Antiviral Treatments for COVID-19 and Evaluation of Their Clinical Benefits

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Abstract. COVID-19 is a disease outbreak that started since the end of 2019. It is caused by the newly identified infectious virus - SARS-CoV-2 - which has infected millions of the people with high mortality rates over the globe because of easy transmission, fast spreading rate of the virus, and low acceptance rate of vaccination. Antiviral treatments for COVID-19 are critical in providing relief of symptoms and cure for infected people as well as protection and prevention for those who are susceptible to the virus. Currently, treatment for the epidemic does not have a complete cure and focuses on symptom relief. This article discusses the different types of treatments for COVID-19 including antiviral drugs, Anti-SARS-CoV-2 monoclonal antibodies, and traditional Chinese medicine. The results, benefits, and side effects concluded from clinical trials were discussed for some major treatments in each category. In order to provide more theoretical basis for the diagnosis and treatment of this disease.

Keywords: COVID-19, Antiviral Treatments, Benefits, Side effects.

1. Introduction

In December 2019, the first few COVID-19 patients were identified and started to show symptoms in a city in China. After one month, this new virus was identified by public health officials in China. Complete and partial SARS-CoV-2 genomes were obtained from infected individuals and sequenced to track the evolution of the virus and pinpoint its most likely place of origin. It was noted that this new coronavirus shared approximately 79% similarity in genetic makeup with SARS-CoV and 88% with two coronaviruses originating from bats that resemble severe acute respiratory syndrome (SARS) which was caused by SARS-CoV-1 discovered in 2003 [1].

Compared to SARS, this new virus spread far more quickly. Since the virus was discovered, it has spread over the globe causing hundreds of millions of infected cases and millions of mortalities as of October, 2022.COVID-19 can spread when virus-contaminated respiratory or oral fluids from infected individuals enter other people's bodies through respiratory routes such as their mouths and noses. These particles may even infect people by entering their bodies through their eyes. Infected people may infect the surfaces they contact. Even those without symptoms who are infected with COVID-19 can spread the disease.

Different people are affected by COVID-19 in various ways. Symptoms may start to show two days to two weeks after being exposed to the virus infection. The symptoms experienced by infected individuals could be very different. Some may experience only a little discomfort, while other may feel severely sick and lose normal body functionality. Infected individuals may experience upset symptoms such as coughing, high fever, losing smell or taste, and body pain.

Mortality is one of the most crucial measures for assessing the impact of COVID-19. Case fatality ratios, which are calculated by dividing total fatalities by the number of confirmed cases, have been recorded for many nations. The overall mortality rate from this pandemic was estimated to be 4.7%, but in older patients. with aged 60 or over, it can increase to approximately 14.8%, This pandemic has caused healthcare systems and economies of many affected nations to collapse [2].

Along with the rising severity of the pandemic situation, the issue of vaccine hesitancy gets more urgent to be solved. Survey research conducted in 33 different nations showed many countries had very low acceptance rates for the COVID-19 vaccination. Kuwait and Jordan showed the lowest acceptance rates which are lower than 30% among these surveyed countries. Italy and Russia also

have COVID vaccine acceptance rates of less than 55%. The United States also shows a relatively low acceptance rate of 56.9%. The unideal acceptance rates of COVID-19 vaccination caused might be a major obstacle to efforts being made throughout the world to contain the COVID-19 pandemic [3]. As of October 2022, tens of billions of vaccine doses have been administered, but it is still far away from reaching herd immunity. Only when a sufficiently high percentage of immune people are present in a population, susceptible people are granted indirect protection against infection.

Because of quick spread rate of the virus, easy routes of transmission, discomforting symptoms, high mortality rate of infected individuals, and low acceptance rate of vaccination, treatments of COVID-19 become essentially important and life-saving for the infected individuals. Most of the times, the patients receive antiviral treatments wich are the most efficient to treat COVID-19 and relive their symptoms. Different types of antiviral treatments include taking drugs (oral medication), infusion of monoclonal antibodies, and Tradition Chinese Medicine therapies, etc.

2. Antiviral Treatment

This new coronavirus has spreaded over the world and this pandemic has impacted billions of people around world. People have learned more about how this coronavirus works, the care and treatment that the infected patients can get depend on their symptoms and the severity level of their sickness (mild, moderate, severe, and critical illness). Different countries may prefer different antiviral treatments, and this section mainly focuses on the opular and efficient antiviral treatments for COVID-19 over the world.

