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Current Potential Options for COVID-19 Treatment in Iraq- Kurdistan Region and the Rest of the World: A Mini-review

Aryan M. Faraj[1], Syamand A. Qadir[1], Othman A. Mohammed[1,2], Peshawa Y. Aziz[1], Marwa Hameed Alkhafaji[3*], Heshu S. Rahman[4], Jeza M. Abdul Aziz[5], Hemn H. Othman[6], Adel Mohan Adai AL-Zubaidy[1]

[1]*Department of Medical Laboratory Sciences, Technical College of Applied Science in Halabja, Sulaimani Polytechnic University, Sulaymaniyah, Republic of Iraq*
[2]*Research Center, Sulaimani Polytechnic University, Sulaymaniyah, Republic of Iraq*
[3]*Department of Biology, College of Science, University of Baghdad, Baghdad, Republic of Iraq*
[4]*Department of Physiology, College of Medicine, University of Sulaimani, Sulaymaniyah, Republic of Iraq*
[5]*Department of Medical Laboratory of Sciences, College of Health Sciences, University of Human Development, Sulaymaniyah, Republic of Iraq*
[6]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Sulaymaniyah, Republic of Iraq*

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Abstract

COVID-19 is an infectious pandemic disease which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Up to date, scientists are trying to identify a new specific antiviral drug to overcome this disease. Different methods are under study and evaluation in the entire world to control the virus, including blood plasma, blood purification, and antimicrobial and antiviral agents; however, there are no approved drugs yet. This review is focused on the conducted clinical trials worldwide, including the Iraq- Kurdistan region, China, USA, and Europe, to find relevant data on the agents with potential efficacy to treat the COVID-19 infection. The utmost commonly assessed therapies for this disease were chloroquine phosphate, hydroxyl-chloroquine, azithromycin, lopinavir/ritonavir, favipiravir, remdesivir, and alternatively, blood plasma, ivermectin in combination with doxycycline, and dexamethazone. This review suggests that blood plasma transfusion, the combination of hydroxyl-chloroquine with azithromycin, and remdesivir were the most abundant and efficient therapies. Thus, more light could be shed on these particular drugs on the road of drug investigation against COVID-19 pneumonia.

Keywords: COVID-19, pandemic infection, treatment strategy, Kurdistan region

الخيارات المحتملة الحالية لعلاج كوفيد-19 في العراق – اقليم كردستان وبقية العالم: مراجعة مصغرة

ئاريان محمود فرج[1*] ، سيامند احمد قادر[1*] , عثمان عبد الرحمن محمد[1،2*]، بيشه وا يونس عزيز[1*]، مروى حميد الخفاجي[3*]، هيشو سليمان رحمان[4*]، جزا محمد عبد العزيز[5*]، هيمن حسن عثمان[6*]، عادل موحان عداي الزبيدي[1*]

[1]قسم علوم المختبرات الطبية، الكلية التقنية للعلوم التطبيقية، جامعة السليمانية التقنية ، السليمانية، جمهورية العراق

[2] مركز الابحاث، ، جامعة السليمانية التقنية ، السليمانية، جمهورية العراق

[3] قسم علوم الحياة، كلية العلوم ، جامعة بغداد، بغداد، جمهورية العراق

*Email: drmarwahameed81@gmail.com

[4] قسم علم وظائف الاعضاء، الكلية الطب، جامعة السليمانية ، السليمانية، جمهورية العراق
[5] قسم علوم المختبرات الطبية، كلية العلوم الصحية ، جامعة التنمية البشرية ، السليمانية ، جمهورية العراق
[6] قسم علوم الصيدلة والسموم، كلية الصيدلة، جامعة السليمانية ، السليمانية، جمهورية العراق

الخلاصة:

COVID−19 هو مرض وبائي معدي يسببه فيروس كورونا −2 المتلازمة التنفسية الحادة الوخيمة (SARS−CoV−2). حتى الآن ، يحاول العلماء تحديد عقار جديد مضاد للفيروسات للتغلب على هذا المرض.

