

# Re-tasking the use of pre-existing medications and potential therapeutic options for coronavirus disease (COVID-19): systematic review of clinical studies

Bushra Hassan Marouf<sup>1,\*</sup>, Kawa Dizaye<sup>2</sup>

<sup>1</sup> Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Sulaimani, Kurdistan Region, Iraq;

<sup>2</sup> Department of Basic Science, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region, Iraq.

**SUMMARY** With the emergence of coronavirus disease 2019 (COVID-19) in late December 2019, many clinical studies on a group of the pre-existing medications have been conducted to treat this disease. The purpose of this review was to compile the clinical evidences on the use of the pre-existing medications and potential therapeutic options for the management of COVID-19. We reviewed the literature to highlight the clinical studies on the use of these medications to be available as a scientific overview for further perspectives. Inadequate clinical evidences are available to be affirmed for the repurposing of old medications, and large scale clinical studies are needed to be carried out to further confirm the use of these agents. The clinical use of these medications should be well explained and follow the framework of Monitored Emergency use of Unregistered Interventions (MEURI) of World Health Organization (WHO).

**Keywords** COVID-19, clinical studies, hydroxychloroquine, pneumonia, SARS-CoV-2

## 1. Introduction

In late December 2019, a novel strain of coronavirus was identified in a group of patients in Wuhan city of China (1). It was preliminarily named as 2019 novel coronavirus (2019-nCoV), then the virus has officially been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Despite local measures by Wuhan the virus has spread beyond China. On the 11<sup>th</sup> of March 2020 World Health Organization (WHO) announced a Coronavirus disease 2019 (COVID-19) as a pandemic disease. There is a diversity in the severity of COVID-19, ranging from mild respiratory tract symptoms to severe or fatal pneumonia. As of 26<sup>th</sup> of April 2020 coronavirus has affected a total of 2,920,877 cases and lead to 203,272 deaths in 212 countries.

Outbreaks of coronavirus groups have been recorded in the last twenty years other than Wuhan's new coronavirus (2019-nCoV). Six other coronavirus strains are known to infect human with different origin and transmission dynamics. Among these, only severe acute respiratory syndrome coronavirus (SARS-CoV) in China in 2003 and middle east respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia in 2012 were with high mortality rate (3) and the

other four coronaviruses (HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43) can only cause mild respiratory infections.

Studies on SARS-CoV and MERS-CoV helped in identifying potentially effective therapies such as: remdesivir, lopinavir/ritonavir, interferon and convalescent plasma. Limited information is available on SARS-CoV-2, however several insights may be gained from its more well-known family member, SARS-CoV (4). The available evidence, and experience from SARS-CoV and MERS-CoV suggests several approaches to manage and limit the spread of SARS-CoV-2. One of these approaches is by targeting the binding protein of the virus with the host receptor which will disrupt the replication and will modulate the immunity of the individual. Coronavirus is an enveloped, positive-strand RNA virus, it is covered with club-shaped glycoproteins which look like 'crowns', or 'halos' so it is called a coronavirus. It forms coronal protrusions at the edges.

For all coronaviruses including SARS-CoV-2, at least three structural proteins are shared on the membrane. First protein is spike (S); the spike protein of these coronaviruses binds angiotensin converting enzyme-2 (ACE-2), which is highly abundant in the lungs and heart, leading to respiratory and potential

cardiovascular damage (5). Angiotensin converting enzyme-2 (ACE-2) serves as the cellular entry point for coronaviruses (6). Second structural protein is the membrane protein (M) and third one is small membrane protein (E). Another four functional proteins were found in almost all coronaviruses: 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase (RdRp) and helicase. A high genomic similarity between SARS-CoV-2 and the previous coronaviruses particularly SARS-CoV has been noticed, it has been found that they share 82% RNA sequence identity, and their RNA-dependent RNA polymerase (RdRp) shares 96% sequence identity with SARS-CoV-2 (4). Therefore, drugs targeting viral RdRp proteins of SARS-CoV are likely to be effective for SARS-CoV-2. To date and according to the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the Food Drug Administration (FDA) there are currently no medications or vaccines proven to be effective for the treatment or prevention of SARS-CoV-2 (7-9).

