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Submission date: 19-May-2022 01:15PM (UTC-0400)
Submission ID: 1839972581
File name: covid19-drug-development-and-kidney-related-problems.pdf (1.24M)
Word count: 5922
Character count: 33389

Sys Rev Pharm 2020;11(7):106-112
A multifaceted review journal in the field of pharmacy

COVID-19: Drug Development and Kidney Related Problems

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ABSTRACT

Coronavirus Disease-2019 (COVID-19) is an extremely contagious disease affecting almost every country in the world. This disease makes some problems in the health system, society, politics, and economy. Several reports showed that mortality in COVID-19 patients was related to abnormal kidney function. This condition should be considered to prevent death. Some investigational drugs are on the way in the preclinical and clinical trials. Some of them no have a study for safety in the kidney especially in chronic kidney disease patients including those who undergo hemodialysis. Some give a satisfying effect. Understanding COVID-19, kidney diseases, and drugs will help us to get the most potent treatment.

Keywords: COVID-19, investigational drugs, kidney disease

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INTRODUCTION

One of the life-threatening coronavirus diseases is first identified in late 2019 from Wuhan, China, and trigger some outbreaks in China and expanded globally.[1,2] The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and officially named by WHO on early February 2020, as Coronavirus Disease-2019 (COVID-19). Recent studies show no established therapy for the disease although some drugs are under discovery and developpent.[3] To prevent more spreading, the health authorities should concern the history of contact or travel of the patient with relatable signs and symptoms.[4,5]

The WHO whistled a public health emergency alarm on January 30, 2020. Some protocols and procedures were given globally. WHO warned transmissions may occur via contact and droplets. Nosocomial infections occurred and need proper infection control in healthcare facilities.[4]

The COVID-19 manifestation commonly mimic respiratory tract infection.[6] Diagnosis for COVID-19 needs laboratory confirmation and should be performed with up to biosafety level 3 in a well-equipped laboratory facilities for the viral culture. The diagnosis commonly uses a reverse transcription polymerase chain reaction (RT-PCR) method to detect viral RNA. Imaging with chest radiography and computed tomography (CT) of chest usually demonstrate bilateral pneumonia (75–98%) with ground-glass opacity and multiple mottling. Laboratory data from COVID-19 patients show similarity to other viral infection: elevated liver enzymes, total bilirubin, lymphopenia, lactate dehydrogenase, and prolonged prothrombin time. Patients in the intensive care unit have worse data. Secondary bacterial infection may occur and induce leukocytosis.[7,8]

COVID-19 AND KIDNEY DISEASE

COVID-19 may damage the kidney and shows the incidence of acute kidney injury (AKI) around 3%–9%. Some studies reveal higher rates of kidney abnormalities. A recent study found massive albuminuria in 34% of 59 patients on the first day of hospitalization with COVID-19, and more than 60% of them proteinuria occur during treatment in the hospital. Blood urea nitrogen also increases by more than a quarter and two-thirds of death patients. The kidney CT scan reveals density reduction with the sign of inflammation and edema.[1]

Patients with COVID-19 mortality were affected by abnormal kidney function. A study from China show of 701 patients with COVID-19 admitted; 113 (16.1%) of them died in hospital, about 44% of them had proteinuria and hematuria and 27% had hematuria on the first admission. The increase of blood urea nitrogen (14.4%) and creatinine serum (13.1%). There are more than 13% of patients with less than 60 ml/min/1.73m^2 estimated glomerular filtration rate (eGFR). AKI occurred in about 5% of patients based on the data. AKI was a main risk factor for the patient's death in hospitalized patients (hazard ratio (HR): 2.10, 95% confidence interval (CI): 1.36-3.26).[1]

The mechanism of kidney worsening in COVID-19 is not described well yet. Proposed mechanisms such as sepsis with direct cellular damage or cytokine storm syndrome caused by the virus. Angiotensin-converting enzyme (ACE) expressed by renal tubular cells were suspected as binding sites for MERS-CoV and SARS-CoV-2. Viral RNA of coronavirus was found in urine and kidney tissue. The urine sample of a patient with COVID successfully isolated and suggesting SARS-CoV-2 has some damage to the kidney.[1]