طرق مختلفة قيد الدراسة والتقييم في العالم بأسره للسيطرة على الفيروس بما في ذلك بلازما الدم وتنقية الدم ومضادات الميكروبات والعوامل المضادة للفيروسات ؛ ومع ذلك ، لا توجد أدوية معتمدة حتى الآن.

تركز هذه المراجعة على التجارب السريرية التي تم إجراؤها في جميع أنحاء العالم بما في ذلك العراق منطقة−كردستان والصين والولايات المتحدة الأمريكية وأوروبا للعثور على البيانات ذات الصلة عن العوامل ذات الفعالية المحتملة لعلاج عدوى COVID−19. كانت أكثر العلاجات التي تم تقييمها شيوعًا لهذا المرض هي فوسفات الكلوروكين ، هيدروكسيل كلوروكين ، أزيثروميسين ، لوبينافير/ ريتونافير ، فافيبيرافير ، ريمديسفير ، وبدلاً من ذلك ، بلازما الدم.

اقترحت هذه المراجعة أن نقل بلازما الدم ، و مزيج من الهيدروكسيل كلوروكين مع كل من الأزيثروميسين وريمديسفير كانت أكثر العلاجات وفرة وفعالية. وبالتالي ، فإن هذه الأدوية تسلط الضوء على تجريب الأدوية المضادة للالتهاب الرئوي المتسبب عن COVID−19.

INTRODUCTION

The COVID-19 virus emerged in December 2019 in Wuhan city, Hubei Province, China, and then spread rapidly all over the world. Currently, an ongoing outbreak of pneumonia is associated with emerging viral infections to global public, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-3] .

Up to now, 6 species of coronavirus are well-known to cause human diseases, whereas 4 species lead to diseases in humans and are causing common cold in immunocompetent individuals, including alpha-Coronaviruses (HCoV-229E and HCoV-NL63) and beta-Coronaviruses (HCoV-HKU1 and HCoV-OC43) [4, 5], while the other species are zoonotic infectious agents. They are named as the Middle East Respiratory Syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) [6, 7]. The causative agent of the SARS-CoV was isolated from an outbreak in China in 2003 [8], while the causative agent of the MERS-CoV was isolated from an outbreak in Saudi Arabia in 2012 [9].

On January 7, 2020, the Chinese authorities announced a new infectious disease which is related to coronavirus [10]. This new virus belongs to the family Coronaviridae and is a non-segmented positive-sense single-strand RNA virus. It broadly distributes and infects a wide variety of animals. Additionally, it infects humans and causes respiratory, hepatic, enteric, and neurologic disorders [5, 7].

This disease was subsequently named as coronavirus disease 2019 (COVID-19) and up to date, there are 31,572,774 reported cases, among which 7,534,413 are active, 24,048,380 were recovered, and 989,981 individuals died from the infection in the world. The majority of severely infected people with COVID-19 have pneumonia with fever and cough, of which 4% mortality rate was estimated by the World Health Organization (WHO) as of September 24, 2020, due to the severe infection [11]. On the other hand, COVID-19 patients with other comorbidities, such as diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVD), hypertension, malignancies, and HIV, could develop a life-threatening situation [12, 13]. Regarding smoking status association with COVID-19 severity, there is controversy in reported data, where some studies stated no association of active

smoking to COVID-19 severity [14], while others stated that active smokers were associated with increased severity and worse outcomes [15].

Thus, for writing this mini-review article, the obtained and analyzed data were the relevant information that depended on media, news, the official website of the Ministry of Health in Kurdistan-Iraq, published papers in reputable journals, and reliable data from the internet.

EPIDEMIOLOGY

More than 31,000,000 COVID-19 recorded cases are present in the entire world, with more than half being recovered and too many deaths [16]. The number of cases is continuously increasing, especially in the USA, UK, Italy, Spain, Germany, and Iran, while the confirmed cases of COVID-19 reported by the Ministry of Health (MOH) since March 1, 2020 until September 24, 2020 in Iraq-Kurdistan Region were 43,989 cases (28,153 recovered, 14,244 actives, and 1,592 deaths) [17].

