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Updating the Novel Therapeutic Interventions in Treating Patients with COVID-19 Pneumonia, COVID-19 Acute Respiratory Syndrome and Severe COVID-19 Illness and Promising Vaccine Candidates

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Patients with COVID-19 pneumonia were detected in Wuhan city, China since late December 2019. More and more cases have been identified in other areas outside Wuhan city of China and abroad, particularly in Italy, Iran and other European countries, including the United Kingdom and the United States. Currently, there is no effective treatment for COVID-19-infected patients. Inhibition of pulmonary inflammatory response is hypothesized to be the key to cure the patients with COVID-19 pneumonia. Chloroquine, a potential broad-spectrum antiviral agent found in 2006, can interfere with the virus's ability to replicate.

Nevertheless, the World Health Organization (WHO) reported that no randomized clinical trials (RCTs) or quasi-experimental studies on the use of chloroquine or hydroxychloroquine on COVID-19 treatment were identified that compared chloroquine to standard care for treatment of COVID-19. There is very low certainty evidence from RCT or quasi-experiment that hydroxychloroquine results in little or no benefit over standard care for treatment of COVID-19. There is also very low certainty evidence of little difference in overall mortality between hydroxychloroquine and standard care. With regards to safety outcomes, there is very certainty evidence that hydroxychloroquine results in more adverse events than standard care. Evidence for other safety outcomes, such as severe adverse events, cardiac arrhythmia, and QT interval prolongation resulting in sudden death was very low certainty. The United States Food and Drug Administration (US FDA) also cautions the use of chloroquine or hydroxychloroquine for COVID-19 outside of the hospital setting or a clinical trial due to the risk of cardiac rhythm problems.

Remdesivir, a nucleoside analogue with a broad-spectrum antiviral activity and as being in the US clinical trials with near approval for use by the US FDA has been also studied in France by Gautretet al from Marseille University. The investigators feel optimistic about the French research data. Previous studies conducted by the researchers from the University of Alberta, Canada and Gilead involving cell cultures and animal models has demonstrated that remdesivir can block the replication of a variety of coronaviruses, hypothesized by blocking the RNA-dependent RNA polymerase, a particular enzyme that is required for viral replication. Remdesivir potently blocks COVID-19 infection at low-micro molar concentration and has a high selectivity index (half-maximal effective concentration (EC50), 0. 77 μM; half-cytotoxic concentration (CC50) > 100 μM; SI > 129. 87). A previous study in the US reported that remdesivir treatment demonstrated promising results. For evaluating the efficacy and safety of remdesivir in patients with COVID-19 disease, a randomized placebo-controlled, double-blind, multicentric phase III clinical trials were initiated on February 5, 2020 in China. The subjects in the study group received a initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days through intravenous infusion in addition to routine treatment. The control group received routine treatment and the same dose of a placebo. By the end of April 2020, the clinical trial is expected to be concluded. Remdesivir was developed by the US pharma giant Gilead Sciences Inc. and previously was tried to treated Middle-East-Respiratory Syndrome (MERS) and Ebola. The Credit Suisse pharma team declares that remdesivir is the most advanced novel drug in treating patients with COVID-19 disease, but concerning about the supply. Gillenwateret al concluded that administration of remdesivir would achieve a greater effect on survival of COVID-19 patients (published in New England Journal of Medicine, July 10, 2020).

On February 4, 2020, investigators in China announced that darunavir inhibited COVID-19 viral replication at a concentration of 300 μM in vitro and its inhibition efficiency was 280-fold that in the control group. Type II trans membrane serine protease (TMSPSS2) inhibitors and BCR-ABL kinase inhibitor-imatinib are other potential drugs. TMSPSS2 inhibitors would block the entry of the cellular protease, TMPRSS2 into the target cells via ACE 2 receptor. Imatinib inhibits the fusion of virions with the endosomal membrane (anti-coronal activity). On January 25, 2020, 30 drugs with potential antiviral activity against COVID-19 performed through the drug screening in silicon and an enzyme activity test, cinanserin, cyclosporin A, TDZD-8, PX-12, tideglusib, ebselen, shikonin, carmofur, disulfiram, chalcone, polydatin, deoxyrhapontin, montelukast, raltegravir, maribavir, elvitegravir, bortezomib, abacavir, presatovir, enzaplatovir, fosamprenavir, tipranavir, darunavir, atazanavir, remdesivir, ritonavir, carfilzomib, lopinavir, saquinavir, and indinavir were reported by a joint research team of the Shanghai Institute of Material Medica and Shanghai Tech University. The same research also demonstrated that Chinese herbal medicines, such as Radix Sophorae Tonkinensis and Rhizoma Polygoni Cuspidatimay contain ingredients against COVID-19. Until now, it has been difficult to get the polymerase complex that contains multiple proteins to function in a test tube.