Large number of the *in vitro*, *in vivo*, preclinical, and clinical studies have been conducted and they have reported certain agents that displayed strong antiviral potential of which some have been permitted to be used in an attempt to combat the disease in clinical trials, including the pre-existing medications that were used for the treatment of other diseases with the aim of repurposing them to treat COVID-19. Some of these studies have demonstrated a particular therapeutic intervention in a clinical basis that could not provide a strict clinical evidence. For this reason, the current review sets out to compile the clinical evidences on the use of pre-existing medications and potential therapeutic options for the management of COVID-19 since the emergence of the outbreak in late December 2019 till April 2020 to be available as a scientific overview for further perspectives. Table 1 summarized some repurposing efforts for the existing approaches in treatment of COVID-19 through demonstrating their clinical efficacy and safety.

## 2. Repurposing of chloroquine/hydroxychloroquine for use as treatment of COVID-19

During any outbreaks of epidemic and pandemic levels, repurposing of the pre-existing drugs is a common practice due to difficulty in development of new drug at that time being. Although repurposing of the old medications for treatment of COVID-19 with safe profile was not apprehended by the virologists, many clinical studies on those medications were carried out in several Chinese hospitals and their clinical efficacy were also being evaluated in many studies (10). Some protocols have included the recommendation for using them (9,11). The factual evidence for the effectiveness of chloroquine/hydroxychloroquine in COVID-19 is

currently very limited. The first clinical outcome of treating over 100 patients with chloroquine phosphate at 500 mg twice daily for 10 days was documented on February 17, 2020 by the State Council of China in a news briefing, the results were superior to the control without serious adverse reaction and was prevented the exacerbation of pneumonia, improved lung imaging findings, and reduced clinical duration of disease markedly, thereafter chloroquine phosphate has been designated as a re-tasking strategy for COVID-19 with a marked efficacy and tolerability in treating severe pneumonia related to COVID-19 in China (12).

Moreover, Gautret and his colleagues in France (13) have conducted the first clinical open label non randomized controlled trial on 36 patients diagnosed with COVID-19 (20 hydroxychloroquine-treated patients and 16 control patients), the treated patients received 600 mg of hydroxychloroquine daily (200 mg, three times per day during ten days), and azithromycin has been given to six patients to protect against a possible superimposed bacterial infection. The patients in other centers did not receive hydroxychloroquine and served as controls, they received only supportive management. The results of this clinical study demonstrated that on day 6, patients in the treatment group were significantly more likely to test negative for the virus than patients in the control group (70% vs. 12.5% virologically cured,  $p < 0.001$ ) and all of the six patients who were treated with a combination of hydroxychloroquine and azithromycin tested negative on day 6. The authors concluded that despite its small sample size their clinical study demonstrated that in the hydroxychloroquine-treated group there was a significant reduction and disappearance of viral load and it was also found that azithromycin synergized its effect.

Subsequent to the promising results of these first clinical trials, guidelines published recommending the treatment of COVID-19 using chloroquine/hydroxychloroquine. The National Health Commission of the People's Republic of China published their recommendation in mid-February, suggesting to treat patients with 500 mg chloroquine phosphate twice per day, for a maximum of 10 days (14). In order to guide and standardize the use of chloroquine in the treatment of the new coronavirus pneumonia, the Guangdong Provincial Department of Science and Technology and the Guangdong Provincial Health and Health Commission's chloroquine treatment of new coronavirus pneumonia multi-center collaboration group, developed the expert consensus after fully discussing the diagnosis of the new coronavirus for patients with pneumonia of mild, common and severe, after chloroquine contraindications were ruled out, chloroquine phosphate tablets could be used 500 mg each time, twice daily for 10 days. Due to the findings from the above studies, China then recommended the

Table 1. Characteristics of the clinical studies re-tasking pre-existing medications for management of the coronavirus disease 2019 (COVID-19)

