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Therapies of SARS-CoV-2

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Abstract: The Coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has resulted in a severe global health crisis. There are no current specialized therapies available to the virus. However, several possible treatments show some effectiveness on treating the virus, such as medication, convalescent plasma therapy, and vaccine. This paper will discuss and evaluate the effectiveness of these treatments on SARS-CoV-2.

Keywords: Coronavirus; Therapies; Health crisis

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1 Introduction

SARS-CoV-2 is a coronal respiratory viral disease, packaged by RNA viruses that are positively stranded in the order of Nidovirales. The virus particles are round or elliptical with a diameter of about 80 to 120 nm, belongs to Betacoronavirus[1,2]. They are wrapped in a lipid bilayer provided by the host cell, which contains nucleic acid and nucleocapsid protein (envelope, membrane, spike protein). The length of each group of SARS-CoV-2 is about 30,000 nucleotides. The gene sequence shows that SARS-CoV-2 also belongs to the Betacoronavirus type, and SARS-CoV-2 is 79% similar to the coronavirus found in Chinese chrysanthemum bats, such as MERS-CoV and SARS-CoV. However, SARS-CoV-2 can also bind with ACE2 as a receptor, enters the lung through respiratory epithelial cells for replication[3,4]. The virus can survive under low temperature, on human hands, droplets, wooden products, stainless steels, etc. The main transmission of SARS-CoV-2 is when two people are in close contact, and one of them inhales the respiratory droplets produced by the infected person through coughing, sneezing, or even talking. The common symptoms of SARS-CoV-2 are fever, cough, short breath, tiredness, and thick phlegm [7,8].

The first case of SARS-CoV-2 was found in Wuhan, China, on December 8th, 2019. The outbreak was announced by WHC; NHC and China CDC were involved in the investigation and response of the virus on December 31st, 2019. By January 11th,2020, the first case was identified outside of China (in Thailand). Then a case was confirmed in another province of China on January 19th, the infected person had traveled from Wuhan [6]. Until this day, there are 22.8 million cases confirmed worldwide, with 796 thousand death from the virus [5].

2 Medical treatment

2.1 Lopinavir-Ritonavir

Researchers haven't discovered a specific therapy that can effectively treat SARS-CoV-2. However, several medications have been confirmed as possible treatments for the disease. Lopinavir-Ritonavir is one of them, which is a medication used for controlling HIV infection. It helps to decrease the amount of HIV in the human body, thus the immune system can function better (But it's not the cure for HIV) [9]. A randomized, controlled, open-label clinical trial was launched in March, in the U.S. In the trial, patients were randomly distributed in two groups with a ratio of 1:1, which either receive Lopinavir-Ritonavir (400mg, and 100mg) twice a day or standard-care for two weeks. However, the result wasn't pleasing. A total of 199 patients who are infected by SARS-CoV-2 undertook the randomization; 99 patients were assigned to the Lopinavir-Ritonavir group, and 100 patients were assigned to the standard-care group.

The time to clinical improvement between these two treatments didn't show an obvious difference, in which the hazard ratio for clinical improvement was 1.31. Moreover, the mortality rate at 28 days between the two treatments is similar: 19.2% (Lopinavir-Ritonavir): 25.0% (standard-care). Additionally, patients experienced gastrointestinal adverse more often in the Lopinavir-Ritonavir group, while severe adverse events were more common in the standard care group. Therefore, Lopinavir-Ritonavir doesn't demonstrate significant benefit beyond the regular treatment, but further clinical trials in patients with the severe condition could help confirm or exclude the possibility of Lopinavir-Ritonavir benefit in treating SARS-CoV-2 [10].

2.2 Hydroxychloroquine

Besides Lopinavir-Ritonavir, Hydroxychloroquine is also a possible therapy for SARS-CoV-2. Chloroquine is a medication used for treating malaria from mosquito bites, as well as other infections caused by a different kind of parasite [11]. An examination of the use of Hydroxychloroquine to SARS-CoV-2 was taken place in a large medical center in New York, with a multivariable Cox model used to compare the results of patients received hydroxychloroquine and those who didn't. Out of 1446 patients, 70 were excluded from the analysis as they either died or were discharged within 24 hours. Among the rest 1376 patients, 881 of them received hydroxychloroquine treatment (600 mg twice on day 1, then 400 mg for a median of 5 days) twice during a median follow-up of 22 days and a half. Compared to those who didn't receive hydroxychloroquine treatment, patients received the treatment demonstrated a more heavy illness at the baseline. 346 patients had a primary end-point event, in which 180 patients received intubation with 66 died subsequently, and 166 died without intubation. The examination shows that there was no significant relationship between hydroxychloroquine treatment and intubation and death. Therefore, the use of hydroxychloroquine wasn't relative to either a greatly decreased or increased risk of the endpoint of intubation or death. This means that a randomized, controlled trial of hydroxychloroquine on SARS-CoV-2 patients is needed to determine its effectiveness [12].

