Potential therapeutic options for coronavirus disease 2019: using knowledge of past outbreaks to guide future treatment

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In December 2019, initial cases of the novel coronavirus (2019-nCoV) infection, termed coronavirus disease 2019 (COVID-19), were first reported in Wuhan, China.[1] In humans, infections with the human coronavirus 229E, OC43, NL63, and HKU1 usually result in mild, self-limiting upper respiratory tract infections. However, other variants have rapid transmission rates and can cause severe respiratory syndrome and death. These variants include severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and the current 2019-nCoV.

These three coronaviruses (CoV) share some similarities in their genomic, clinical, and pathologic features. CoV comprise four genera (α-, β-, γ-, and δ-CoV). These three viruses are all β-CoV, with MERS-CoV belonging to lineage C and SARS-CoV and 2019-nCoV belonging to lineage B. Animal to human transmission is thought to be at the origin of these three viruses with bats as the possible natural reservoir. MERS-CoV uses dipeptidyl peptidase 4 as the primary entry receptor, which has been reported to be expressed in the human lower respiratory tract as well as kidney and T-cells but not in the upper respiratory tract. That may explain the relative lower transmission rate and increased mortality rate of MERS-CoV compared to SARS-CoV. On the contrary, 2019-nCoV was predicted to use the same primary receptors angiotensin-converting enzyme 2 as SARS-CoV, which is widely expressed in the respiratory tract on epithelial cells and alveolar monocytes and macrophages. Moreover, COVID-19 mostly resembles SARS with symptoms from fever, cough, myalgia, fatigue, to severe acute respiratory distress syndrome leading to death. This newly identified virus is spread through close contact, in particular through respiratory droplets from coughs and sneezes. Compared with MERS-CoV and SARS-CoV, 2019-nCoV is believed to have a higher transmission rate and lower mortality rate. A panel of experts from the World Health Organization (WHO) estimated that mortality is 2%, in contrast with >10% and >35% for SARS and MERS, respectively.[2] According to the current data, more than 90,000 people have been reported to be infected and more than 3000 deaths have been reported, much higher than the other two variants.[3]

According to the WHO guidelines, supportive therapies are recommended to treat COVID-19 symptoms, as specific treatments for COVID-19 do not currently exist. However, direct treatments have been recommended and applied in clinics within China. These schemes include interferon (IFN)-α, lopinavir/ritonavir, ribavirin, chloroquine phosphate, Arbidol, and traditional Chinese medicine. Clinical experience showed some benefits from treatments such as chloroquine phosphate and convalescent-phase plasma from recovered patients, but there is no evidence to support the efficacy and safety of these therapies in a large clinical trial.

Efforts to investigate the history of treatments for similar outbreaks are necessary to extrapolate potential direct anti-viral therapies. Since 2019-nCoV shares phylogenetic

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Table 1: Potential treatments for COVID-19.

Treatment	Type	Evidence of therapeutic effect
Ribavirin	Anti-viral	Contradictory evidence for its use in SARS, with no clinical improvement over no intervention. No clinically significant improvement seen in MERS.
Lopinavir/ritonavir	Anti-viral	Anti-CoV effects have been observed in SARS and MERS models. Improvement seen in two cases of COVID-19.
Remdesivir	Anti-viral	Potential new therapeutic in COVID-19 with beneficial effects seen in SARS and MERS models. Administration in one patient in the US showed clinically significant improvement by the next day.
Interferon-based	Host-targeted	Type-I IFNs, particularly IFN-β, may have a time-dependent effect in COVID-19.
Corticosteroid-based	Host-targeted	Corticosteroid use was associated with more adverse outcomes and delays in viral clearance in SARS and MERS.
Baricitinib	Host-targeted	Machine learning has predicted the use of baricitinib as an inhibitor of viral endocytosis of 2019-nCoV. May be combined with other anti-viral therapies.

COVID-19: Coronavirus disease 2019; SARS-CoV: Severe acute respiratory syndrome coronavirus; MERS-CoV: Middle East respiratory syndrome coronavirus; IFN: Interferons.

traits with SARS-CoV and MERS-CoV despite being genetically distinct, anti-viral treatments that were used to target SARS-CoV and MERS-CoV may provide some insight into future 2019-nCoV therapies. Potential treatments are summarized in Table 1.

Several case reports including the first report of SARS outbreak described the use of the anti-viral drug ribavirin and a corticosteroid in patients with contradictory clinical outcomes. Lee et al[4] observed that most patients receiving ribavirin and the corticosteroid prednisolone had their fever and lung opacities resolved within 2 weeks. On the other hand, significant toxicity has been reported due to ribavirin in Toronto, Canada. The use of ribavirin with IFN was also described in MERS-CoV patients with no clinical improvement. Furthermore, a retrospective cohort study showed that the group receiving ribavirin and IFN therapy had no difference in survival by 28 days compared to the untreated group.[5] Thus, for both SARS and MERS, the use of ribavirin was not beneficial, and may subsequently not be useful for treatment of COVID-19.