On February 15, 2020, favipiravir, a new type of RNA-dependent RNA polymerase (RdRp) inhibitor that was first approved in Japan in March 2014 for establishing preparedness against the possible outbreak of novel or re-emerging influenza virus infections was approved for treatment of COVID-19 disease in China. In addition to favipiravir' s anti-influenza virus activity, it can block the replication of alpha-, arena-, bunya-, filo-, flavi, and other RNA viruses. Favipiravir inhibits RNA polymerase activity by the conversion of favipiravir into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase. A clinical trial on favipiravir for the treatment of COVID-19 disease was initiated by the Third People's Hospital of Shenzhen and the Clinical Medical Research Center of the National Infectious Diseases, China on February 14, 2020 achieved the promising results. The preliminary results from a total of 80 patients with COVID-19 disease, including the control group and the experimental group demonstrated that favipiravir had more potent antiviral activity than that of lopinavir/ritonavir. Favipiravir treatment group demonstrated no significant adverse reactions and had significantly fewer adverse effects than the lopinavir/ritonavir group. The In April 2020, the Japanese Association for Infectious Diseases reported that an clinical

improvement was observed in 90 %, 85 %, and 61 % after 14 days for the initiation of favipiravir, in mild, moderate, and severe COVID-19 cases, respectively.

This is not a proven treatment, but is a possible treatment. The immunoglobulin's is the previously COVID-19-exposed individuals' circulating virus-free convalescent plasma could potentially provide a benefit to severely COVID-19-infected patients. Currently, several trials on mesenchymal stem cells in treating patients with COVID-19 pneumonia are ongoing. For examples, trial sponsored by Innovative Precision Medicine Group (IPM), China, Wuhan Houshenshan Hospital, Wuhan, China, and Tianjin Haihe Hospital. Trials on several vaccine candidates, currently are also ongoing, for examples; phase I trial sponsored by Modern Therapeutics, CanSino Biologics, Arcturus Therapeutics (Preclinical stage), BioNTech (Preclinical stage), CureVac (Preclinical stage), GlaxoSmithKline (Preclinical stage), Inovio Pharmaceuticals (Preclinical stage), Johnson & Johnson (Preclinical stage), and Pfizer (Preclinical stage), Sanofi (Preclinical stage). Usually, vaccine development takes more than 5 years and requires much capital investment. There is no guarantee of success though the traditional pharma giants' experience involving seasonal flu, particularly their specializing in mRNA molecules that are used to instruct the human body to produce its own response to combat a range of diseases. On July 15, 2020, WHO reported that 75 countries submit expression of interest to COVAX Facility, joining up to 90 further nations which could be bolstered by the COVAX Advance Market Commitment (AMC). The objective of COVAX is before the finish of 2021 to convey two billion dosages of protected, powerful antibodies that have passed administrative endorsement and additionally WHO prequalification, while a Chinese-made immunization created by private Chinese pharmaceutical firm Sinovac-Biotech against COVID-19 entered the last phase of testing in July 2020 in Brazil, where volunteers get the main portions of what authorities expectation will be a distinct advantage in the worldwide pandemic. This vaccine became the third in the world to enter Phase 3 clinical trials, the last step before regulatory approval. Under this clinical trial, around 9,000 health workers across six Brazilian states will receive the vaccine.

In conclusion, currently, there are no finally verified antivirals and vaccine candidates specific to COVID-19. Further preclinical and clinical trials are urgently needed to successfully treat patients with COVID-19 disease and preventing individuals from COVID-19 infection.