Review Article

Current and Repurposing Medication for SARS-CoV-2 Infection

Kittiya Jantarathaneewat[1], Korakoch Kangwantas[1], Nattapong Tidwong[2]

Abstract

In the crisis of COVID-19 pandemic, there is no specific agent to treat SARS-CoV-2 infection. Repurposing medication can be an alternative agent. Remdesivir is the first antiviral drug that has been approved for COVID-19 treatment whereas lopinavir/ritonavir and hydroxychloroquine, which was early used in SARS-CoV-2 widespread, are against by well-known guidelines due to lack of efficacy and potential toxicity. Corticosteroids are an essential supportive care in COVID-19 patient with severe disease to reduce lung inflammation. Favipiravir may have a potential benefit for COVID-19 patient, but the data is still uncertain. Ivermectin, an antihelmintic agent, may be used against SARS-CoV-2 but further studies are needed. Immunomodulatory such as tocilizumab in combination with dexamethasone can be used for reducing inflammatory storm during severe COVID-19. Baricitinib is considered as an alternative agent for patients with COVID-19. Repurposing drugs with possible mechanism against SARS-CoV-2 are essential key to combat with SARS-CoV-2 during the specific medications under investigation.

Keywords: SARS-CoV-2, COVID-19, Repurposing agents, Antiviral, Remdesivir

Received: 7 July 2021 **Revised: 24 August 2021** **Accepted: 26 August 2021**

[1] Department of Pharmaceutical care, Faculty of Pharmacy, Thammasat University, Pathum Thani 12120, Thailand
[2] Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand
Corresponding author: Korakoch Kangwantas, Department of Pharmaceutical care, Faculty of Pharmacy, Thammasat University, Pathum Thani 12120, Thailand Email: korakoch@staff.tu.ac.th

Introduction

The burden of Coronavirus disease 2019 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has affected worldwide public health. As of June 2021, more than 180 million COVID-19 cases have been confirmed including 3.9 million death.[1] SARS-CoV-2 belongs to Coronaviridae family which can cause respiratory and gastrointestinal infection. This SARS-CoV-2, also Middle East respiratory syndrome coronavirus (MERs) and Severe Acute Respiratory Syndrome-associated Coronavirus (SARS-CoV), are categorized as causes of severe diseases leading to death in human. The presentations of SARS-CoV-2 infection range from asymptomatic and acute upper respiratory disease to severe multiorgan failure. Due to the potential of asymptomatic carriers, this coronavirus can transmit from human-to-human effectively via respiratory droplet and close contact and spread globally since 2019.[2] Since there is no specific medication for COVID-19 treatment, urgent repurposing drugs for COVID-19 are essential. In this review, we aimed to summarize the current and repurposing medication for the treatment of SARS-CoV-2 infection.

SARS-CoV-2 mechanism of infection

SARS-CoV-2 entering the host cell is mediated by viral proteases and the binding activity of transmembrane spike (S) protein to the host cell receptor angiotensin-converting enzyme 2 (ACE2). Then, the virus forms endosomes, releases its genome to cytoplasm and replicates. After that, the new virus particle is assembled and budded to the extracellular environment. SARS-CoV-2 has a similar structure to many familiar viruses such as hepatitis B, hepatitis C, human immunodeficiency virus (HIV) and other coronaviruses. Repurposing medication, which has a detrimental effect on previously mentioned viruses, is also one of the most reasonable strategies during this urgent situation. In aspect of immune response in COVID-19, these patients have an immune response dysregulation which can lead to viral hyperinflammation and may cause cytokine storm. Moreover, COVID-19 can cause abnormal blood coagulation which leads to severe symptoms and death.[3] These negative effects on immune response and blood clotting may be promising targets for drug development to alleviate the effect of COVID-19 immune response dysregulation. However, the process of these novel drug development against COVID-19 may take a long period of time to prove efficacy and safety in human.