Drug /Approach	Type of clinical study	Dosage	Intervention group	Comparison group	Outcome measures	Ref.
Chloroquine Phosphate	Multicenter clinical study	500 mg twice daily for 10 days	Chloroquine Phosphate	Control group	Detail not included however the results were superior to the control	12
Hydroxychloroquine (HCQ) and Azithromycin (Azi)	Open label non-randomized clinical study	HCQ; 200 mg, 3 times/day for 10 days, Azi; 500 mg on day 1 followed by 250 mg/day, the next four days	20 patients received HCQ; Azi were added to 6 of them	16 control patients received supportive management	Virological clearance, clinical follow-up, side effects.	13
Hydroxychloroquine (HCQ)	Randomized clinical study (A pilot study)	400 mg per day for 5 days	HCQ plus conventional treatments	Control group: conventional treatment	Virological clearance (rRT-PCR-SARS-CoV-2) in respiratory pharyngeal swab on days 7, adverse drug event	16
Hydroxychloroquine (HCQ)	Randomized clinical study	400 mg/day; (200 mg twice daily) for 5 days	HCQ plus standard treatment	Standard treatment, with or without corticosteroids	TTCR, clinical characteristics, and radiological results	17
Hydroxychloroquine (HCQ)	Multicenter, randomized, open-label, parallel clinical study	Loading dose = 1,200 mg daily for 3 days, maintenance dose = 800 mg for 2 - 3 weeks	HCQ plus standard care	Standard care	Negative conversion rate of COVID-19 virus, improvement rate of clinical symptoms.	18
Remdesivir	Case report	I.V. Remdesivir	I.V. Remdesivir for 7 days	NA	Cycle threshold values (Ct), Patient's rRT-PCR-SARS-CoV-2 in nasopharyngeal and oropharyngeal swabs	26
Lopinavir-ritonavir	Open-label randomized clinical study	lopinavir-ritonavir (400 - 100 mg) twice daily for 14 days	Lopinavir-ritonavir treated group (n = 99)	Conventional therapy group (n = 100)	Time to clinical improvement, clinical status seven-category ordinal scale on days 7 and 14, mortality at day 28, the duration of mechanical ventilation, the duration of hospitalization	33
Convalescent plasma (CP)	Pilot clinical study	One dose of 200 mL CP obtained from recently COVID-19 recovered patients	Severe patients confirmed by rRT-PCR-SARS-CoV-2 received One dose of 200 mL CP	Pre- and post CP transfusion comparison.	The outcome measures: safety of CP transfusion, clinical improvement and amelioration of laboratory values within 3 days after CP transfusion	41
Convalescent plasma (CP)	Uncontrolled case series	2 consecutive transfusions of 200 to 250 mL of ABO blood type-compatible convalescent plasma	400 mL of convalescent plasma in total on the same day it was obtained from the donor. The patients received antiviral agents continuously until the SARS-CoV-2 viral loads became negative.	Pre- and post CP transfusion comparison.	Clinical symptoms, changes in body temperature, organ failure assessment (SOFA) score, virology parameters, hematological and biochemistry parameters, the ratio of the partial pressure to fraction of inspired oxygen (PAO <sub>2</sub> /FIO <sub>2</sub> )	42

rRT-PCR-SARS-CoV-2: real-time reverse-transcriptase-polymerase-chain-reaction; ABO: blood type; TTCR: Time to clinical recovery.

use of chloroquine in prevention and management of COVID-19 (12). In Italy, the L. Spallanzani National Institute for the Infectious Disease published their recommendations for treatment of COVID-19 on the 17th of March, which included the provision of 400 mg of hydroxychloroquine per day or 500 mg chloroquine per day, in combination with another antiviral agent (15). Additionally, in a systematic review on the safety and efficacy of chloroquine the authors identified and mentioned 23 ongoing clinical trials on chloroquine in COVID-19. The ongoing trials varied in study design, severity of the disease in the target population and in dosing and duration of the treatment (10).