2.1. Antiviral Oral Drugs

Most countries mainly practice Western medicine, with a basis on the study of pathogenesis, to treat COVID-19. The infected patients may go through four phases of disease progression from early infection to critical illness phase. According to the Treatment Guidelines Panel posted by the United States government about how to treat COVID-19, there are several different small-molecule antiviral drugs which are recommended COVID-19 treatments, including paxlovid (ritonavir-boosted nirmatrelvir), remdesivir, bebtelovimab, and molnupiravir.

2.1.1. Remdesivir

The efficacy of remdesivir to treat COVID-19 remains controversial even though it has been approved by the U.S. Food and Drug Administration. A randomized and double-blind trial that uses placebo as control was conducted in 1062 hospitalized adult patients with COVID-19 to test intravenous remdesivir. The clinical results showed that remdesivir shortens the time of recovery in adult patients that are hospitalized because of COVID-19 compared to placebo and it also reduces respiratory tract infection. However, 24.6% of the patients who got remdesivir and 31.6% of the patients who received a placebo suffered serious adverse events [4]. A randomized and open-label trial was conducted in three phases in 2020, at 105 hospitals across several continents. The goal of this trial was to compare the effectiveness of remdesivir treatment to conventional care on the clinical conditions of 584 patients with moderate symptoms. After receiving assigned treatment for 11 days, hospitalized patients that had moderate symptoms and got randomly assigned to 5 days of remdesivir treatment had a significantly better clinical condition than those who were assigned to standard care based on the statistics, but the clinical significance of such a difference was still questionable. For those who were randomly assigned to 10 days of treatment, their clinical outcomes were not significantly different from those who received conventional care. In a trial that was placebo-controlled, remdesivir showed therapeutic benefits in people that had severe symptoms, but its impact on those with moderate disease is yet uncertain [5].

2.1.2. Paxlovid

The guideline panel also specifically recommends that paxlovid is a more preferred treatment than remdesivir in treating nonhospitalized patients. When compared to placebo, paxlovid significantly

lowers the admission rates of patients in hospitals and mortality of infected patients who are highly likely to develope severe conditions. 1219 adult patients were included in the preliminary analysis of a randomized trial in 2021. Researchers discovered that among all the patients who received treatments within three days since their symptoms appeared, the group received paxlovid had 89% lower hospital admission rate and mortality rate from all causes related to COVID-19 compared to the group received placebo. These results were reported to have strong statistical significance ($P < 0.0001$). The researchers also performed the same analysis on a larger saple size. A group of 1881 patients was included in the analysis in order for examining how safe paxlovid was. Similar numbers of patients in the paxlovid treatment group and the placebo control group experienced side effects, the majority of which were mild. Serious side effects were observed in patients in both groups. However, the frequency of occurrence of severe adverse events in the antiviral group (1.7%) was lower than that in the control group (6.6%) and fewer participants in the antiviral group (2.1% vs. 4.1%) quit the study due to an adverse event [6].

2.2. Monoclonal Antibodies

Another major antiviral treatment is intravenous (IV) therapy of monoclonal antibodies that specifically targets SARS-CoV-2 virus. Bebtelovimab, sotrovimab, casirivimab plus imdevimab, tixagevimab plus cilgavimab, and bamlanivimab plus etesevimab and are monoclonal antibodies therapies that are available to treat or prevent COVID-infection.

2.2.1. Paxlovid Efficiency of Infusion against Omicron Variant

Only bebtelovimab infusion is recommended as an alternative when both paxlovid and remdesivir are unavailable or clinically inappropriate. At the end of 2021 year, the omicron variant was discovered. Since then, it spread quickly around the planet. BA.2 subvariant of omicron is very prevalent worldwide as of May 2022. It was not after a long time that more virus subvariants appeared, and some subvariants are now exceeding BA.2 in numerous nations [7]. All the other monoclonal antibodies are not recommended, because clinical trials have shown that in vitro susceptibility of these monoclonal antibodies greatly reduces when responding to the Omicron variant and its subvariants, while bebtelovimab is still effective in in-vitro neutralization against Omicron subvariants in circulation [8]. Numerous mutated genes in the viral spike protein are responsible for variants developing resistance towards vaccinations and monoclonal antibody infusion. The spike protein is a part of the four structural proteins that have major functions in the coronavirus. It contains two subunits that allow the coronavirus to attach and invade the host cell [9]. Most of the new omicron subvariants are detected to have more mutations in their spike proteins. It was discovered that the sensitivity of the subvariants to vaccine-induced neutralizing antibodies is impacted by L452R/Q substitution mutation in the spike proteins [10]. Knowing the mutations of the subvariants, they were expected to have lower sensitivity to monoclonal antibodies. Psedoviruses containing the spike proteins that are unique on these virus subvariants were created to test this assumption. The results showed casirivimab, bamlanivimab, imdevimab, tixagevimab, and etesevimab had low efficacy against omicron BA.2 subvariants compared to their efficacy against the parental coronavirus. They were also less effective against the other newly discovered subvariants. Bebtelovimab showed an approximately 2 times higher efficacy in combating BA.2 subvariant and many other omicron subvariants tested compared to their efficacy against the parental virus [7].