The HIV anti-retroviral drug lopinavir/ritonavir has been used in SARS and MERS patients with beneficial effects. In several studies, lopinavir/ritonavir was shown to have anti-CoV effects in vitro, in MERS-infected primate models, and in SARS-infected humans. Indeed, in vitro, lopinavir/ritonavir was shown to inhibit the SARS-CoV protease 3CLPro. Initial treatment with lopinavir/ritonavir in SARS patients was associated with lower intubation rate, lower adverse clinical events and mortality compared to ribavirin and corticosteroid. Furthermore, in a single MERS patient, a triple-combination therapy of ribavirin, IFN and lopinavir/ritonavir resolved viremia in 2 days following initiation of treatment.[6] Currently, one placebo-controlled, double-blind randomized controlled trial on the efficacy of lopinavir/ritonavir in MERS (No. NCT02845843) is ongoing. Lopinavir/ritonavir use has also recently been reported for COVID-19 treatment.[7-9] In two reports from China and Korea, the use of lopinavir/ritonavir in patients with COVID-19 improved recovery and reduced viral load.[7,8] However, Chen et al[9] showed that lopinavir/ritonavir and the anti-influenza treatment Arbidol had no clinically significant improvement in 134 people with mild

COVID-19. These conflicting results suggest that the use of lopinavir/ritonavir in the treatment of COVID-19 may require more research as the outbreak progresses.

Remdesivir, a recently-described broad-spectrum anti-viral nucleotide analog, has shown potent activity against diverse RNA viruses such as Ebola virus, and of note, SARS-CoV and MERS-CoV.[10,11] Recently, Sheahan et al[12] reported that combination remdesivir and IFN-β was superior to lopinavir/ritonavir in reducing lung viral load and restoring pulmonary function in a MERS-infected mouse model. In light of the current outbreak, Wang et al[13] described the in vitro inhibition of 2019-nCoV by remdesivir at lower concentrations compared to ribavirin. Holshue et al[14] described the use of intravenous remdesivir in the first COVID-19 patient in the United States with no adverse effects and clinical improvement by the next day. These findings suggest that remdesivir may be effective at controlling viral infections at lower concentrations than existing treatments. Future anti-viral therapies such as remdesivir may provide some much-needed firepower to combat epidemic coronavirus strains like 2019-nCoV.

Optimistically, two clinical studies on anti-viral COVID-19 treatment have recently come into fruition: the use of lopinavir/ritonavir in a phase 4, randomized controlled trial (No. NCT04255017); and the use of remdesivir in a phase 3, randomized, double-blind, placebo-controlled study (No. NCT04252664). Rapid responses such as these may help guide treatment and improve clinical outcome for those affected by 2019-nCoV.

The natural progression of the host anti-viral response involves the triggering of the type-I IFN-α and -β, which play key roles in viral innate immunity. Interestingly, both SARS-CoV and MERS-CoV evade or inhibit IFN-α and -β signaling, allowing uncontrolled viral replication and leading to progressive systemic inflammation. The use of exogenous IFN-α and -β in clinical isolates of SARS-CoV in cell lines showed that both IFNs were effective at reducing viral replication, with IFN-β being 5 to 10 times more potent than IFN-α.[15] It was also demonstrated that pre-incubation of IFN-α and -β in cell lines reduced viral replication of clinical SARS-CoV isolates. Further, in a MERS-infected rhesus

macaque model, IFN-α-2a and ribavirin dual therapy reduced systemic inflammation and viral replication and improved outcome compared to untreated macaques. Remarkably, Hart et al[16] reported that IFN-β alone showed more potent inhibition of MERS-CoV in vitro, compared to IFN-α-2a and ribavirin. These findings suggest that type-I IFNs, in particular IFN-β, may be effective in a time-dependent manner in reducing viral replication of SARS- and MERS-CoV, and may be relevant for COVID-19 treatment.

Pneumonia and lung inflammation are common clinical features in severe 2019-nCoV, SARS-CoV, and MERS-CoV infections. As reported in the COVID-19 outbreak, higher levels of pro-inflammatory markers were detected in intensive care unit (ICU)-admitted patients compared to non-ICU patients.[17] In an effort to combat inflammation and improve clinical outcome, corticosteroid use has been described in SARS, MERS, and COVID-19. Notably, Huang et al[17] observed that all patients infected with 2019-nCoV in their cohort had pneumonia and 22% were receiving corticosteroid treatment. However, the use of corticosteroid in coronavirus infections is controversial and may not benefit patients with coronavirus infections but may instead prolong infection and delay viral clearance.[18] As such, in the context of COVID-19, the use of corticosteroids to control inflammation may not be beneficial and other options should be pursued.

The incorporation of artificial intelligence into the immunology field has also highlighted potential drugs for COVID-19. Notably, the existing therapy baricitinib has been pinpointed as a potential host-targeted treatment.[19] Baricitinib was predicted to prevent viral endocytosis in lung cells and could be combined with lopinavir/ritonavir or remdesivir. Further implementation of new technologies will greatly improve the response to directly targeting new outbreaks such as COVID-19.

In the future, ongoing efforts to control transmission between humans such as preventing close contact, regular hygienic practices in public places, and widespread education on prevention should be continued. Additionally, measures to improve healthcare infrastructure that can withstand the pressure of emerging zoonotic diseases should be implemented to further improve response times and limit transmission.

Conflicts of interest

None.

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