The current review further elaborated one pilot study of using hydroxychloroquine in treatment of patients with COVID-19 (16). The study prospectively enrolled 30 patients with confirmed COVID-19 after informed consent at Shanghai Public Health Clinical Center had been obtained. The patients were randomized 1:1 to hydroxychloroquine group and the control group. Patients in hydroxychloroquine group were given 400 mg hydroxychloroquine per day for 5 days plus conventional treatments, while those in the control group were given conventional treatment only. The primary outcome measure was a negative conversion rate of the real-time reverse transcription PCR testing for SARS-CoV-2 (rRT-PCR-SARS-CoV-2) in respiratory pharyngeal swab on days 7 after randomization. The results showed no significant difference in outcomes between those who received the drug and those who received conventional treatment. The main findings are one patient developed severe disease and the authors stated that developing severe disease did not appear related to the medication. One week after hospitalization, 13 (86.7%) of patients in the experimental group and 14 (93.3%) of patients in the usual care group tested negative. This difference was not statistically significant, ( $p$  value > 0.05) median time for Patients' temperatures to return to normal was comparable in both groups. Disease progression in chest CT images was statistically comparable between both groups (5 (33.3%) of the hydroxychloroquine treated-group and 7 (46.7%) of the conventional group). At two weeks, all patients in both groups tested negative and showed improvement in their symptoms, regarding side effects short-term diarrhea and abnormal liver function occurred in 4 (26.7%) of the hydroxychloroquine group and 3 (20%) of the control group. The rate of adverse events was similar in both groups. The authors recommended larger size trials and they estimated that a trial would require 784 patients with no drop-outs to determine whether hydroxychloroquine definitively results in better or worse outcomes.

Recently in a larger scale, efficacy of hydroxychloroquine in patients with COVID-19 in a randomized clinical trial has been evaluated in 62 patients in another hospital of China (17). All patients

were randomized in a 1:1 ratio, each group was of 31 patients. Standard treatment was given for both group (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids), hydroxychloroquine-treated group received 5-day hydroxychloroquine (400 mg/day; 200 mg twice daily), time to clinical recovery (TTCR), clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment to evaluate the effect of hydroxychloroquine. The results showed that TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the hydroxychloroquine treated group. A larger proportion of patients from hydroxychloroquine treated group 25 (80.6%) versus 17 (54.8%) in control group showed improvement confirmed by chest CT. Four patients in the control group found to have to severe illness. However, only 2 hydroxychloroquine treated patients found to have mild adverse reactions including skin rash and headache. The results suggested that the use of hydroxychloroquine could significantly shorten TTCR and promote the absorption of lung lesion. They concluded that despite the efficacy, tolerability and affordability of hydroxychloroquine, the detrimental effects of this drug cannot be ruled out.

Most recently another clinical study designed in a randomized, open-label, multicenter, parallel trial has been conducted in China. The study enrolled 150 COVID-19 patients from 16 designated COVID-19 treatment centers of three provinces in China to assess the effectiveness and safety of hydroxychloroquine (18). Half of the patients ( $n = 75$ ) were allocated to receive standard care of the hospitals alone while the other half ( $n = 75$ ) to receive standard care plus hydroxychloroquine. Hydroxychloroquine was given as 1,200 mg loading dose daily for three days then followed by 800 mg as maintenance dose daily for duration of two weeks for mild/moderate to three weeks for severe patients.

The primary endpoint was a negative conversion rate of COVID-19 virus while the secondary endpoints included a 28-days improvement rate of clinical symptoms. The result of the study showed that almost collectively a 28-day negative conversion rate of the virus was similar between the two groups. The Kaplan-Meier estimate for negative conversion rate was 85.4% versus 81.3%,  $p = 0.341$ . Additionally, no difference in mitigation of symptoms in a 28-day duration was seen between the two studied groups. The authors stated that using hydroxychloroquine with the standard care did not provide any additional virologic response and its effect on the mitigation of symptoms was more evident when the confounding effects of other antiviral agents were removed. Further they emphasized on that the adverse effects of hydroxychloroquine should be closely monitored. Despite the larger scale of the latest clinical study ( $n = 150$ ) on re-tasking



hydroxychloroquine against COVID-19, the efficacy and safety of hydroxychloroquine need to be further monitored.

Moreover, additional investigation on the safety and efficacy of chloroquine and hydroxychloroquine has been included in this systematic review (19) to demonstrate the preference of hydroxychloroquine over the chloroquine although the antimalarial activity of hydroxychloroquine is equivalent to that of chloroquine. Hydroxychloroquine is preferred over chloroquine for its lower ocular toxicity (20). The authors focused on retinopathy and QT-prolongation as a safety and risk concern for chloroquine and hydroxychloroquine comparison, they identified retinopathy as a dose-limiting adverse effect of hydroxychloroquine (21) they also highlighted the advantages of hydroxychloroquine over chloroquine concerning its easily obtainability, less drug interaction with other protease inhibitors especially lopinavir/ritonavir as a clarification for the preference of hydroxychloroquine.