2.2.2. Pre- and Post-exposure Prophylaxis

The anticipated effects and activity of different monoclonal antibodies therapies with different circulating variants may significantly vary. It is recommended to infuse tixagevimab plus cilgavimab to prevent getting COVID-19 for pre-exposure prophylaxis. Unfortunately, there is no monoclonal antibodies available for post-exposure prophylaxis of COVID-19.

2.3. Traditional Chinese Medicine

The Western antiviral treatments mentioned above are also utilized in China. Moreover, the Chinese government has also adopted a very special type of COVID-19 treatment. Traditional Chinese medicine (TCM) is utilized simultaneously with Western medicinal practice to effectively treat SARS-CoV-2 infection [11], following the previous experience combating SARS. In patients receiving glucocorticoids to treat SARS, such a combination of therapy had considerably lowered death rate, reduced abnormalities in chest radiograph, decreased fever time, and treated secondary fungal infections [12]. Evidences have showed that TCM is remarkably effective in treating patients of COVID-19 at all stages over the past year in China [11], and it is also proven to have effects on the prevention of coronavirus infection. During the pandemic outbreaks, TCM has had an outstanding curative effect while more than 90% of Chinese citizens have used it. It may act as an antiviral in two different ways: It may directly inhibit the virus by clearing heat and detoxification or it can strengthen the body's immunity to inhibit the inflammatory response caused by the virus. With an emphasis on the body's overall regulation, it may accomplish multiple targets in regulating the systems [13]. There are various TCMs that are advised for the prevention and treatment of SARS-CoV-2 infection, including all infection stages, covering the suspected carriers of the virus in the quarantine and observation period through the confirmed cases in the therapeutic period of receiving corresponding treatments. Lianhua Qingwen capsules, Jinhua Qinggan granules, and Xuebijing injections are traditional Chinese medicines with patents, which have been proven to be efficient and safe in treating COVID-infected patients [11].

2.3.1. Lianhua Qingwen Capsule

Lianhua Qingwen capsule is widely used in China to treat diseases like colds and influenza for a long history of time. It is one of the most famous traditional Chinese medicines in China that have great antiviral effects on infectious diseases. In 2003 during the SARS outbreak, the China National Medical Products Administration approved Lianhua Qingwen to be used as a new drug for treating SARS. The major components of Lianhua Qingwen capsule include 13 herbs. It is effective to stimulate detoxification, lung ventilation, and heat discharging in human bodies. On the perspective of Western pharmacodynamic studies, Lianhua Qingwen has broad-spectrum clinical benefits because its natural ingredients have great clinical effects on combating viral infection, bacterial infection, as well as inflammation. They can also relieve coughing and regulate the body's immune response [14]. The safety and efficacy of Lianhua Qingwen capsules in COVID-19-infected patients were tested by adopting a multicenter open-label randomized trial. Two groups of patients that were randomly divided received either regular treatment for 14 days or combined with Lianhua Qingwen capsules. The results of this clinical trial show that Lianhua Qingwen capsules markedly improved the recovery rate of coughing, fever, and fatigue symptoms. No serious side effects of Lianhua Qingwen capsules occurred in the patients, supporting the safety of using Lianhua Qingwen capsules on COVID-19 patients. Overall, Lianhua Qingwen capsule could be considered for treating COVID-19 considering both efficacy and safety, and more clinical trials should be performed to fully evaluate its clinical benefits to treat COVID-19 in a larger patient population [15].

