory-confirmed case of COVID-19 was reported from Kerala on January 30, 2020 (*https://pib.gov.in/PressReleseDetail.aspx?PRID=1601095*). Subsequently, two more cases were reported from Kerala. All cases had recently returned from Wuhan, PR China, had mild illness and were managed symptomatically. More such cases can be expected amongst individuals travelling from China, and Wuhan in particular, and amongst their close contacts. As COVID-19 is an emerging virus, an effective treatment has not been developed for disease resulting from this virus. In view of the earlier evidence about the effectiveness of lopinavir/ritonavir against SARS and MERS-CoV, the Indian Council of Medical Research (ICMR) has suggested off-label emergency use of lopinavir/ritonavir combination for symptomatic COVID-19 patients detected in the country. Use of IFN-β1b and ribavirin was not considered due to their reported toxicity, whereas oseltamivir was not considered due to its unproven efficacy against CoVs. This article describes the protocol for the administration of lopinavir/ritonavir to such patients and their clinical monitoring.

Proposed protocol

This protocol is to be implemented along with the WHO guidelines on clinical management of severe acute respiratory infection when nCoV infection is suspected: Interim Guidance[26].

Patient eligibility criteria

Inclusion criteria: Include (1) Adult over 18 yr of age; (2) Laboratory confirmation of COVID-19 infection by real-time reverse transcription-polymerase chain reaction (qRT-PCR) from the recommended sample (3) Symptomatic patients with any one of the following: (*i*) Respiratory distress with respiratory rate ≥22/min or SpO_2 of <94 per cent, (*ii*) Lung parenchymal infiltrates on chest X-ray or CT scan, (*iii*) Hypotension defined as systolic blood pressure <90 mmHg or need for vasopressor/inotropic medication, (*iv*) New-onset organ dysfunction (one or more of the following): (a) Increase in creatinine by 50 per cent from baseline, glomerular filtration rate (GFR) reduction by >25 per cent from baseline or urine output of <0.5 ml/kg for six hours, (b) Reduction of Glasgow Coma Scale (GCS) score by two or more, and (c) Any other organ dysfunction; (*v*) High-risk groups with age >60 yr, and those with hypertension, diabetes mellitus, renal failure, chronic lung disease and immunocompromised persons; (*vi*) Informed consent from patient and caretaker. Consent from legally authorized representative in case the patient is not able to provide the same due to his/her medical condition.

Exclusion criteria: (*i*) A patient with hepatic impairment [Child Pugh C or alanine aminotransferase (ALT) over 5X the upper limit of normal]; (*ii*) Use of medications that are contraindicated with lopinavir/ritonavir and that cannot be replaced or stopped, *e.g.*, rifampicin, benzodiazepines, simvastatin, voriconazole and sildenafil; and (*iii*) Known HIV-infected individual receiving other protease inhibitors containing regimens that cannot be replaced by lopinavir/ritonavir.

***Dosage of lopinavir/ritonavir*:** (*i*) Lopinavir/ritonavir 200 mg/50 mg - two tablets every 12 h for 14 days or for seven days after becoming asymptomatic, whichever is earlier; and (*ii*) For patients who are unable to take medications by mouth, 400 mg lopinavir /100 mg ritonavir 5 ml suspension every 12 h for 14 days or seven days after becoming asymptomatic whichever is earlier, *via* a nasogastric tube.

***Baseline laboratory investigations*:** (*i*) Haemogram; (*ii*) Liver function tests (LFTs); (*iii*) Renal function tests (RFTs); (*iv*) Haemoglobin A_{1c} and blood sugar, if required; (*v*) RT-PCR for SARS-CoV-2 (respiratory samples: nasopharyngeal swab, oropharyngeal swab, in addition, sputum, bronchoalveolar lavage (BAL), if available); (*vi*) PT/international normalized ratio, electrolytes, arterial blood gas; (*vii*) Lipid profile; (*viii*) Chest X-ray; (*ix*) Electrocardiogram (ECG); (*x*) Hepatitis B and C; and (*xi*) Other investigations as deemed appropriate by the treating physician.

***Laboratory sample collection (other than investigations for routine clinical monitoring)*:** (*i*) Oropharyngeal swabs (every third day) - for SARS-CoV-2 RT-PCR (samples to be transported to ICMR-National Institute of Virology, Pune, as per the guidelines); (*ii*) Blood sample (every week) - Haemogram, LFT (alternate days), RFT and electrolytes (to monitor drug-induced adverse events); (*iii*) ECG; and (*iv*) Other investigations as deemed appropriate by the treating physician.

All samples would be stored for future-related tests.

***Frequency and duration of monitoring*:** (*i*) Patients should be monitored daily until discharge from the hospital and followed up till 90 days; and

(*ii*) Patient should be discharged on clinical recovery and after obtaining two consecutive negative RT-PCR results at least 24 h apart from oropharyngeal swabs (to demonstrate viral clearance).