Current and repurposing medication according to drug classes

Antiviral agents

Favipiravir

Favipiravir was first discovered in Japan and has been approved for the treatment of novel or re-emerging influenza virus since 2014. Favipiravir has an activity against RNA viruses such as Rhinovirus, Ebolavirus, and Flavivirus.[3] Moreover, favipiravir has potent viral activity against SARS-CoV-2 and its half-maximal effective concentration (EC_{50}) against the virus is 61.88 μM. Favipiravir is a purine base analog which is then converted into an active form, favipiravir ribofuranosyl-5B-triphosphate (RTP) via intracellular phosphoribosylation. RTP is a selective potent inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA virus resulting in chain termination.[4] Favipiravir has a non-linear pharmacokinetic property and is metabolized mainly by aldehyde oxidase and partly by xanthine oxidase. Moreover, favipiravir can reversibly inhibit aldehyde oxidase and CYP2C8 enzyme. Significant drug interactions are described in Table 1. The recommended dosage of favipiravir is 1,800 mg every 12 hours on the first day, followed by 800 mg every 12 hour until the treatment course is complete, usually 5-14 days. The common adverse reactions include gastrointestinal disturbance, uric acid elevation and increase of liver function test. Dosage adjustment for patient with renal impairment is unnecessary but the dosage regimen for patient with severe liver impairment (defined as Child-Puge C) should be adjusted[4] (Table 2). Patient with history of gout or hyperuricemia should be treated with caution during favipiravir administration. Pregnancy during first trimester is contraindicated because of teratogenicity in animal studies.[5] Favipiravir is recommended as a first line therapy in Thailand national guidelines to treat patient with symptomatic COVID-19 with or without pneumonia[6] and it is approved to use in several countries such as Russia, Indonesia, and India.[7] In contrary, National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) do not recommend favipiravir as a

Table 1 Significant interaction between medication for SARS-CoV-2 infection and concomitant medications

Medication	Mechanism of interactions	Example of co-medications	Effect
Favipiravir	inhibit aldehyde oxidase	famciclovir, sulindac	decrease of concomitant drug level
	inhibit CYP2C8	repaglinide	increase of concomitant drug level
	interaction with xanthine oxidase	theophylline	increase of favipiravir level
Remdesivir	CYP3A4, OATP1B1, P-glycoprotein substrate	no relevant significant drug interaction via CYP450	
	CYP3A4, OATP1B1, OATP1B3, MATE1 inhibitor	no relevant significant drug interaction via CYP450	
Lopinavir/ritonavir	potent inhibitor of CYP3A	ergot derivatives, simvastatin, sildenafil, triazolam, dexamethasone	increase of plasma concomitant drug level
Ivermectin	p-glycoprotein and CYP3A4 substrates	no relevant significant drug interaction via CYP450	
Hydroxychloroquine, chloroquine	exhibit antagonist effect on the intracellular metabolic activation and antiviral activity of remdesivir	remdesivir	diminish the therapeutic effect of remdesivir
Tocilizumab	downregulates CYP450 enzyme	oral contraceptives, lovastatin, atorvastatin	decrease of concomitant drug level
Baricitinib	OAT3 substrate	probenecid	increase of baricitinib level
Dexamethasone	moderate CYP3A4 inducer CYP3A substrate	voriconazole	decrease of concomitant drug level
	unclear	warfarin	enhance effect of warfarin

CYP, Cytochrome P450; OAT, Ornithine aminotransferase; MATE, Multidrug and toxic compound extrusion

Table 2 Dosage adjustment of recommended medication for SARS-CoV-2 in renal and liver impairment

Medication	Usual dose	Renal impairment	Liver impairment
Favipiravir	1,800 mg every 12 hours in first day, follow by 800 mg every 12 hours	No dosage adjustment necessary	Child-Pugh C: 800 mg every 12 hours in first day, follow by 400 mg every 12 hours
Remdesivir	200 mg IV loading dose, follow by 100 mg IV every 24 hours	eGFR ≥ 30 ml/min: No adjustment eGFR < 30 ml/min: Not recommended	No dosage adjustment necessary
Tocilizumab	Single dose of tocilizumab 8 mg/kg (actual body weight) IV (maximum dose 800 mg)	No dosage adjustment necessary	Not recommended in patient with baseline ALT or AST more than 5 times of upper normal limit
Baricitinib	4 mg daily in combination with remdesivir	eGFR 30 to < 60 ml/min/1.73 m^2: 2 mg daily eGFR 15 to < 30 ml/min/1.73 m^2: 1 mg daily eGFR < 15 ml/min/1.73 m^2: Not recommended	No dosage adjustment necessary
Dexamethasone	6 - 20 mg of dexamethasone for at least 5 - 7 days	No dosage adjustment necessary	No dosage adjustment necessary