CURRENT COVID-19 POTENTIAL DRUG OPTIONS

There is no verified therapy for COVID-19 yet. The existing modalities are symptomatic and supportive treatment only and treat complications, such as organ dysfunction and secondary infections. Because this disease is a life-threatening, many studies investigate the best possible treatment in combating COVID-19. The efficacy and safety of these potential treatments should be validated in good preclinical and clinical trials. Table 1 shows some potential drugs for COVID-19 and how to use in kidney disease.[4,5]

Potency of some antimicrobials against SARS-CoV-2

Chloroquine is commonly used as an autoimmune disease and antimalarial therapy. It has some immunomodulating properties. Its antiviral mechanism is suggested as the result of its action in inhibiting viral enzymes such as virus assembly, viral DNA and RNA polymerase, particle transport, protein glycosylation, and release of virus. It also inhibits cellular receptor of ACE2, immunomodulation of cytokine release and inhibiting fusion of the virus. A study proves chloroquine has activity to inhibit SARS-CoV-2 in preclinical data (*in vitro*).[9–11] Chloroquine is in clinical trial phase IV. For the COVID-19 case, the drug should be given after the hemodialysis session. One of the renal adverse events is renal lipidosis. Chloroquine has some issues for treatment, among them, are risk of prolonged QT interval, retinal damage, glucose-6-phosphate dehydrogenase deficiency (G6PD), awareness in diabetics and significant drug interactions, especially with long term use.[12,13]

Hydroxychloroquine (HCQ) is a derivate of chloroquine and also commonly used drug for malaria and autoimmune disease. Mechanisms of HCQ may include viral enzymes inhibition include assembly of virus, DNA and RNA polymerase, particle transport, virus release, and viral protein glycosylation. Other mechanisms may also involve immunomodulation of cytokine release, inhibition of ACE2 cellular receptor and inhibit fusion of the virus.[14,15]

HCQ has activity to inhibit SARS-CoV-2 based on *in vitro* experiment. One study shows that HCQ shows a more potent antiviral effect compared to chloroquine. The half-maximal effective concentration (EC50) values for HCQ are better than the EC50 values for chloroquine.[14] A study with an open-label design, the non-randomized clinical trial study that compares HCQ treatment to placeboshows that the proportion of negative PCR patients was higher in HCQ group significantly compare to those in placebo-treated patients. Seventy percent of patients with HCQ were virologically cured compared to only 12.5% in the untreated group on day 6. Some supplementary related to clinical efficacy of HCQ for COVID-19 are being evaluated.[14,15]

A recent study evaluates the efficacy of HCQ for patients with COVID-19. Among them, 31 patients were given additional 5-day HCQ 400 mg once daily treatment compared to control. Time to clinical recovery (TTCR), the cough remission time and the body temperature recovery time were significantly better in the HCQ treatment group. Also, patients with pneumonia improvement in the HCQ treatment group (80.6%) are better compared to the control group (54.8%).[16]

There are some safety issues related to HCQ, almost similar with chloroquine: risk of QT prolongation, retinal damage, caution in patients with G6PD deficiency, diabetics and significant drug interactions. HCQ is in clinical trial phase III.[17] For the COVID-19 case, it should be given after the hemodialysis session. The renal adverse events are renal lipidosis and raise proteinuria.[13] No more use these drugs both chloroquine and hydroxychloroquine, to against COVID-19 from WHO.

A combination of drugs for the human immunodeficiency virus (HIV) treatment named lopinavir/ritonavir may have potency to treat COVID-19..[18] A report from Chu *et al.* showed that the combination has some activities to interfere the activity of SARS-CoV-2 in *in vitro* and clinical studies. Ribavirin, a broad-spectrum nucleoside analog with antiviral effects may be a candidate to cure COVID-19. A study reported treatment with lopinavir/ritonavir and ribavirin in 41 patients with severe acute respiratory syndrome (SARS) had a lower risk of acute respiratory distress syndrome (ARDS) and death compared to 111 patients with SARS and treated by ribavirin monotherapy.[9]

Lopinavir/ritonavir is on clinical trial phase IV/III. It can be given at a normal dosage after the hemodialysis session for COVID-19 infection. The renal adverse event is AKI. There are some safety concerns for these drugs include the risk of prolonged QT interval, awareness in patients with liver disease and drug interactions.[18,19]