2.3.2. Jinhua Qinggan Granules

Jinhua Qinggan granules are made of 12 herbs originated from Maxing Shigan Tang and Yinqiao San formula, which was able to effectively reduce fever duration in H1N1 influenza patients. It can disperse the lungs and remove heat and toxins [14]. A retrospective analysis of 80 diagnosed cases was conducted in a hospital in Beijing, China to evaluate if Jinhua Qinggan granules are efficient and safe in treating COVID-infected patients with a focus on duration of pneumonia absorption improvement and viral nucleic acid (NA) detection. The treatment group had a positive detection of SARS-CoV-2 NA persisted for an average of 7 days. In comparison, the control group had continuous detection that persisted for 10 days ($P = 0.010$) until the appearance of negative NA test results. Within 7 days or less time, 56.82% of the treatment group and 27.78% of the control group had negative NA test results. This indicates that the treatment group had a significantly higher rate of viral

clearance within 7 days relative to the control group (P = 0.009). In addition, the chest CT showed that patients in the treatment group recovered from pneumonia within about 8 days. This was substantially shorter than the recovery time for pneumonia in the control group (10 days) (P = 0.021). After using this medication, no adverse effects were reported in the treatment group. This clinical trial shows that Jinhua Qinggan granules can efficiently decrease the time it takes to clear out this coronavirus in COVID-19 patients and improve inflammatory exudate absorption caused by pneumonia without causing any evident adverse effects [16].

2.3.3. Xuebijing Injection

Xuebijing injection is an injection medicine, composed of five herbs, that was developed during the SARS outbreak. It was originated from a modified Xuefu Zhuyu decoction and has a therapeutic indication for detoxification and dissolving stasis [20]. A clinical trial was conducted in 2020 in China to examine how Xuebijing injection affects the inflammation indicators and prognosis of COVID-infected patients. 60 COVID-19 patients with severe symptoms admitted into hospitals were randomly divided into three groups - routine treatment, 50 mL injection group, and 100 mL injection group. The three groups' white blood cell (WB) counts and lymphocyte counts (LP) all increased following therapy, while C-reactive protein (CP) and erythrocyte sedimentation (ES) rate decreased. The number of WBs of the 100 mL injection group considerably raised in comparison with the control group ($P < 0.05$), and the CP and ES rate levels of the 50 mL and 100 mL injection groups greatly reduced ($P < 0.05$). The rise in WB counts and reduction in CP and ES rate in the 100 mL injection group were more significant when compared to the 50 mL injection group ($P < 0.05$). After treatment, the patients in all three groups had improvements in their physical conditions. Eight out of nine cases in the control group turned to common type while one patient turned to critical. Nine cases and twelve cases in the 50 mL and 100 mL injection groups changed to common type. In comparison to the 50 mL injection group and the routine treatment group, 100 mL injection group improved significantly (both $P < 0.05$). The result showed that the prognosis and inflammatory markers of COVID-19 patients with severe symptoms can be improved efficiently by receiving Xuebijing injection [17].

3. Conclusions

Nowadays, since the COVID-19 pandemic situation is still worsening and the hope for reaching herd immunity continues to lessen, antiviral treatments are becoming more important. Oral drugs, monoclonal antibody infusion, and traditional Chinese medicine have the ability to stop the SARS-CoV-2 virus from replicating through different mechanisms. Since the coronavirus replicates most actively during the early course of COVID-19, these antiviral therapies may be most effective before the appearance of hyperinflammatory state in the later stages [11]. It is critical to understand how these antiviral treatments work in treating people with different severity levels of symptoms in order to give them optimal treatment. Certain antiviral drugs, such as paxlovid and remdesivir, have more clinical benefits compared to other drugs. Bebtelovimab monoclonal antibody infusion is more efficient in treating the Omicron variant of the virus. Traditional Chinese medicine, such as Lianhua Qingwen capsules, Jinhua Qinggan granules, and Xuebijing injections, has shown high efficiency in treating and preventing COVID-19 with minimal adverse effects. Western countries may combine treatments of antiviral drugs, monoclonal antibody infusion, and traditional Chinese medicine for better outcomes just like China does. Since the virus mutates continuously, more clinical trials should be done on these COVID-19 treatments to ensure their safety and efficiency against COVID-19. Many other antiviral treatments that are not discussed in this paper are still being tested in clinical trials and some have had promising results. With all the efforts and research done by scientists and healthcare workers, there is a bright future for humans combating this coronavirus.

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