IV, intravenous; eGFR, estimated glomerular filtration rate; AST, Aspartate transaminase; ALT, alanine transaminase
Adapted from: Marra F, Smolders EJ, El-Sherif O, et al. Recommendations for Dosing of Repurposed COVID-19 Medications in Patients with Renal and Hepatic Impairment. *Drugs R D.* 2021;21(1):9-27.

first line therapy for COVID-19 due to lack of large relevant study to show the benefits of favipiravir on clinical outcomes and viral clearance.[8, 9]

Many studies show the effectiveness of using favipiravir in COVID-19 patients.[10-12] Patients who received favipiravir had shorter mean time of viral clearance than lopinavir/ritonavir group.[10] A randomized controlled trial study in China found that participants who received favipiravir with standard treatment had better clinical recovery in day 7 compared with patients who received umifenovir (arbidol) with standard treatment.[11] In a meta-analysis study, favipiravir showed significantly higher rate of clinical improvement in day 7 (P = 0.04) and 14 (P = 0.005) compared with other antivirals agents or standard of care (e.g., protease inhibitors, hydroxychloroquine, or arbidol). However, there are no significant differences between the two groups on viral clearance, clinical deterioration, oxygen support requirement, and adverse effects.[12]

Remdesivir

Remdesivir was approved by the United States Food and Drug Administration (USFDA) for COVID-19 treatment in October 2020. Initially, remdesivir was developed for Ebola hemorrhagic fever. *In vitro* and *in vivo* animal data showed that remdesivir had an activity against coronaviruses including MERS, SARS-CoV, and SARS-CoV-2. Remdesivir is a prodrug of an adenosine analog which is metabolized in cells and tissues into an active drug.[13] It binds to viral RNA-dependent RNA polymerase and inhibits viral replication by RNA transcribing termination.[14] Remdesivir has linear pharmacokinetics and short plasma half-life. Therefore, a loading dose in the first day of therapy is essential.[15] The recommended dosage regimen is 200 mg on the first day, followed by 100 mg every 24 hours. Remdesivir has no significant drug interaction when concomitantly administer with other medications (Table 1). Remdesivir is mainly excreted by the kidney and its intravenous form contains an excipient called sulfobutylether betacyclodextrin sodium (SBECD) which is also primarily eliminated by the kidney. This intravenous drug should be used with caution in patients with renal impairment[9, 16] (Table 2). However, a recent report showed that remdesivir was well tolerated in patient with acute kidney injury or chronic kidney disease including hemodialysis.[17] Common side effects of remdesivir includes nausea, liver function test elevation, and infusion reactions.[13]

There have been many studies proving the effectiveness of remdesivir in COVID-19 treatment.[18-20] A multinational randomized controlled trial found that patients with severe COVID-19 receiving remdesivir required shorter recovery time and gained higher clinical improvement compared to the placebo group. However, no statistical difference in all-cause mortality was detected (hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.52 - 1.03).[19] Spinner, et al. trial also showed that patients who received remdesivir had better clinical outcomes than the standard of care, although the difference of mortality rates between these two groups was not observed (may be due to low mortality rate).[20] The recent meta-analysis showed that remdesivir group had higher clinical improvement and clinical recovery compared to control group. Moreover, lower 14-day mortality rate was observed in remdesivir group (odd ratio (OR) 0.61, 95%CI 0.41 - 0.91).[21] Notably, the SOLIDARITY trial did not show a significant reduction in mortality for remdesivir monotherapy (rate ratio 0.95, 95%CI 0.81 - 1.11). The possible reason was small numbers of deaths.[18] The benefit of remdesivir was apparently shown in hospitalized patients who needed supplemental oxygen.[19] Correspondingly, remdesivir is recommended in relevant guidelines such as IDSA and NIH for patients who required supplemental oxygen or has severe symptoms but not for patients with mild symptoms.[8, 9]

