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Review

Current off-label Pharmacotherapeutics in the management of novel coronavirus disease (COVID-19)

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, Severe acute respiratory syndrome SARS-CoV-2, that was first recognized in Wuhan, China, in December 2019. There are no FDA- approved therapeutics or drugs to treat, cure or prevent COVID-19. Some reported case studies indicated the significance of Chloroquine use in mild cases and Lopinavir and Ritonavir in severe cases of COVID-19 respectively. Indian Council of Medical Research, India issued a protocol which is to be implemented along with the WHO guidelines on clinical management of mild and severe acute respiratory infection when COVID-19 infection is suspected in Indian patients as a restricted public health emergency use.

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, SARS-CoV-2, that was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that SARS-CoV-2 is a betacoronavirus closely linked to the SARS virus.[1,2] The World Health Organization (WHO) has declared the COVID-19 outbreak a pandemic on 11 March 2020 and till the 19th March 2020 WHO reports the 209,839 confirmed cases, 8778 deaths and 168 countries, areas or territories with cases worldwide affected.[3] While most people with COVID-19 develop a mild or uncomplicated illness, approximately 14% develop severe disease requiring hospitalization and oxygen support and 5% require admission to an intensive care unit.[1]

In severe cases, COVID-19 can be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury.[4] Older age and co-morbid disease have been reported as risk factors for death, and recent multivariable analysis confirmed older age, higher (Sequential Organ Failure Assessment) SOFA score and d-dimer > 1 μg/L on admission were associated with higher mortality. The study also observed the median duration of viral RNA detection was 20.0 days (IQR 17.0–24.0) in survivors, but the SARS-CoV-2 virus was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.[5,6]

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PHARMACOTHERAPEUTICS

While there are no FDA-approved therapeutics or drugs to treat, cure or prevent COVID-19, there are several FDA-approved treatments that may help ease the symptoms from a supportive care perspective.

Chloroquine:

The FDA has been working closely with other government agencies and academic centers that are investigating the use of the drug chloroquine, which is already approved for treating malaria, lupus and rheumatoid arthritis, to determine whether it can be used to treat patients with mild-to-moderate COVID-19 to potentially reduce the duration of symptoms, as well as viral shedding, which can help prevent the spread of disease. Studies are underway to determine the efficacy of using chloroquine to treat COVID-19. Chloroquine is recommended to be included in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future.[7-9]

Remdesivir:

The National Institutes of Health (NIH) began a randomized controlled trial for the treatment of COVID-19 patients with the investigational antiviral drug Remdesivir. The FDA has been working with the drug sponsor, Gilead Sciences Inc. to find multiple pathways to both study the drug under the FDA's investigational new drug requirements, and thus collect helpful data about the efficacy of the drug, as well as provide the drug to patients under emergency use. Controlled clinical trials are needed to determine if it safe and effective for the treatment of COVID-19 infection.[7,9]

Lopinavir/Ritonavir:

One case study from Korea reported the use of Lopinavir/Ritonavir significantly decreases the β-coronavirus viral loads and no or little coronavirus titers were observed. The 54-year old male was the third patient diagnosed with COVID-19 infection in Korea. He is a worker for a clothing business and had mild respiratory symptoms and intermittent fever at the beginning of hospitalization, and pneumonia symptoms on chest computerized tomography scan on day 6 of admission. This patient caused one case of secondary transmission and three cases of tertiary transmission.[10]

Ritonavir-boosted Lopinavir was approved for use amongst HIV-infected individuals in September 2000 by the U.S. Food and Drugs Administration. 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.[11,12]

Sarilumab:

Innovators are looking at products in a variety of areas, including the assessment of antiviral drugs that might treat the specific virus, as well as host targets, such as interleukin-6 (IL-6) receptor inhibitors that may be helpful in reducing lung inflammation and improving lung function in COVID-19 patients, thereby potentially slowing the progression of severe respiratory symptoms. Regeneron Pharmaceuticals Inc. has announced the initiation of a randomized controlled clinical trial of Sarilumab, an antibody to the IL-6 receptor, to assess whether the modification of the inflammatory response by this treatment provides benefit to COVID-19 patients.[7]

Immunoglobulin:

There's also interest in evaluating whether therapies, such as convalescent plasma and hyperimmune globulin, antibody-rich blood products that are taken from blood donated by people who have recovered from the virus, could shorten the length, or lessen the severity, of the illness. The FDA is taking the lead on an urgent cross-government approach to facilitate the development of all of these products. Facilitating the ultimate widespread use and availability of safe and effective medical countermeasures is critical for a number of reasons, including that reducing the

severity and duration of respiratory or other symptoms through medical treatments could help lessen the burden on medical personnel, equipment, and facilities.[7]

Vaccine:

The FDA is also working with interagency partners, product developers, and international public health organizations to expedite the development of vaccines to the greatest extent possible. Earlier this week, NIH announced the start of Phase 1 clinical trial in Seattle in 45 healthy adult volunteers to test the safety of an investigational vaccine designed to protect against COVID-19 infection.[7, 13]

INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR) PROTOCOL:

ICMR, India issued a protocol which is to be implemented along with the WHO guidelines on clinical management of mild and severe acute respiratory infection when COVID-19 infection is suspected.[14,15]

COVID-19 Positive patient without lung infection:

Chloroquine 500 mg tablet every 12 hours and Oseltamivir 150 mg tablet every 12 hours for the 14 days or till the negative COVID-19 result.

COVID-19 Positive patient with lung infection:

Patient eligibility criteria:

Inclusion criteria:

(1) Adult over 18 years 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 SpO2 of <94 percent, (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 percent from baseline, glomerular filtration rate (GFR) reduction by >25 percent 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 years, and those with hypertension, diabetes mellitus, renal failure, chronic lung disease, and immunocompromised persons; (vi) Informed consent from patient and caretaker. Consent from a legally authorized representative in case the patient is not able to provide the same due to his/her medical condition.

Exclusion criteria:

(1) A patient with hepatic impairment [Child Pugh C or alanine aminotransferase (ALT) over 5X the upper limit of normal]; (2) 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 (3) 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 hours 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 hours 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 A1c 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) Prothrombin time/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 or 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.

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

DISCUSSION
No effective and approved treatment has been recommended for COVID-19 up till, except for supportive care. The ICMR, India 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 MERSCoV[16-18], as well as the docking studies conducted by the National Institute of Virology, Pune.[19,20] The Indian Regulatory Authority, Central Drugs Standard Control Organization, has accorded approval for restricted public health emergency use of this treatment protocol.
The treatment significance amongst the first few cases would be useful in guiding clinical management of COVID-19 cases in the 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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