The earliest symptoms of the COVID-19 in the infected patients were identified in December 2019 [18] when the Chinese health authorities reported that most cases of the infected people were epidemiologically linked to the animal market [7, 19, 20]. On February 11, 2020, the Chinese Center for Disease Control and Prevention reported 72314 cases. Also, 44672 (62%) cases were classified as confirmed cases of COVID-19, based on the positive test result of the viral nucleic acid.

Also, based on exposures and symptoms of the recorded cases, among 16186 cases, 22% were recorded as suspected cases, while based on symptoms and lung imaging features of pneumonia, 15% were described as clinically diagnosed cases. While only 1% of the cases were identified as positive based on the presence of the viral nucleic acid sequence in the specimens without any symptoms [14]. These positive patients aged 30 to 79 years (87%), 3% aged 80 years or older, 1% aged 10 to 19 years, and 1% aged 9 years or younger [20]. The majority of confirmed death cases were in those patients aged 70 to 79 years or older (2.3%, 1023 among 44672 cases). However, there was no death among those people aged 9 years or younger [14].

TRANSMISSION

The extent of human-to-human transmission of COVID-19 is completely not clear, but there is evidence of some routes of transmission. Confirmed cases in travelers from Wuhan, China were announced on 15 January in Japan, on 13 and 17 January in Thailand, and on 19 January in Korea [10]. Transmission of the COVID-19 occurs mainly through respiratory droplets by coughing, sneezing, or close contact with an infected person [21]. It was also reported that the virus could be isolated from the urine and feces of asymptomatic carriers [22]. Therefore, these carriers may be potential sources of the infection and contamination of the environment through contact or aerosol transmission [23].

CLINICAL CHARACTERISTICS

The common clinical signs of the COVID-19 infection are fever, cough, dyspnea, myalgia, fatigue [2, 7], headache, rash, sneezing, sputum production, nasal congestion, shortness of breath, nausea, vomiting, and sore throat [12],. Respiratory failure also occurred due to severe alveolar damage and hemoptysis, especially in older people [20]. On the other hand, the laboratory outcomes usually include increases in C-reactive protein (CRP), leukopenia, lymphopenia [21], D-dimer, alanine aminotransferase, and total bilirubin. Also, CT scan showed bilateral ground-glass opacity and subsegmental area of consolidation after symptom onset [2].

TREATMENT

General treatment

The patients should be allowed to take enough rest and provided with healthy food and drinks, especially fresh vegetables and fruits. Besides, routine monitoring of blood and urine , CRP, biochemical indicators, such as the liver and myocardial enzymes, renal function, coagulation

function, arterial blood gas, chest imaging, and type-2 cytokines , such as IL6, is required [23] . Punctually, providing oxygen therapy [23, 24], including nasal catheter, high flow oxygen therapy, and mask oxygenation, is a necessary measure [23]. Patients with a mild clinical presentation, without pneumonia and hypoxia, may not initially require hospitalization and they will be able to encounter their illness at home [24].

Blood plasma transfusion

The Ministry of Health in the Iraq-Kurdistan Region provided a combination of hydroxyl-chloroquine with azithromycin, which is recognized as a drug for overcoming pneumonia produced as a result of COVID-19 infection. Despite that, a mixture of fresh lemon and orange juice was provided each day as a rich source of vitamins to keep the patients in high immunity. On the other hand, convalescent plasma (CP) transfusion for severe cases of pneumonia that required oxygen ventilation was recommended. According to the Ministry of Health in the Kurdistan regional government, CP lowered the severity of pneumonia and improved the health condition of the patients. Thus, CP treatment is possible to be used for patients with rapid disease progression and those with severe and critical illness [23, 25].

CP has the benefit that, while it stops the viral replication by its antibodies, other components can likewise apply valuable effects, such as refilling the consumed coagulation factors. The problem with CP is that it shows an individual-dependent variability in antibody titers and specificities, while H-Ig prepared by using standardized doses of the antibody. According to Abdullah *et al*., the patients received a single dose of 200 ml of CP from a previously recovered COVID-19 patient (14 days after his last negative RT-PCR test) after doing necessary investigations for the donor's plasma (hemoglobin level and viral screen). The patients started to improve clinically 4 days later and they were quite stable. Additionally, no serious adverse effect was observed in these cases during and after transfusion [26].