Lopinavir/ritonavir

Lopinavir/ritonavir has been approved antiretroviral agent for HIV infection. *In vitro* data suggested that lopinavir/ritonavir was a potential agent against SARS-CoV-2 due to supported data on similar coronaviruses including SARS-CoV and MERS.[22] Lopivinavir/ritonavir can inhibit viral entry by binding with 3C-like protease (3CL pro) in SARS-CoV-2 infected cell.[23] However, the plasma concentration of lopinavir/ritonavir to achieve the therapeutic level for inhibiting SARS-CoV-2 replication is 60- to 120- fold higher than the usual dose (lopinavir 400 mg/ritonavir 100 mg administered every 12 hours).[24] Furthermore, lopinavir/ritonavir did not show clinical efficacy (e.g., reduce length of

stay and initiation of ventilation) and did not reduce mortality, in COVID-19 patients in two randomized controlled trials.[18, 25] Therefore, several guidelines do not recommend the use of lopinavir/ritonavir for COVID-19 patients.[8, 9]

Antiparasitic agents

Ivermectin

Ivermectin is an antiparasitic agent used to treat malaria, trypanosomiasis, and leishmaniasis. An *in vitro* data showed that the half-maximal inhibitory concentration (IC_{50}) of ivermectin against SARS-CoV-2 was 2 μM.[26] The proposed mechanism of ivermectin against SARS-CoV-2 is inhibition of the host importin (IMP) alpha/beta-1 nuclear transport proteins which interfere intracellular infection process. Furthermore, ivermectin may hinder SARS-CoV-2 spike protein attachment to host cell membrane. However, the plasma ivermectin concentration in order to reach the therapeutic effect is 100 folds of conventional dose.[9] Ivermectin highly binds to serum protein (93%) which limits lung penetration and cellular uptake.[26] Ivermectin is also a p-glycoprotein and CYP3A4 substrates, but no significant drug interaction is reported (Table 1). The adverse effects of ivermectin, including dizziness, pruritis, nausea, and diarrhea, are well tolerated. Some studies reported benefits of ivermectin use including shorter time to resolution and viral clearance, greater reduction in inflammatory marker levels, and lower mortality rates when compared with standard of care or placebo.[27] On the other hand, some studies showed no benefit of ivermectin use in COVID-19 patients.[9] In recent meta-analysis study, most trials included mild patients, showed that ivermectin did not reduce all-cause mortality, length of stay, and viral clearance.[28] However, these results should be interpreted with caution due to lack of rigorous methodology randomized controlled trial to confirm the efficacy of ivermectin for COVID-19 treatment.[29] In IDSA and NIH guideline, ivermectin is not recommended for COVID-19 treatment due to insufficient data.[8, 9] Hence, further studies to evaluate ivermectin effectiveness is needed.

Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine are antimalaria agents. They possess immune-modulatory effects which can be used to treat autoimmune diseases like rheumatoid arthritis. These drugs can increase endosomal pH resulting in inhibition of SARS-CoV-2 fusion with the host cell membrane. Therefore, chloroquine analogs are considered as promising agents for COVID-19 treatment.[13] In the RECOVERY study, hydroxychloroquine did not decrease 28-day mortality and had a longer median length of hospital stay compared with standard of care.[30] Furthermore, the observational study did not find any significant clinical improvement compared with standard of care.[31] Hydroxychloroquine and chloroquine can cause QTc prolongation, especially when concomitantly administered with azithromycin. According to the current clinical benefit and toxicity of these drugs, many guidelines are against the use hydroxychloroquine and chloroquine for COVID-19 patients.[8, 9]

Immunomodulating agents

Tocilizumab

Tocilizumab is a recombinant humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody approved for rheumatic disease and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR T-cell) therapy. The mechanism of action is blocking the signal transduction of IL-6 leading to the reduction of inflammatory storm processed by SARS-CoV-2 infection. Tocilizumab plasma half-life is 4 days. Therefore, the recommended dose of tocilizumab is 8 mg/kg (actual body weight) single dose in combination with dexamethasone (Table 2). The maximum dose of tocilizumab is 800 mg. Tocilizumab down-regulates CYP450 enzyme. This inhibitory effect can persist for weeks thus there is some possible drug interaction when co-administered with other medications. The side effects of tocilizumab include infusion-related reaction (7 - 8%), hypertension (4 - 7%), alanine transaminase (ALT) level raised (3%), diarrhea (6%), constipation (6 - 13%), nausea (4%), neutropenia (1.8 - 3.7%), and thrombocytopenia (up to 4%).[32] For patients who live in the area where strongyloidiasis is endemic, ivermectin should be used as a prophylaxis prior to tocilizumab treatment. Tocilizumab should be avoided in patients who is severely immunocompromised, have the level of alanine aminotransferase more than 5 times of the upper limit of normal, have a high risk for gastrointestinal perforation or have an uncontrolled serious infection.[9]