Furthermore, the prophylaxis role of chloroquine against COVID-19 has been supported based on the preliminary clinical evidences of chloroquine in COVID-19 and an optimal dosing regimen to reach a preventive effect of chloroquine against SARS-CoV-2 inhibition in respiratory tissues with acceptable safety profile was formulated as stated by the two authors Raymond Chang and Wei-Zen Sun in their review articles (22).

### 3. Repurposing of remdesivir for use as treatment of COVID-19

With the emergence of the COVID-19 it had been suggested that remdesivir might be an option for the therapy of patients with COVID-19 (4). Remdesivir is a broad-spectrum antiviral agent, is a nucleotide analog inhibitor of RNA-dependent RNA polymerases (RdRps). It is a monophosphoramidate prodrug and is an adenosine analog. Although currently there are no approved antiviral medications for the treatment of COVID-19. Preclinical data with the nucleotide analogue remdesivir and its safety profile encourages repurposing the use of this drug as a treatment for COVID-19 (23). This drug shows a wide range of antiviral activities against several RNA viruses (24) including SARS-CoV and MERS-CoV. Remdesivir was originally developed for the treatment of Ebola virus disease (EVD) (25). It was synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection. The first case of COVID-19 in Washington, USA (although transmission dynamics and the full spectrum of clinical illness was not fully understood) was compassionately treated with I.V. remdesivir for the progression of pneumonia on day 7 of hospitalisation and the case has been reported as case study by Holshue ML *et al.* (26). The authors in this

study demonstrated cycle threshold values (Ct) (lower cycle threshold value indicates higher viral load) as an indicator for a decline in a viral load of the patient. Patient's rRT-PCR-SARS-COV-2 in nasopharyngeal and oropharyngeal swabs remained positive at 4 days after the administration of remdesivir, but the authors recorded a trend in the decline of viral load in nasopharyngeal swabs. Despite the patient's initial mild symptoms, the Ct values (18 to 20 in nasopharyngeal specimens and 21 to 22 in oropharyngeal specimens) on illness day 4 suggest high levels of viral load in these specimens. Nasopharyngeal and oropharyngeal specimens obtained on illness days 11 and 12 showed a trend toward decreasing levels of viral load (day 11, Ct was 33-34; and day 12 Ct was 37-40 for nasopharyngeal swab). The oropharyngeal specimen tested negative for SARS-CoV-2 on day 12. The patient's condition improved and no obvious side effects were observed. The rRT-PCR-SARS-CoV-2 results for serum obtained on these dates are still pending. The authors in this case report highlighted the necessity to identify the pathophysiology, duration of viral stay and other features of COVID-19 to provide more information on clinical management. Although it is not plausible to conclude the direct antiviral effect of remdesivir on enhanced clearing of viral loads in the respiratory tract only by a case report, it indeed suggests a promising therapeutic effect of remdesivir.

Currently there are two phase 3 randomized, double-blind, placebo controlled multicenter clinical trials ongoing in China. These trials have been submitted to ClinicalTrials.gov and are designed to assess the safety and efficacy of parenteral remdesivir in hospitalized adults with mild-to-moderate and severe COVID-19 (27). The number of the planned-recruited cases is 308 and 452, respectively. A treatment protocol will be 200 mg loading dose on first day, then 100 mg maintenance doses per a day for nine successive days in both studies. This protocol of remdesivir therapy was used in the randomized clinical trial of Ebola virus disease (28). Clinical efficacy of remdesivir on COVID-19 still unknown, and researchers are waiting the final outcomes of these ongoing clinical trials.