Antiviral therapy

Several antiviral drugs have been used in hospitals. The National Health Commission and State Administration of Traditional Chinese Medicine has published a protocol of using drugs or antivirals for the COVID-19 treatment [23] . In addition, other published articles over the world had been describing the usage of antivirals or drugs to treat this virus. Such as: Alpha-interferon (5 million U or equivalent dose for adults, adding 2.0 ml sterilized water, atomization inhalation twice daily). Lopinavir/Ritonavir (200 mg/50 mg for adults, twice daily, two pills each time, no longer than 10 days). In addition, Ribavirin, suggested to be used together with interferon or lopinavir/ritonavir, 500 mg for adults, two or three times of intravenous injection daily, no longer than 10 days. Also, Chloroquine phosphate, 500 mg twice daily, for 7 days, for adults between 18 to 65 years old, with body weight 50 kg or more; as well as 500 mg twice daily, for two days, then a single dose per day for 7 days for adults below 50 kg [23]. Chloroquine, or related formulas, was very effective in reducing viral replication. This is a known virus infection blocker that acts by interfering with the glycosylation of the cellular receptor of COVID-19 and increasing endosomal pH [24]. Besides, hydroxyl-chloroquine has been used in France, being provided by the national pharmacy of France on nominative demand, with effectiveness against COVID-19. It was also shown by the Mediterranean Infection University Hospital Institute in Marseille that the combination of the hydroxyl-chloroquine 200 mg/ 3 times per a day with azithromycin and zinc (depending on patients' clinical presentation) was more effective on those patients who had both upper respiratory tract infection and bronchitis (pneumonia) [27]. Arbidol (200 mg three times, for adults, no longer than 10 days) was used as another broad-spectrum antiviral compound. Adverse reactions and contraindications must be taken into account; for example, chloroquine is not possible to be used for patients with heart disease, since this could result in the interactions between arbidol and other drugs [23] . Remdesivir antiviral was used in the first case from the United States of America and seemed successful [28, 29]. Favipiravir is

the first approved drug with a potential curative effect on coronavirus, which will play an important role in the prevention and control of the infections. It was first used against coronavirus in Wuhan at the beginning of the pandemic and approved in Italy for emergency use. It is currently in use in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan, but also in some countries of the Middle East, such as Saudi Arabia, UAE, and Egypt, In addition, it is being used in Iraq, including the Kurdistan region. Favipiravir received the approval for the first time for usage as a treatment for mild and moderate cases of corona virus in India [20]. Furthermore, it is not recommended to use 3 or more antiviral drugs at the same time. Also, blind or inappropriate antibiotic drug treatment should be avoided, particularly in combination with broad-spectrum antibiotics [23] .

Treatment of severe and critical cases

According to the protocol of the National Health Commission and State Administration of Traditional Chinese Medicine, the complications of severe and critical situations should be prevented. Because of that, treatments should be applied and organs should be supported appropriately with secondary infection preventions [23].

Respiratory support

The most important support for patients with severe symptoms is provided through nasal cannulas or masks for oxygen inhalation, high-flow nasal-catheter oxygenation, high-flow nasal cannula oxygen therapy, or non-invasive ventilation. This can be considered when respiratory distress and/or hypoxemia of the patient cannot be alleviated after receiving standard oxygen therapy. Tracheal intubation and invasive mechanical ventilation should be used if conditions do not recover or even get worse in a short time (1-2 hours) [23] . The oxygen should be given by face mask to patients with hypoxemia, at a high concentration at first, and then adjusted according to the results. The patient with respiratory failure should be provided by endotracheal intubation and ventilation [30].

Circulatory support

Adequate fluid resuscitation is required to improve the microcirculation, via the use of vasoactive drugs, with closely monitoring the changes in blood pressure, heart rate, and urine volume, as well as lactate ratio and base excess in arterial blood gas analysis. The liquid balance is very important to avoid excess or insufficient fluid intake [23].

