Possible treatments for SARS-CoV-2 infection: what do we know?.

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In December 2019, a novel coronavirus designated SARS-CoV-2was identified in Wuhan (China). This one has caused an international outbreak of respiratory illness termed COVID-19. Initially, most infected people reported exposure to a large seafood and wet animal market in Wuhan, indicating a possible animal-to-human transmission; current data has demonstrated that person-to-person transmission is the most important way of spread. On 30 January 2020, the WHO declared the COVID19 outbreak as a public health emergency of international concern [1]. At the time of preparing this manuscript the WHO reported 372 757 confirmed cases and 16 231 deaths in more than 180 countries. Currently, no therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2. Several pre-existing and potencial drugs candidates including chloroquine, remdesivir, lopinavir and ritonavir have been considered[1].

The hydroxychloroquine (HCQ) and chloroquine have shown to have an in vitro activity against SARS-CoV-2 and a great number of virus and intracellular micro-organisms. The HCQ and chloroquine had multiple activities that may explain the anti-viral effects, one of which is to alkalize the phagolysosome, which hampers the low-pH dependent step of viral replication including fusion and uncoating, as well as interfering with the glycosylation of cellular receptors of SARS-CoV. However, the in vitro activity of these drugs has not translated into clinical effective activity for any viral infection. Based on recent report from China, the administration of chloroquine showed superiority compared with the control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance. These results were obtained in absence of side effects [2]. These results have led to include the chloroquine in the recommendation for management of COVID-19 pneumonia. Regarding the treatment with HCQ both prescribing clinicians and patients should be aware that drug efficacy for COVID-19 is unclear because there is not sufficient evidence from randomized clinical trials. In the context of COVID-19 treatment, the HCQ will be more effective if initiated as soon as possible. The principal candidates are patients with high-risk of poor outcomes. For optimal treatment, it may be necessary to administer a loading dosage (400 mg by mouth ever 12 hour) followed by a maintenance dosage (400 mg by mouth every day). Patients with gastrointestinal intolerance may receive a dosage reduction. The optimal therapy duration is unclear, but should be prescribed for 5 days. The treatment with HCQ is not recommended for patients with multiorgan failure, prolonged QT interval at baseline, documented cardiomyopathy or myocarditis. There is no experience to support the use of HCQ for pre-exposure or post-exposure prophylaxis in individuals with confirmed or suspected exposure to SARS-CoV-2.

Remdesivir is an adenosine analogue that has demonstrated an in vitro anti-viral activity against SARS-CoV-2. This drug has not been approved anywhere. Remdesivir has been recognized as a promising antiviral drug against a wide array of RNA (including SARS-CoV and MERS-CoV), based on the evidence that the SARS-CoV and the SARS-CoV-2 share 82% RNA identity and their RNA-dependent RNA polymerase (RdRp) share 96% sequence identity, those drugs targeting viral RdRp proteins of SARS-CoV (like remdesivir) are likely to be affective against SARS-CoV-2 [3]. Recently, a report about the first case of COVID19 in Washington, USA, was published. This case was treated with remdesivir for the progression of pneumonia and the patient condition improved without side effects [4]. Although this preliminaries data on the anti-viral activity of remdesivir are promising, the translation of these into clinical practice is needed. There are two phase 3, randomized (ClinicalTrials.gov Identifier: NCT04252664 and NCT04257656), doubled-blind, placebo-controlled multicenter clinical trials currently ongoing in China. These trials are designed to evaluate the efficacy and safety of remdesivir in hospitalized adults with mild-to-moderate and severe COVID-19 pneumonia. These clinical trials may open the window to an effective anti-viral therapy.

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, it has demonstrated in vi-

tro activity against both SARS-CoV and MERS-CoV. Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450. Previous study suggested that the addition of lopinavir-ritonavir to ribavirin reduced the risk of adverse clinical outcome (acute respiratory distress syndrome [ARDS] or death) as well as viral load among patients with SARS. In the context of SARS-CoV-2 infection, the use of lopinavir-ritonavir was recently evaluated in hospitalized adult patients. This trial conclude that no benefit was observed with lopinavir-ritonavir treatment beyond standard care [5].

Oral oseltamivir has been widely used for COVID-19 or suspected cases in China hospital. Oseltamivir is a neuraminidase inhibitor that has been used as antiviral treatment in influenza. The neuraminidase inhibitors are effective as empirical treatments in MERS-CoV infection, however, there is no exact evidence that oseltamivir is effective in the treatment of COVID-19 [1]. Various agents have been reported with potential antiviral activity against SARS-CoV-2. These agents are indinavir, saquinavir, carfilzomib, atazanavir, darunavir, tipranavir, fosamprenavir, enzaplatovir, presatovir, abacavir, botezomib, elvitegravir, maribavir, raltegravir, deoxyrhapontin, polydantin, chalcone, cyclosporine A, ebselen and cinanserin. The efficacy and safety of these drugs in the treatment of COVID-19 need to be confirmed in further preclinical and clinical trials.

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