The RECOVERY trial reported that tocilizumab can reduce 28-day mortality in severe or critical COVID-19 patients with hypoxemia (rate ratio 0.86; 95%CI: 0.77 - 0.96).[33] Similar result was also shown in the REMAP-CAP trial.[34] In tocilizumab group, participants also had significantly higher inflammatory response compared with the usual care group. Sarilumab has the same mechanism as tocilizumab. It was also included in REMAP-CAP trial but the number of participants in the study was small. Further investigation on the benefit of sarilumab is ongoing. The recommendation of IDSA and NIH suggest anti-IL-6 receptor such as tocilizumab use in combination with dexamethasone in case of patient who has severe or critical COVID-19.[8, 9]

Baricitinib

Baricitinib is an oral Janus kinase (JAK) 1/JAK2 inhibitor approved for rheumatoid arthritis. Inhibition of JAK1/JAK2 results in downregulation of inflammatory response. It also has a potential antiviral effect by blocking SARS-CoV-2 entry and inhibiting host lung cells infection. Baricitinib primarily metabolizes by hepatic CYP3A4 and eliminates through kidney. The recommended regimen is 4 mg per day orally in combination with remdesivir for 14 days. The dosage of baricitinib needs adjustment when administered to patient with renal impairment (Table 2). The dosage modification is also recommended when concomitantly administered with a strong OAT3 inhibitor such as probenecid. The adverse reactions of baricitinib includes ALT level raised (18%), AST level raised (11.5%), venous thromboembolism (3%), infectious disease (13%), herpes zoster (1%), and pulmonary embolism (1.4%).[35] Patient who has a high risk of thrombosis or gastrointestinal perforation should be used baricitinib with cautions. Baricitinib is contraindicated in patient who has severe renal or liver impairment, active tuberculosis and severe neutropenia (absolute neutrophil count less than 500 cells/microliter) or lymphopenia (absolute lymphocyte count less than 200 cells/microliter).[9] The ACTT-2 trial showed that baricitinib plus remdesivir improved recovery time and clinical status among COVID-19 patients who required supplemental oxygen but not invasive mechanical ventilation when compared with remdesivir monotherapy.[36] The IDSA recommends baricitinib in combination with remdesivir when corticosteroids are contraindicated in severe COVID-19 patients.[8] In NIH guideline, there is an insufficient data to recommend baricitinib use in practice but baricitinib combined with remdesivir may be used in hospitalized COVID-19 patients who corticosteroids cannot be administered.[9]

Corticosteroids

Corticosteroids are anti-inflammatory agents which may benefit among severe COVID-19 patients by reducing lung inflammation and lung injury that leads to acute respiratory distress syndrome (ARDS).[37] ARDS occurs in 20 - 42% in hospitalized COVID-19 patients and 67 - 85% in patients who admitted to an intensive care unit (ICU) with COVID-19.[38] The mechanism of action is binding to glucocorticoid receptor that plays role in the modulation of immune cells biological function. Corticosteroids can suppress proinflammatory cytokines, neutrophils, macrophages, and lymphocytes inflammatory activity. Corticosteroids are agonists at glucocorticoid receptors and/or mineralocorticoid receptors. Dexamethasone may be beneficial in ARDS due to its anti-inflammatory effects without mineralocorticoid properties. Dexamethasone is a moderate CYP3A4 inducer which may affect concomitant drugs that metabolize via CYP3A4 (Table 2). The adverse effects of corticosteroids such as hyperglycemia, secondary infections, and psychiatric effects should be concerned. The use of systemic corticosteroids can increase risk of fungal opportunistic infection (e.g., aspergillosis and mucormycosis), risk of *Strongyloides* hyperinfection, especially in tropical regions, and risk of hepatitis B virus reactivation.[9]

