

Bat-Human Coronaviruses: A Global Health Problem and a Therapeutic Challenge

Journal of Medical Clinical Case Reports

Review Article

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Submitted : 14 April 2020 ; Published : 18 May 2020

There are four genera of coronaviruses including α -coronaviruses, β -coronaviruses, γ -coronaviruses, and δ -coronaviruses. α and β -coronavirus can infect mammals, while γ -coronavirus and δ -coronavirus generally infect birds. Four coronaviruses are known to cause mild upper respiratory infection in humans of all ages including infants. The transmission of coronaviruses from animals (birds) to causes respiratory illness has been reported as early as 1969 by Kapikian et al. Community-wide outbreak associated with 229E-like coronavirus has been reported as early as 1970 by Cavallaro and Monto [1-7].

Until December, 2020, two β -coronaviruses (SARS coronaviruses and MERS-coronaviruses) were known to cause severe, potentially fatal pneumonia-like illness [7, 8].

Increasing number of cases of severe potentially fatal pneumonia caused by a new β -coronavirus was reported from Wuhan China in December 2019, and human-to-human transmission was confirmed early. On the 12th of January, 2020 the World Health Organization (WHO) officially named the condition coronavirus disease 2019 (COVID-19). The Coronavirus Study Group of the International Committee suggested naming the new coronavirus "SARS-CoV-2" [9, 10]. As of April, 2020, 13 (9 am, GMT), a total of 1,930,272 cases have been confirmed throughout the world including 119,815 deaths.

The SARS-CoV-2 which is an enveloped non-segmented positive-sense RNA virus β -coronavirus (subgenus sarbecovirus, Orthocoronavirinae subfamily), and 96.2% its genome is identical to a bat coronavirus RaTG13, and 79.5% of its genome is similar to SARS coronavirus. Therefore, bats have been considered a possible natural host of virus, which was possibly transmitted to a human from bats through an intermediate host. It was found that SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE2), the receptor of

SARS-CoV to infect humans [11, 12]. In fact, bats are the natural host of a wide variety of coronaviruses including SARS-CoV-like and MERSCoV-like viruses [1, 13, 14].

Apart from supportive therapies, little evidence is available that can support a specific antiviral treatment. Antiviral drugs (oseltamivir, peramivir, zanamivir, ganciclovir, acyclovir, ribavirin monotherapy) and systemic corticosteroid are better to be avoided based on the previous experiences with treatment of coronaviruses [15, 16]. Previous experience with treatment of coronaviruses suggested that lopinavir and ritonavir, protease inhibitors used to treat patients with human immunodeficiency virus (HIV) improved the outcome of MERS-CoV and SARS CoV patients [17-19].

The first SARS coronavirus infection was causing respiratory failure in about 20% of patients, therefore, empiric treatments were justified including protease inhibitors (lopinavir/ritonavir) in combination with ribavirin [7, 17]. Chu et al (2004) reported the treatment of 41 patients with SARS with a combination of lopinavir/ritonavir and ribavirin. The clinical and virological outcomes were compared with 111 patients treated with ribavirin monotherapy. Poor clinical outcomes including acute respiratory distress or death were significantly lower in the lopinavir/ritonavir treated patients [17].

The experimental work of Chan et al (2015) showed that treatment with lopinavir/ritonavir or interferon- β 1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset [20].

Park et al (2019) studied the efficacy of ribavirin and lopinavir/ritonavir as Post-exposure prophylaxis for healthcare workers exposed to patients with severe MERS-CoV pre isolation pneumonia. They found that therapy

was associated with a 40% decrease in the risk of infection without the occurrence of severe adverse effects [21].

β -coronavirus viral loads of a COVID-19 in a Korean patient were markedly reduced following lopinavir/ritonavir treatment [22].

Combined treatment with lopinavir/ritonavir, arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine) was associated with improvement in pneumonia caused by COVID-19 [23].

Sheahan et al (2017) reported that remdesivir (GS-5734) which was developed for treatment of Ebola virus disease, can inhibit SARS-CoV and MERS-CoV replication in multiple in vitro systems, including primary human airway epithelial cell cultures with submicromolar IC50 values. According to Sheahan et al, remdesivir was also effective against bat coronaviruses, prepandemic bat coronaviruses, and circulating contemporary human CoV in primary human lung cells suggesting that remdesivir has broad-spectrum anti-CoV activity. Sheahan et al also reported that in a mouse model of SARS-CoV early treatment with remdesivir significantly reduced lung viral load and improved clinical signs of disease and respiratory function [24].

Agostini et al (2018) reported that remdesivir effectively inhibits human and zoonotic coronaviruses in vitro and in SARS-CoV mouse model. They showed that remdesivir inhibits murine hepatitis virus (MHV) with similar 50% effective concentration values (EC50) as SARS-CoV and MERS-CoV [25].

Brown et al showed that remdesivir has effective antiviral activity against endemic human Coronaviruses OC43 (HCoV-OC43) and 229E (HCoV-229E) with submicromolar EC50 values. They emphasized that the delta coronavirus genus have the most divergent RdRp as compared to SARS- and MERS-CoV and both avian and porcine members harbor a native residue in the RdRp that confers resistance in beta-Coronaviruses. However, remdesivir is highly effective against porcine delta coronavirus [26].

Remdesivir was used in the treatment of the first patient with COVID-19 in the USA and treatment was considered successful [27].

Chloroquine was thought to have an effect on SARS-CoV infection and spread which can be attributed to immunomodulatory effects, suppression of the production/release of TNF- α and IL-6, autophagy inhibition, and interference with the glycosylation of cellular receptors of SARS-Co. Chloroquine may act on entry and at post-entry stages of the COVID-19 infection in Vero E6 cells [28-30]. Baron et al (2020) reported teicoplanin; an antibiotic used to treat staphylococci infection which was previously reported to be effective in inhibiting the first stage of MERS-coronavirus viral cycle in human cells was also active against the SARS-Cov-2 [31].

In conclusion, the little available scientific evidence suggests

that lopinavir/ritonavir, remdesivir, and teicoplanin are possibly at the top of the list weapons that have the potential to enable humans to win the fight against bat-human coronaviruses.

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