2.3 Dexamethasone

Moreover, Dexamethasone is considered as a possible viable medication for SARS-CoV-2.

It is used to treat arthritis, immune system disorders, allergic conditions, breathing issues, and even certain cancers. Additionally, it is utilized as a test for adrenal gland disorder. Dexamethasone is a corticosteroid hormone, which decreases the natural defensive response of human bodies and reduces symptoms, such as swelling and allergic reactions [13]. A controlled, open-label clinical trial was launched in the U.S. Patients were randomly assigned to oral or intravenous Dexamethasone (dose of 6 mg per day) or to receive usual care. A total of 2104 patients were assigned to the Dexamethasone group and 4321 patients were assigned to the usual care group. 482 patients who received dexamethasone treatment and 1110 patients who received usual care died 28 days after randomization. Researchers found that the proportion of mortality and absolute differences between groups varies greatly based on the level of respiratory support that patients received at randomization. In the Dexamethasone group, the mortality rate was lower than those patients who received invasive mechanical ventilation (29.3% vs. 41.4%), and those who received oxygen without invasive mechanical ventilation (23.3% vs. 26.2%). However, it was higher than those who received no respiratory support at randomization (17.8% vs. 14.0%). Therefore, Dexamethasone resulted in a lower mortality rate among those who received either invasive mechanical ventilation or oxygen alone at randomization in 28 days, but not among patients who received no respiratory support [14].

2.4 VRemdesivir

Remdesivir is considered as an attainable therapy to treat SARS-CoV-2. However, Remdesivir hasn't approved globally for any use, as it is a nucleotide analog with a broad-spectrum antiviral activity that is under investigation currently. Based on the investigation, Remdesivir demonstrates in both vitro and vivo activities in animal models against the MERS and SARS viruses. SARS-CoV-2 is structurally similar to the MERS and SARS, so Remdesivir is a potential cure against it [15]. A randomized, double-blinded, placebo-controlled, multicenter trial of Remdesivir was launched in Hubei, China. Patients were randomly distributed in a 2:1 ratio to intravenous Remdesivir (200 mg on day 1, 100 mg on day 2 to 10) or the same volume of the

placebo group for 10 days. Patients were also allowed to receive Lopinavir-Ritonavir interferons and corticosteroids. The primary goal was time to clinical improvement up to day 28, determined as the days from randomization to a decline of two levels on the six-point ordinal scale of clinical status or discharge from hospital. A total of 237 patients underwent randomization, which 158 was in the Remdesivir group and 79 were in the placebo group. Based on the results, patients who received Remdesivir had a faster clinical improvement than those who received a placebo. Severe conditions among the patients were reported in 102 of 155 patients in the Remdesivir group, and 50 of 78 patients in the placebo group. 18 patients stopped the use of Remdesivir and 4 patients stopped the use of placebo due to severe conditions. Therefore, Remdesivir doesn't show significant clinical benefits to SARS-CoV-2 patients, but the reduction in time to clinical improvement to those treated earlier needs confirmation in larger studies [17].

In May, another double-blind, randomized, placebo-controlled trial of intravenous Remdesivir was conducted in the U.S. A total of 1063 patients were assigned to either Remdesivir (200 mg loading dose on day 1, 100mg for another 9 days) or placebo for 10 days at randomization. The main result was the recovery time, determined by either discharge from the hospital or hospitalization for infection-control purposes. According to the initial results from 1059 patients (538 assigned to Remdesivir and 521 to placebo), patients who received Remdesivir had a median recovery of 11 days, but those who received placebo had a median recovery of 15 days. Additionally, the mortality rate with Remdesivir in 14 days it was 7.1%, and the mortality rate for placebo was 11.9%.

The clinical trial also states that 114 out of 541 patients who received Remdesivir and 141 out of 522 patients who received a placebo showed severe conditions at randomization. Therefore, the researchers concluded that Remdesivir was more effective than a placebo in shortening the recovery time from SARS-CoV-2 [16].

At this point, the cure to treat SARS-CoV-2 still doesn't exist. Lopinavir-Ritonavir doesn't show significant benefits in treating the virus, as its clinical improvement and mortality rate on patients are similar to those patients who only received regular treatment. Additionally, patients who took this mediation often experienced gastrointestinal adverse. Hydroxychloroquine doesn't have a remarkable relationship to either a huge decrease or an increase in the risk of the endpoint of intubation or death on SARS-CoV-2patients, and Dexamethasone was only effective on treating patients who received invasive mechanical ventilation or oxygen at the same time. In the end, the two clinical trials of Remdesivir contradicted with each other. The trial launched by the U.S. suggests that Remdesivir was effective in shortening the recovery time from SARS-CoV-2, but the one launched in China states that Remdesivir doesn't demonstrate outstandingly clinical benefits to SARS-CoV-2patients. Therefore, it seems like Dexamethasone is the only mediation that has a clear result in nursing SARS-CoV-2. However, we still can't consider these medications as a complete failure in treating SARS-CoV-2. Lopinavir-Ritonavir needs further clinical trials in patients with a severe condition to determine the possibility of the clinical benefits of Lopinavir-Ritonavir. Hydroxychloroquine needs a randomized, controlled clinical trial to further determine its effectiveness on SARS-CoV-2. For Redmesivir, other countries must conduct the same clinical trials and then compare the results together. Moreover, the WHO needs to step out and be the leader to conduct the study of the effectiveness of Redmesivir on SARS-CoV-2.