Recent studies in early ADRS patients found that initiation of a corticosteroid including methylprednisolone, hydrocortisone, or dexamethasone within 1 - 7 days of ARDS diagnosis can decrease ICU and overall mortality.[39-42] However, only the patients received dexamethasone showed reduction in 28-day all-cause mortality, particularly in patients who required mechanical ventilator or supplemental oxygen therapy.[38] The RECOVERY trial conducted a study in hospitalized patient who infected with SARS-CoV-2 virus and received either the usual standard of care alone or the usual standard of care plus oral or intravenous dexamethasone

(at a dose of 6 mg/day) for up to 10 days.[43] The result showed a benefit of dexamethasone in COVID-19 patients who required mechanical ventilation compared with standard of care (28-day mortality of 29.3% vs 41.4%, rate ratio 0.83, 95%CI: 0.75 - 0.93) but not among mild symptoms patients without respiratory failure (28-day mortality of 17.8% vs. 14%, rate ratio 1.19, 95%CI: 0.92 - 1.55). This reduction of 28-day mortality has been confirmed by a recent prospective meta-analysis.[44] However, there is still no supportive data for a long-term use (more than 10 days) of corticosteroids to prevent post disease fibrosis in COVID-19 patients who at risk of pulmonary fibrosis.[45] In Thailand national guideline, dexamethasone is recommended in COVID-19 patients with risk factors for severe disease or having co-morbidity or mild pneumonia or severe disease.[6] The recommended dose is 6 - 20 mg of dexamethasone for at least 5 - 7 days. In IDSA guideline, dexamethasone is recommended among hospitalized critically ill or severe COVID-19 patients. The suggested dexamethasone dose is 6 mg for 10 days or until discharge.[8] Alternative glucocorticoids such as methylprednisolone 32 mg or prednisolone 40 mg may be used if dexamethasone is unavailable. Similarly to the IDSA guideline, the NIH guideline also recommends using dexamethasone in severe COVID-19 patients.[9] If dexamethasone is unavailable, either methylprednisolone, prednisolone, or hydrocortisone can be an alternative.

Discussion

In the era of SARS-CoV-2 pandemic, there are many repurposing agents that have possible mechanism of action against the virus. Medications commonly used for hepatitis B, hepatitis C, HIV, and other coronaviruses such as MERS or SARS-CoV are the promising agents to treat SARS-CoV-2 infection while waiting for new specific antiviral drugs. Remdesivir, primarily developed to treat Ebola infection, is the first drug approved by the USFDA for SARS-CoV-2 infection and is recommended in several guidelines for treating patients who required supplemental oxygen or has severe symptoms. There are many clinical trials supporting the effectiveness of remdesivir in severe COVID-19 patients. But patients with renal impairment should be concerned when remdesivir is administered. Corticosteroids are the main supportive treatment for patients with severe COVID-19 who mechanical ventilation or oxygen supplement therapy is required. The treatment is aimed to reduce lung inflammation and risk of ARDS. The relevant studies showed that corticosteroids significantly reduced 28-day all-cause mortality in severe COVID-19 patients. In Thailand national guideline, favipiravir is recommended as a first line therapy for patient with symptomatic COVID-19 with or without pneumonia while remdesivir is reserved for severe patients. Favipiravir shows a benefit on viral clearance and clinical recovery in several studies, but it still lacks in study with large number of participants. In contrary, lopinavir/ritonavir and hydroxychloroquine are not recommended in many guidelines due to lack of proved efficacy. Besides, administration of these drugs in very high doses potentially cause toxicity. Among antiparasitic agents, ivermectin is the most promising agent against SARS-CoV-2 in mild illness patients but the data of its efficacy is still uncertain. Both tocilizumab and baricitinib are the immunomodulating agents which can be used to treat COVID-19, especially for patients with excessive inflammatory response. There are also other potential candidates, for examples, saquinavir, ledipasvir, velpatasvir, galdesivir, nitazoxamide, emetine, and anakinra. Therefore, further investigations are still needed.

In conclusion, remdesivir obviously shows an effectiveness against SARS-CoV-2 and has been approved by USFDA for COVID-19 treatment, while favipiravir has been used for COVID-19 in countries where remdesivir is limited. Corticosteroids use in patient with severe COVID-19 is essential to reduce lung inflammation. Other repurposing drugs, which may have a beneficial for COVID-19 treatment such as tocilizumab and baricitinib, are authorized under an emergency use. The evidence of some repurposing drugs such as ivermectin is inconsistent. Hence, further clinical studies on promising agents should be urgently conducted.