### 4. Repurposing lopinavir-ritonavir protocol as a treatment in COVID-19

Previous experiences and preclinical studies on other coronaviruses (SARS-COV, MERS-CoV) identified lopinavir as a potential therapy against COVID-19. Lopinavir, a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, has *in vitro* inhibitory activity against SARS-COV (29). Ritonavir is used in lower doses to enhance the activity of other protease inhibitors by improving their bioavailability, plasma half-life and inhibiting their metabolism. Lopinavir is now available only in combination with ritonavir to

improve bioavailability and plasma half-life of lopinavir through the inhibition of cytochrome P450. Lopinavir has activity, both *in vitro* (30) and in an animal model (31) against MERS-CoV, and case reports have suggested that the combination of lopinavir-ritonavir with ribavirin and interferon alfa resulted in virologic clearance and survival (32). After the emergence of COVID-19 and the urgent need of an antiviral therapy, also because lopinavir was clinically available for HIV-1 infection and a study of lopinavir plus the protease inhibitor ritonavir demonstrated clinical efficacy for SARS-CoV, researchers conducted an open-label randomized trial at one hospital in China (33). They recruited 199 adult COVID-19 patients (assigned randomly to the lopinavir-ritonavir treated group ( $n = 99$ ) and conventional therapy group ( $n = 100$ )). The conventional group received a standard care alone while the treated group received oral lopinavir-ritonavir (400-100 mg) twice daily for 14 days. The results showed that the treated group and those receiving standard care did not differ significantly in time to clinical improvement, duration of intensive care unit stay, days of mechanical ventilation, or days of oxygen support. Patients who received lopinavir-ritonavir had lower 28-day mortality (19% vs. 25%), but the differences between the groups was not significant. The results of rRT-PCR-SARS-CoV-2 testing of throat swabs did not differ between the two groups. The authors concluded no clinical advantage of using lopinavir-ritonavir treatment over the standard care, they stated that further clinical trials are needed to confirm the effectiveness of these medications in COVID-19 treatment.

### 5. Convalescent plasma uses as a potential therapy for COVID-19

Convalescent plasma (CP) therapy, is a classic adaptive immunotherapy, has been used in a therapy for many infectious diseases since last century. In the last twenty years, CP therapy was well used in the management of SARS, MERS, with reasonable efficacy and safety (34). In 2014, the use of CP collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks (35). A protocol for the use of CP in the treatment of MERS was established in 2015 (36). No adverse events were observed. The possible mechanism of action of CP is antibody associated suppression of viraemia. Because the virological and clinical characteristics are sharing similarities among SARS, MERS, and COVID-19 (37), scientists believed that CP therapy might be a promising treatment option as COVID-19 rescue (38). A viewpoint by Casadevall A and Pirofski LA has argued the use of convalescent serum as an option for COVID-19 treatment (39). Furthermore, there are reports that CP was used for therapy of patients with COVID-19 in China during the current outbreak (40).

Feasibility of CP transfusion to treat severe patients was investigated in one pilot study conducted prospectively in China (41). The study enrolled ten severe patients confirmed by rRT-PCR-SARS-CoV-2. One dose of 200 mL CP obtained from recently COVID-19 recovered patients with the neutralizing antibody titers above 1:640 was transfused to the patients as an addition to maximal supportive care and antiviral agents. The primary outcome measure was the safety of CP transfusion. The second outcome measures were the clinical improvement and amelioration of laboratory values within 3 days after CP transfusion. The results showed that CP was well tolerated and could increase or maintain the neutralizing antibodies at a high level in a significant manner, leading to the removal of viremia in 7 days. There was improvement in clinical symptoms of the patients as well as other laboratory parameters promptly within 3 days. Radiological examination showed different degrees of absorption of lung lesions within 7 days. Although the results were promising the authors of this study affirmed the necessity of conducting randomized clinical trial.

Furthermore, most recently an uncontrolled case series which included 5 critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS) who met the inclusion criteria were reported in China (42). CP-transfusion was given between 10 and 22-day post admission. Clinical symptoms were compared pre and post CP transfusion. The main outcome measures were changes in body temperature, organ failure assessment (SOFA) score, virology parameters, hematological and biochemistry parameters, the ratio of the partial pressure to fraction of inspired oxygen ( $PAO_2/FIO_2$ ) pre and post CP transfusion. The results showed that following the CP-transfusion, temperature reduced in 4 patients, SOFA score decreased, and  $PAO_2/FIO_2$  increased after 12 days of CP-transfusion. Viral load detected by rRT-PCR-SARS-CoV-2 test became negative and ARDS resolved in 4 patients and specific ELISA and neutralizing antibody titers for SARS-CoV-2 increased on 7-day post transfusion. After 14 days of treatment, 3 out of the 5 patients were withdrawn from mechanical ventilation, hospitals stay for two patients was 37 days then the patients discharge with a stable condition, while three patients have been discharged after (53, 51, and 55 days).