A study with 199 COVID-19 patients with open-label, randomized, controlled, trial method showed the lopinavir/ritonavir treatment for 14 days was not significantly different from the standard of care (HR 1.24; 95% CI, 0.9 to 1.72) in the time to clinical improvement. There was not significantly different from mortality at 28 days between the two groups (19.2% *vs* 25%, respectively). ITT analysis of lopinavir/ritonavir had a median time to clinical improvement that was better by 1 day (HR, 1.39%; 95% CI, 1 to 1.91). Therefore The European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) Surviving Sepsis Campaign do not recommend routine use of lopinavir; ritonavir in critically ill COVID-19 patients.[20]

Favipiravir is an inhibitor of RNA-dependent RNA polymerase (RdRp). Favipiravir may inhibit the replication of some RNA viruses. It is metabolized into a phosphoribosylated form, a prodrug active in cells and it is identified as a substrate by viral RNA polymerase, thus inhibit RNA polymerase activity. Based on some studies, favipiravir may have antiviral role on COVID-19. It was approved in China for COVID-19 therapy on February 2020. This drug is on clinical trials to treat COVID-19. The preliminary data showed that favipiravir had better potency as antiviral compared to the lopinavir/ritonavir from a total of 80 patients. Favipiravir treatment group had significantly lower adverse events compared to the lopinavir/ritonavir treatment.[9,21] This study recently *temporarily removed* and the reason for the removal of the article will be specified, or the article will be reinstated.[21] There is no dose adjustment and renal adverse event-related data reported yet, but it has potential mitochondrial toxicity.[19]

Remdesivir is one of the novel nucleotide analog prodrugs for SARS and Ebola treatment (unapproved yet). A case report from the United States on the first case of COVID-19 used remdesivir on day 11 after illness improves the clinical condition and viral loads decrease in nasopharyngeal and oropharyngeal samples However the safety and efficacy of this drug for COVID-19 therapy in randomized controlled trials is not well-established yet.[4] A report from Wang *et al.* showed that remdesivir can inhibit SARS-CoV-2 infection at low-micromolar concentrations.[22] Current study related remdesivir treatment for severe hospitalized patients with COVID-19 found better clinical outcomes in more than one-third of patients. The patients were administered remdesivir for 10 days (day 1 200 mg,

followed by 100 mg daily). From 53 patients analyzed, 30 patients were on mechanical ventilation and 4 patients with extracorporeal membrane oxygenation. Until the end of follow-up,25 patients were discharged from hospital and 7 patients passed away. Among patients with invasive ventilation, the mortality was 18% (6 of 34) and 5% (1 of 19) without invasive ventilation.[23] Remdesivir is on clinical trial phase III on February 5, 2020, in China. There is no dose adjustment and renal adverse event reported yet, but it also has potential mitochondrial toxicity.[19]

A recent study in China showed darunavir may inhibit SARS-CoV-2 ac *in vitro*. Darunavir is a second-generation drug of HIV-1 protease inhibitors. Cell experiments showed that darunavir can inhibit viral replication significantly and the inhibition was 280-fold compared to the untreated group.[5] Darunavir is on clinical trial phase II/III. It may be given at common dosage and regardless of hemodialysis session for COVID-19 infection. The renal adverse events are nephrolithiasis dan elevation of creatinine level.[19]

Imatinib is a type II transmembrane serine protease (TMSPSS2) inhibitors.[24,25] A study from Hoffmann *et al.* indicated that SARS-CoV-2 uses ACE2 and the cellular protease TMPRSS2 to invade target cells. Imatinib potentially blocks entry and inhibits the fusion to the endosomal membrane. There are no data for renal impairment in the COVID-19 related to imatinib yet.[9,26]

Tocilizumab is an inhibitor monoclonal antibody receptor of interleukin-6 (IL-6). IL-6 is a proinflammatory cytokine plays important roles in various physiological processes. Various cell types produced IL-6 including monocytes, T and B cells, and fibroblasts. Tocilizumab blocks IL-6-mediated signaling by competitively binding to IL-6 receptors.[5]