Renal failure and renal replacement therapy

Attention should be paid for renal function in critical cases, with a focus on the body fluid balance, acid-base balance, and electrolyte balance, as well as on nitrogen balance, the supplementation of energies, and trace elements [23] .

Blood purification treatment

This treatment comprises plasma exchange, perfusion, absorption, and blood/plasma filtration, which is applied in the early and middle stages of “cytokine storm”. The advantage of blood purification treatment is the removal of the inflammatory factors responsible for the cytokine storm and damage owing to inflammatory reactions [23]. Anti-cytokine storm target therapy should be considered shortly for cytokine-storm alleviation by the artificial-liver blood-purification system, which reduces mortality in severely ill patients with COVID-19 [31].

Immunotherapy

Tocilizumab can be used as a treatment with different doses for patients with severe cases and an increased level of IL-6, and those who have extensive lung lesions. The doses start from an initial 4-8 g/kg with more than one hour of infusion into the body. One extra dose can be given after 12 hours if the first dose is not effective. Attention should be paid not to use more than two administrations with a single dose of 800 mg, allergic reaction, and administration to patients with an active infection, such as tuberculosis [23].

Other therapeutic measures

Glucocorticoids can be used in a short period, three to five days, 1-2 mg/kg/day, with the care that a higher dose of glucocorticoid will cause adjournment for removing coronavirus due to immunosuppressive properties [23]. Clinical trial results from the United Kingdom showed that dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth. However, the CDC of the United States of America has avoided corticosteroids. Besides, Wang *et al*. showed that methylprednisolone, 1-2 mg/kg, 3-7 days, was effective when used for 46 hospitalized patients in Wuhan China [32]. Intestinal microecological regulators were used to maintain balance in intestinal microecology and stop secondary bacterial infections. Finally, γ-globulin was given intravenously to a child with a severe and critical illness [23]. A group of researchers in Iraq conducted an experiment on the effects of Ivermectin with doxycycline on patients with COVID-19. They found that those patients received treatment and who progress to more advanced stage of disease had less time of recovery In addition, Ivermectin with doxycycline reduced mortality rate in severely ill patients from 22.72% to 0%. Taken together, the earlier Ivermectin in combination with doxycycline are administered, the higher rate of successful therapy [33].

DISCUSSION

Coronavirus was initially noticed in 1960 [34] and it had been treated as a simple non-deadly virus from 1960 to 2002. Several cases of severely acute respiratory tract infections were reported in 2003, with proofs of coronavirus that killed more than 1000 patients in many different countries. While, the new coronavirus infection was reported in 2004 in Japan and Saudi Arabia in 2012 [35, 36]. Lastly, an outbreak of fatal pneumonia occurred in December 2019 at Wuhan, China [8]. According to a WHO report on 25 March 2020, the pandemic disease spreads rapidly across more than 190 countries [37]. There are no effective medications to treat and prevent SARS-CoV-2 [2, 28]. Consequently, several approaches or antiviral drugs were used as therapeutic agents against this virus [23].

Current publications have focused on the notion that chloroquine is perhaps useful as a broadly used antimalarial drug and also for the treatment of SARS-CoV-2 cases. Using this drug to treat viral infections is still under negotiation. Some Chines experts have suggested using chloroquine to treat COVID-19 patients [38, 39] and a recent publication reported the positive activity of chloroquine phosphate on COVID-19 associated pneumonia patients in China. Thus, it is recommended to include this drug in the next version of the guidelines for the prevention, diagnosis, and treatment of the COVID-19 infection which is issued by the National Health Commission of the People's Republic of China [40]. Additionally, the Chinese experts indicated that this drug could minimize the hospitalization period of patients [39, 41], which might be due to the alkalinization of phagolysosome [42, 43]. However, using chloroquine phosphate without physician guidance and supervision may have negative health consequences [44].