The authors stated that despite the promising effect of CP in those critically ill patients the sample size and the uncontrolled study design were the main limitation for the study to be declared as an affirming therapy therefore this approach necessitate to be evaluated in further randomized control trial to confirm its potential effectiveness for COVID-19.

### 6. Conclusion

Few clinical evidences are available to be affirmed for

the repurposing of chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir and convalescent plasma as a treatment and/or prophylaxis for COVID-19. Further large scale randomized control clinical studies are needed to assure the use of these agents as antiviral therapy for COVID-19 although *in vitro*, *in vivo*, preclinical trials and safety profile for these old drugs are promising. Medication repurposing may be supported by expert judgments, however clinical use of these drugs in patients with COVID-19 should be clearly justified and should follow the framework of Monitored Emergency Use of Unregistered Interventions (MEURI) or approval of a clinical trials as stated by the World Health Organization.

## References

- Zhu N, Zhang D, Wang W, *et al.* A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020; 382:727-733.
- Gorbalenya AE, Baker SC, Baric RS, *et al.* Severe acute respiratory syndrome-related coronavirus: The species and its viruses—a statement of the Coronavirus Study Group. *bioRxiv.* 2020; doi: <https://doi.org/10.1101/2020.02.07.937862>.
- Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012; 367:1814-1820.
- Liu W, Morse JS, Lalonde T, Xu S. Learning from the past: Possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem.* 2020; 21:730-738.
- Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* 2020; 17:259-260.
- Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, Zhu J, Zhang Q, Wu J, Liu L. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. *J Med Virol.* 2020; 92:595-601.
- World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected) (accessed June 24, 2020).
- Centers for Disease Control and Prevention (CDC). <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html> (accessed June 24, 2020).
- U.S Food and Drug Administration. [https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds?utm\\_campaign=What%27sNew2020-03-24&utm\\_medium=email&utm\\_source=Eloqua](https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds?utm_campaign=What%27sNew2020-03-24&utm_medium=email&utm_source=Eloqua) (accessed June 24, 2020).
- Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care.* 2020; 57:279-283.
- Korea Biomedical Review. <http://www.koreabiomed.com/news/articleView.html?idxno=7428>. Italian Society of Infectious and Tropical Diseases. Handbook for the care of people with disease-COVI 19. eds. 2.0, March 13, 2020
- Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends.* 2020; 14:72-73.
- Gautret P, Lagier JC, Parola P, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* 2020;105949.
- Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther.* 2020; 14:58-60.
- Nicastri E, Petrosillo N, Bartoli TA, Lepore L, Mondì A, Palmieri F, D'Offizi G, Marchioni L, Murachelli S, Ippolito G, Antinori A. National institute for the infectious diseases "L. Spallanzani", IRCCS. recommendations for COVID-19 clinical management. *Infect Dis Rep.* 2020; 12:8543.
- Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, Ling Y, Huang D, Song S, Zhang D, Qian Z, Li T, Shen Y, Lu H. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. <http://www.zjujournals.com/med/CN/10.3785/j.issn.1008-9292.2020.03.03> (accessed June 24, 2020). (in Chinese)
- Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B, Zhang Z. Efficacy of hydroxychloroquine in patients with COVID-19: Results of a randomized clinical trial. *MedRxiv.* 2020; doi: <https://doi.org/10.1101/2020.03.22.20040758>.
- Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W. Hydroxychloroquine in patients with COVID-19: An open-label, randomized, controlled trial. *MedRxiv.* 2020; DOI: 10.1101/2020.04.10.20060558 .
- Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): Chloroquine or hydroxychloroquine. *Int J Antimicrob Agents.* 2020; 55:105945.
- Lim HS, Im JS, Cho JY, Bae KS, Klein TA, Yeom JS, Kim TS, Choi JS, Jang IJ, Park JW. Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by *Plasmodium vivax*. *Antimicrob Agents Chemother.* 2009; 53:1468-1475.
- Jorge AM, Melles RB, Zhang Y, Lu N, Rai SK, Young LH, Costenbader KH, Ramsey-Goldman R, Lim SS, Esdaile JM, Clarke AE. Hydroxychloroquine prescription trends and predictors for excess dosing per recent ophthalmology guidelines. *Arthritis Res Ther.* 2018; 20:133.
- Chang R, Sun WZ. Repositioning chloroquine as ideal antiviral prophylactic against COVID-19 – time is now. *Preprints.* 2020; 2020030279 (doi: 10.20944/preprints202003.0279.v1)
- Sheahan TP, Sims AC, Leist SR, *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun.* 2020; 11:222.
- Siegel D, Hui HC, Doerffler E, *et al.* Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo [2, 1-f][triazin-4-amino] adenine C-nucleoside (GS-5734)