A retrospective study showed from 21 patients with tocilizumab were added to standard COVID-19 therapy may have clinical benefit as adjunctive therapy. Patients got improvement from clinical symptoms, lymphocyte percentage, C- reactive protein levels, and CT opacity changes but no comparators were reported. Additional data related to clinical efficacy and safety for COVID-19 are being investigated.[27] Tocilizumab may have gastrointestinal perforation risk, interfere hepatotoxicity, infusion-related reactions, thrombocytopenia, and neutropenia. Tocilizumab is on clinical trial phase IV. The renal adverse event is autoimmune glomerulonephritis. This drug may be given at the common dosage and regardless of hemodialysis session for COVID-19 infection.[19]

Table 1. Potential drugs for the COVID-19, dosage adjustment in kidney disease and potential kidney damage.[19]

Drugs	Development status	Kidney disease dose adjustment	Adverse events related to kidney	References
Chloroquine	Phase IV	Dose adjustment based on standard recommendation. The drug is given after hemodialysis session.	Renal lipidosis	11,12,28
Hydroxychloroquine	Phase III	Dose adjustment based on standard recommendation. The drug is given after hemodialysis session.	Renal lipidosis	16,29
Lopinavir/ Ritonavir	Phase IV/III	The drug is given at common dosage and not affected by hemodialysis schedule	Reversible AKI	17,18
Darunavir	Phase II/III	The drug is given at common dosage and not affected by hemodialysis schedule	Nephrolithiasis and false creatinine level increase	19,30
Favipiravir	Phase II	No available data yet	No available data yet. Related to mitochondrial toxicity	17,21
Remdesivir	Phase III	No available data yet	No available data yet. Related to potential mitochondrial toxicity	22,31
Tocilizumab	Phase IV	The drug is given at a normal dosage	No available data yet	27,32

Some studies evaluate the potential immunomodulatory agents (e.g., alfa-interferon, sarilumab) as adjunctive therapy. Corticosteroids for viral pneumonia are not recommended; however, it may be considered in patients with severe respiratory disorder or refractory shock.[33] Non steroid anti-inflammatory drugs (NSAIDs) are commonly used to relieve the symptoms of COVID-19. A published letter stated that ibuprofen may increase ACE2 expression and induce worse outcomes in COVID- 19 patients. COVID-19 symptoms worsening has been considered for NSAIDs use, but the data is insufficient. ESICM and SCCM Surviving Sepsis Campaign recommend acetaminophen in critically ill adults for temperature control.[4,20]

Azithromycin is a macrolide antibiotic with potential bacterial infection preventions and may have immunomodulatory features in pulmonary inflammatory disorders. It may reduce excessive cytokine production and downregulate inflammatory responses. Immunomodulatory properties may include reduction of neutrophil chemotaxis to the lungs by inhibiting cytokines, mucus hypersecretion reduction, reactive oxygen species product reduction, increase neutrophil apoptosis, and inhibition of nuclear transcription factors activation.[5,29]

Azithromycin was administered in combination with hydroxychloroquine in a non-randomized clinical trial, open label (n = 26) to prevent bacterial infection in 6 patients. The data show the azithromycin potency as an

adjunct therapy. A combination of HCQ and azithromycin results in 100% patient virologically cured on day 6. Meanwhile, only around half of patients treated with HCQ (n= 20) were having negative PCR results.[29] However, azithromycin may increase the risk of prolonged QT interval and significant drug interactions.[34]

The COVID-19 pandemic may interfere with antibiotic availability. Environmental microbiologists warned that excessive antibiotic use would lead to more bacterial infection resistance. This condition not only for pneumonia with bacterial causes but also for other diseases. Azithromycin's uncontrolled use for typhoid in Pakistan could compromise the treatment of an extensively drug-resistant outbreak. The resistance is not followed by the development of new antibiotics.[35,36]

Convalescent plasma therapies are withdrawn from persons who have recovered from SARS-CoV-2that may contain antibodies are also suggested as a COVID-19 potential therapy. Currently, clinical trials are being investigated to evaluate the effectiveness and safety from convalescent therapy to treat patients with severe or immediately life-threatening SARS-CoV-2 infections. Case series of 5 critically ill COVID-19 patients with convalescent plasma treatment showed some improvements in their clinical status.[37,38] Currently, COVID-19 convalescent plasma is not indicated for prevention.[38]

There is no vaccine available yet to prevent COVID-19 infection. The spike protein is a potential vaccine, but the efficacy and safety to the human requires further investigation.[4,39]