Outcome assessment

Clinical outcomes: (*i*) Hospital length of stay; (*ii*) Intensive care unit (ICU)-free days; (*iii*) Requiring use of ventilator; (*iv*) Mortality in the ICU; (*v*) Mortality in the hospital; and (*vi*) Mortality at 14, 28 and 90 days.

Safety outcomes: (*i*) Acute pancreatitis (defined as having: (a) abdominal pain radiating to the back; (b) serum amylase at least three times greater than the upper limit of normal; (c) radiological evidence, such as contrast CT/magnetic resonance imaging/ultrasonography, of acute pancreatitis); (*ii*) Elevation of ALT to more than five-fold upper normal limit; (*iii*) Anaphylaxis; and (*iv*) Adverse events and serious adverse events.

Laboratory outcomes: (*i*) Viral RNA loads and cycle threshold values in serial samples of nasopharyngeal and oropharyngeal swabs and blood, collected every third day (to document viral replication kinetics).

The schedule of key investigations is given in the Table.

Discussion

The complete clinical picture of COVID-19 is not fully understood. The clinical manifestations in infected patients could range from mild illness to severe disease requiring ICU admission and ventilatory support. The CFR of COVID-19 is lower than that of SARS (CFR: 14-15%) and MERS (34%)[27,28]. Till now, no effective treatment has been recommended for COVID-19, except meticulous supportive care[26]. The ICMR has suggested lopinavir/ritonavir combination therapy for laboratory-confirmed COVID-19 patients based on the observational studies of clinical benefit amongst patients with SARS-CoV and MERS-CoV[19-21], as well as the docking studies conducted by the National Institute of Virology, Pune[29]. The Indian Regulatory Authority, Central Drugs Standard Control Organization, has accorded approval for restricted public health emergency use of this treatment protocol.

The initial treatment protocol was for administering the combination treatment to all laboratory-confirmed patients. However, the first three laboratory-confirmed patients from Kerala had mild symptoms on diagnosis and had a stable course of illness. Hence, lopinavir/ritonavir treatment was not administered in these patients. It is however, crucial to initiate the treatment before patient develops features of severe

Table. Schedule of investigations for the administration of lopinavir/ritonavir combination

Parameters	Days during admission period														
	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14
Haemogram[@]	✓		✓		✓		✓		✓		✓		✓		✓
Liver function test[*]	✓		✓		✓		✓		✓		✓		✓		✓
Renal function test[#]	✓		✓		✓		✓		✓		✓		✓		✓
HbA_{1C} and blood sugar	✓														
qRT-PCR for SARS-CoV-2	✓			✓			✓			✓			✓		
Electrolytes	✓		✓		✓		✓		✓		✓		✓		✓
PT/INR, arterial blood gas	✓														
Lipid profile	✓														
Chest X-ray	✓							✓							✓
ECG	✓		✓		✓		✓		✓		✓		✓		✓
HBV and HCV ELISA	✓														

[@]Hb%, total leucocyte count and differential WBC - neutrophils, lymphocytes, eosinophils, monocytes and basophils, RBC count, platelet count; [#]Renal function test - BUN, Creatinine; [*]Liver function test - albumin, bilirubin, ALT, AST, alkaline phosphatase. AST, aspartate transaminase; ALT, alanine aminotransferase; RBC, red blood cell; WBC, white blood cell; BUN, blood urea nitrogen; HBV, hepatitis B virus; HCV, hepatitis C virus; ECG, electrocardiogram; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; qRT-PCR, real-time reverse transcription-polymerase chain reaction; PT, prothrombin time; INR, international normalized ratio; HbA_{1c}, haemoglobin A_{1c}; Hb, haemoglobin

illness. In view of this, the treatment protocol was subsequently amended to include additional criteria of severity as well as organ damage for initiating the combination treatment. The inclusion criteria also include high-risk group patients associated with higher risk of mortality (age >60 yr, hypertension, diabetes mellitus, renal failure, chronic lung disease and immunocompromised persons) for initiating the combination therapy. The treatment protocol also emphasizes the need for obtaining written informed consent and patients to be enrolled into this protocol on case-to-case basis. It is also equally important to monitor COVID-19 patients closely to generate reliable data about clinical, laboratory, as well as safety outcomes.

This treatment protocol has a limitation. The combination treatment is approved for emergency public health use, only amongst laboratory-confirmed patients with moderate degree of severity and not designed as a controlled clinical trial. However, the treatment outcomes amongst the first few cases would be useful in providing guidance about clinical management of COVID-19 cases in future. If found useful in managing initial COVID-19 infected patients, further evaluation using a randomized control trial design is warranted to guide future therapeutic use of this combination.

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***Conflicts of Interest*:** None.

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