- for the treatment of Ebola and emerging viruses. *J Med Chem.* 2017; 60:1648-1661.
25. Warren T, Jordan R, Lo M, *et al.* Nucleotide prodrug GS-5734 is a broad-spectrum filovirus inhibitor that provides complete therapeutic protection against the development of Ebola virus disease (EVD) in infected nonhuman primates. *Open Forum Infect Dis.* 2015; 138:311-320.
  26. Holshue ML, DeBolt C, Lindquist S, *et al.* First case of 2019 novel coronavirus in the United States. *N Engl J Med.* 2020; 382:929-936.
  27. Severe 2019-nCoV remdesivir RCT. <https://clinicaltrials.gov/ct2/show/NCT04257656> (accessed February 13, 2020).
  28. Mulangu S, Dodd LE, Davey RT Jr, *et al.* A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med.* 2019; 381:2293-2303.
  29. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JSM, Yuen KY. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. *Thorax.* 2004; 59:252-256.
  30. de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, Van Den Hoogen BG, Neyts J, Snijder EJ. Screening of an FDA-approved compound library identifies four small molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother.* 2014; 58:4875-4884.
  31. Chan JFW, Yao Y, Yeung ML, *et al.* Treatment with lopinavir/ritonavir or interferon- $\beta$ 1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis.* 2015; 212:1904-1913.
  32. Kim UJ, Won EJ, Kee SJ, Jung SI, Jang HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon- $\alpha$  for Middle East respiratory syndrome. *Antivir Ther.* 2016; 21:455-459.
  33. Cao B, Wang Y, Wen D, *et al.* A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med.* 2020; 382:1787-1799.
  34. Ko JH, Seok H, Cho SY, *et al.* Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: A single center experience. *Antivir Ther.* 2018; 23:617-622.
  35. World Health Organization (WHO). Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks. 2014. <https://www.who.int/csr/resources/publications/ebola/convalescent-treatment/en/> (accessed June 24, 2020).
  36. Arabi Y, Balkhy H, Hajeer AH, *et al.* A. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: A study protocol. Springerplus. 2015; 4:709.
  37. Lee PI, Hsueh PR. Emerging threats from zoonotic coronaviruses—from SARS and MERS to 2019-nCoV. *J Microbiol Immunol Infect.* 2020; 53:365-367.
  38. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis.* 2020; 20:398-400.
  39. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest.* 2020; 130:1545-1548.
  40. News. China puts 245 COVID-19 patients on convalescent plasma therapy. [http://www.xinhuanet.com/english/2020-02/28/c\\_138828177.htm](http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm) (accessed March 10, 2020).
  41. Duan K, Liu B, Li C, *et al.* The feasibility of convalescent plasma therapy in severe COVID-19 patients: A pilot study. medRxiv. 2020; doi: <https://doi.org/10.1101/2020.03.16.20036145>.
  42. Shen C, Wang Z, Zhao F, *et al.* Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA.* 2020; 323:1582-1589.
- Received May 24, 2020; Revised June 25, 2020; Accepted June 27, 2020.
- \*Address correspondence to:  
Bushra Hassan Marouf, Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Sulaimani, Kurdistan Region, Iraq.  
E-mail: bushra.marouf@univsul.edu.iq