Eurycoma longifolia as Candidate Treatment for COVID-19

Several recent studies showed more than 30 agents from Western medicines, natural products, and traditional Chinese medicines may have potential efficacy against SARS-CoV-2.[9] Some of them have been tested in clinical studies and demonstrated preliminary efficacy against SARS-CoV-2. In Indonesia, there is *Pasak Bumi* (*Eurycoma longifolia*) Jack is a popular traditional herbal medicine for aphrodisiac effects as well as intermittent fever likely malaria in Indonesia.[40] *Pasak Bumi* is a flowering plant of the family *Simaroubaceae*, also native to Malaysia (as *Tongkat Ali*), Vietnam, Cambodia, Myanmar, Laos and Thailand (Fig. 1). *Pasak Bumi* has demonstrated antiviral activity.[41,42] *Eurycoma longifolia* have effect to treat *herpes simplex virus* 1 infection about reducing plaque formation.[43] Further research is needed to prove this effect to COVID-19. *Pasak Bumi* (*Eurycoma longifolia*) can be a candidate drug or complimentary or/and an alternative medicine to against COVID-19 should be considered to get the best treatment in the population.

Figure 1. *Eurycoma longifolia* (a) tree (b) root and (c) capsule formulation. (adapted and modified from Rehman *et al.,* 2016[40] dan Bhat *et al.,* 2010[44])

Is *ivermectin* a new hope for COVID treatment?

Ivermectin is a widely used anthelmintic drug to treat parasitic worms and insect pest's infection in humans and animals. Ivermectin is an FDA approved drug that has the activity to prevent the multiplication of the SARS-CoV-2 *in vitro*.[45] The treatment may reduce the virus around 5000-fold in cell culture at 48h. Ivermectin is considered interfere the host nuclear transport importin α/β1 heterodimer and inhibits the nuclear entry of the virus. There are no data for renal impairment related to ivermectin in the SARS-CoV-2 infection yet.[46,47]

ACE Inhibitor and SARS-CoV-2

Some patients are at risk of COVID-19, include patients with diabetes mellitus. hypertension chronic kidney disease, heart disease, and the elderly. Those patients commonly are treated with some renin-angiotensin system blockers. Some studies show that ACE2 protein facilitates coronavirus entry into cells and treatment with renin-angiotensin system blockers may increase the risk of SARS-CoV-2 infection.[48] ACE2 plays a role in the degradation of several substances including angiotensin I and II. ACE inhibitors do not inhibit ACE2 because ACE and ACE2 are different enzymes. Animal data showed that elevation of ACE2 expression as conferring potential protective pulmonary and cardiovascular effects.[49] Based on the recent evidence, AHA, ESC recommends continuing treatment with renin-angiotensin system blockers in concerns of coronavirus infection.[50–53]

Prevention

It is very important to get rid of infection or further spreading because there is no standard therapy for COVID-19 yet. For healthcare staff, proper use of personal protective equipment should be trained. Effective treatment against coronavirus includes heat and steam. The virus also sensitive to many active ingredients include 70% ethyl alcohol, povidone-iodine (1% iodine), sodium hypochlorite (0.1%–0.5%), etc.[4] For people, contact to COVID-19 patients, travel to the epidemic area of COVID-19, or eating wild animal are prohibited.[4,7,24]

A lot of medical professionals have died tragically during the COVID-19 epidemic. There are more than 70 doctors died in Indonesia till the end of July 2020. The lack of personal protective equipment, inability to detect suspicious COVID-19 patients, the lies and ignorance of the people are supposed to be the cause of this sad disaster.[54,55]

CONCLUSION

COVID-19 is a life-threatening disease. Recent works of literature show no well-established therapy for the disease and supportive strategies were the best we can do. Many experimental drugs are investigated, and the most appropriate strategy is to prevent the worsening of outbreak and infection control. The investigational drugs give us some hope to cure the disease although it is still a long way to go. Kidney involvement in COVID-19 should be considered to get the best treatment in the population.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflicts of interest related to the manuscript.

ACKNOWLEDGMENTS

This work was supported by the Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia. We thank our colleagues for their contributions.

AUTHOR CONTRIBUTIONS

MR made the review and drafted the manuscript. HWN and DAAN provided the critical analysis of drugs. RB and RMAR wrote the discussion and impact about kidney disease. All authors have approved the final manuscript.

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