For the post-exposure prophylaxis against SARS-CoV-2 infection, hydroxychloroquine is currently under analysis in clinical trials for the treatment of patients with COVID-19 [45]. Hydroxy-chloroquine has been used for long periods; thus, it would be one of the suitable choices for the treatment of this virus [46]. Hydroxychloroquine has been used for intracellular bacterial infections for 30 years, particularly to treat the bacterium *Coxiella burnetiid* [47, 48]. There is no clinical prescription from Randomized Clinical Trials (RCTs) which helps for prophylaxis or treatment of SARS-CoV-2 infection. It is still unknown how much and how long hydroxychloroquine should be used for the treatment of COVID-19. However, some of the United States clinicians have reported the use of various doses of hydroxyl-chloroquine; 400 mg twice on the first day, then 200 mg twice/day for 4 days; 600 mg twice on day one, then 400 mg daily on days 2-5 [49].

Combinations of drugs occasionally have more effects on the treatment of diseases. An *in vitro* study has shown that azithromycin is active against Zika [50] and Ebola viruses [51] as well as when administrated to patients with severe respiratory tract viral infection [52]. Gautret *et al*. suggested a synergistic effect of the combination of hydroxychloroquine and azithromycin in patients with COVID-19, regarding the association of two drugs that have not been established yet [27]. The hydroxychloroquine effect was observed in COVID-19 patients after only 3-6 days [27]. The shortened incubation period of the virus is critical because a recent paper showed that the duration of viral shedding in patients with COVID-19 in China was 20 days to sometimes up to 37 days [24]. However, caution is advised when these two drugs are used together, especially in patients with chronic medical conditions such as renal failure or hepatic disease [49]. Also, the combination of lopinavir and ritonavir (Anti-HIV drugs) is tested in clinical trials under an *in vitro* study. This has shown an activity against SARS-CoV and also appeared to have activity against SARS in clinical cases infected with SARS-CoV [53, 54]. Furthermore, according to a human MERS-CoV case report from South Korea, the use of the combination of lopinavir/ritonavir with interferon-β1b provided an effective viral clearance [55].

Remdesivir and Favipiravir drugs might be the other crucial candidates for the inhibition of the replication of the coronaviruses. *In vitro* studies on human airway epithelial cell infections have shown that remdesivir had therapeutic efficacy against each of MERS-CoV and SARS-CoV [56], but importantly also against COVID-19 pneumonia, and the related zoonotic bat CoVs [28, 41, 49, 53, 57]. Regarding the antiviral effectiveness of favipiravir, in a case study of 116 patients enrolled, the drug was effective against COVID-19. The clinical recovery time for ordinary patients in 7 days was 71.43% and for severe patients was 28.57%, while the time of cough relieves and fever reduction was short. Thus, favipiravir could be effective for patients in the mild condition that does not have hypertension and oxygen inhalation [20].

Plasma transfusion and blood purification are other crucial optional methods of controlling not only SARS but also this new disease. Some studies reported a shorter hospital stay and decreased mortality in patients treated with this method, as compared with others who were not treated [58, 59]. This might relate to the antibodies from convalescent plasma that may suppress viremia. An *in vivo* trial on HIV-1-infected cells explained that the effectiveness of the antibody did not only decrease the free viral particles and stop new infections, but also improved the clearance of the infected cells [60]. In viral infections, viremia peaks in the first week. The patient normally makes a primary immune response after 10 to 14 days. Thereafter, the virus might be cleared. Therefore, it is assumed that the administration of the convalescent plasma at the beginning stage of the viral disease may be more effective [59]. Thus, it is proposed that therapeutic plasma exchange is one of the possible treatments for the COVID-19 [26]. In a local study in Iraq, a model was used to predict vulnerable populations to covid-19 infections, and the model was precisely reliant on the level of the confirmed data [61]. Covid-19 infections penetrate all life aspects, altering the natural and artificial environments and destroying global economy [62].

CONCLUSION

Currently, there are no verified agents the can be specifically utilized to treat COVID-19 infection. A review on the data collected on the options for COVID-19 therapy is crucial for the different involved sectors, especially researchers, to prevent and treat the new disease. These data might support the current clinical trials of the treatment of COVID-19 and enhance the development of new trials in the future. The efficiency and safety of these current optional agents need to be studied in further clinical trials.

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CONFLICT OF INTEREST

The authors declared no conflict of interest to this review article.

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