3 Convalescent plasma therapy

There are other therapies besides medication treatments on SARS-CoV-2, convalescent plasma therapy is one of them. This therapy uses the blood of people who've recovered from disease to treat other patients for recovery. Blood donated by recovered patients has antibodies to the disease, and its blood cells need to be removed before injecting into the patient's body, which leaves plasma and antibodies behind [18]. Therefore, convalescent plasma is a potential option to treat SARS-CoV-2. From February 14th, 2020, to April 1st, 2020, an open-label, multicenter, randomized clinical trial was launched in seven different medical centers in Wuhan, China. A total of 103 patients with either severe or life-threatening condition due to SARS-CoV-2, 52 of them was distributed into the convalescent plasma group, and 51 of them was distributed into the control group. The result states that 101 of them completed

the trial, a clinical improvement was shown within 28 days in 51.9% (27/52) of the convalescent plasma group and 43.1% (22/51) in the control group. Additionally, there was no huge difference in 28-days mortality or time from randomization to discharge between two groups. Moreover, convalescent plasma therapy was negatively correlated with a 72-hour viral PCR conversion rate of 72.5% of the control group in the 72-hour recovery plasma group. In the end, two patients had adverse events after the blood injection but were improved with supplementary treatments. Therefore, convalescent didn't demonstrate a significant clinical improvement within 28 days between patients who received convalescent plasma therapy and those who received standard treatment [19].

4 Vaccine

At the same time, the development of a vaccine for SARS-CoV-2 is on the process. Researchers have developed a recombinant adenovirus type-5 (Ad5) vectored SARS-CoV-2 vaccine and launched a dose-escalation, single-center, open-labeled, non-randomized, first-in-human trial in Wuhan, China. Between March 16th and 17th, 2020, 108 healthy participants (51% male, 49% female, mean age 36 years old) have received the low dose (5 × 1010 viral particles), or the median dose (1 × 1011 viral particles), or the high dose (1•5 × 1011 viral particles) of the vaccine. Severe incidents during the first 7 days post-vaccination occurred in 30 (83%) participants in the low dose group, 30 (83%) participants in the middle dose group, and 27 (75%) participants in the high dose group. The pain was the most common severe incident, and the most common systemic severe incidents were fever, headache, and fatigue. However, the severity of these cases was mostly mild or moderate. After the 28 days post-vaccination, no adverse event was reported. On day 14, ELISA and neutralized antibodies increased significantly and peaked at day 28. T-cell response peaked at day 14 post-vaccination. The Ad5 vectored SARS-CoV-2 vaccine is tolerable and immunogenic at 28 days post-vaccination. And humoral responses against SARS-CoV-2 reached its peak at day 28, and T-cell responses were noted from day 14 post-vaccination. Therefore, the Ad5 vectored SARS-CoV-2 vaccine is worthy of further study [22].

Besides the development of the Ad5 vectored SARS-CoV-2 vaccine, BBIBP-CorV, an inactivated SARS-CoV-2 vaccine is also under enlargement. BBIBP-CorV demonstrates high levels of neutralizing antibodies in mice, rats, pigs, guinea, rabbits, and nonhuman primates to protect against SARS-Co-V-2. Two doses (2 μg/ dose) of immunization of BBIBP-CorV show effective protection against the SARS-Co-V-2 intratracheal challenge in rhesus monkeys and antibody-dependent infection enhancement effect wasn't detected. Moreover, BBIBP-CorV presents a high efficiency and genetic stability for the production of the vaccine. Therefore, a clinical trial would be needed to further test the efficiency of BBIBP-CorV [21]. Additionally, researchers have been working on the development of the PiCoVacc, which is also an inactivated SARS-CoV-2 vaccine. This vaccine demonstrates neutralized antibodies in mice, rats, and nonhuman primates. These antibodies have neutralized 10 representative SARS-CoV-2 strains, which means that a possible wider ability of neutralization against other strains could take place. Using two different doses (3 or 6 μg/ dose) provided partially or completely protection against SARS-CoV-2 for nonhuman primates without visible antibody-dependent enhancement of infection. Therefore, these results support the clinical development and evaluation of PiCoVacc in humans [20].

Currently, There are no specific drugs to treat SARS-CoV-2, but a progressive development of vaccine has been done. The next step is to evaluate the safety and efficiency of them, which requires lots of time to prove. Nevertheless, prevention and control on the spread of the disease would be the priority task to do, as researchers have predicted that a second wave would come as early as possible in winter [23].

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