Acknowledgements

Financial support. None reported.

Transparency declarations. None to declare.

Conflict of interest

All authors report no conflict of interest relevant to this article.

References

1. WHO Coronavirus (COVID-19) Overview. World Health Organization. https://covid19.who.int/. Updated June 27, 2021. Accessed June 28, 2021.
2. Pal M, Berhanu G, Desalegn C, Kandi V. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. *Cureus*. 2020;12(3):7423.
3. Tarighi P, Eftekhari S, Chizari M, Sabernavaei M, Jafari D, Mirzabeigi P. A review of potential suggested drugs for coronavirus disease (COVID-19) treatment. *Eur J Pharmacol*. 2021;895:173890.
4. Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis*. 2021;102:501-508.
5. Report on the Deliberation Results: Avigan. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau. https://www.pmda.go.jp/files/000210319.pdf. Published 2014. Accessed July 3, 2021.
6. Thailand Clinical Practice Guideline (update May 6, 2021). Department of Medical Services. https://covid19.dms.go.th/backend/Content/Content_FIle/Bandner_(Big)/Attach/25640507102416AM_CPG_COVID_v.14_n_20210506.2.pdf. Updated May 6, 2021. Accessed July 3, 2021.
7. Swift R. Fujifilm starts new late-phase trial of Avigan in Japan for COVID-19 patients. Reuters. https://www.reuters.com/business/healthcare-pharmaceuticals/fujifilm-starts-new-late-phase-trial-avigan-japan-covid-19-patients-2021-04-21. Published April 21, 2021. Accessed August 8, 2021.
8. Bhimraj A, Morgan RL, Shumaker AH, et al. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management. Updated June 25, 2021. Accessed July 3, 2021.
9. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. https://www.covid19 treatment guidelines.nih.gov. Updated June 17, 2021. Accessed July 3, 2021.
10. Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering* (*Beijing, China*). 2020;6(10):1192-1198.
11. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. *medRxiv*. 2020. doi: 10.1101/2020.03.17.20037432.
12. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. *Virol J*. 2020;17(1):141.
13. Barlow A, Landolf KM, Barlow B, et al. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. *Pharmacotherapy*. 2020;40(5):416-437.
14. Malin JJ, Suárez I, Priesner V, Fätkenheuer G, Rybniker J. Remdesivir against COVID-19 and Other Viral Diseases. *Clin Microbiol Rev*. 2020;34(1).
15. Humeniuk R, Mathias A, Cao H, et al. Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID-19, in Healthy Subjects. *Clin Transl Sci*. 2020;13(5):896-906.
16. Marra F, Smolders EJ, El-Sherif O, et al. Recommendations for Dosing of Repurposed COVID-19 Medications in Patients with Renal and Hepatic Impairment. *Drugs R D*. 2021;21(1):9-27.
17. Thakare S, Gandhi C, Modi T, et al. Safety of Remdesivir in Patients With Acute Kidney Injury or CKD. *Kidney Int Rep*. 2021;6(1):206-210.
18. Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511.
19. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826.
20. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With

Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(11):1048-1057.
21. Shrestha DB, Budhathoki P, Syed NI, Rawal E, Raut S, Khadka S. Remdesivir: A potential game-changer or just a myth? A systematic review and meta-analysis. *Life Sci*. 2021;264:118663.
22. Ford N, Vitoria M, Rangaraj A, Norris SL, Calmy A, Doherty M. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. *J Int AIDS Soc.* 2020;23(4):25489.
23. Uzunova K, Filipova E, Pavlova V, Vekov T. Insights into antiviral mechanisms of remdesivir, lopinavir/ritonavir and chloroquine/hydroxychloroquine affecting the new SARS-CoV-2. *Biomed Pharmacother.* 2020;131:110668.
24. Schoergenhofer C, Jilma B, Stimpfl T, Karolyi M, Zoufaly A. Pharmacokinetics of Lopinavir and Ritonavir in Patients Hospitalized With Coronavirus Disease 2019 (COVID-19). *Ann Intern Med.* 2020;173(8):670-672.
25. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2020;396(10259):1345-1352.
26. Kaur H, Shekhar N, Sharma S, Sarma P, Prakash A, Medhi B. Ivermectin as a potential drug for treatment of COVID-19: an in-sync review with clinical and computational attributes. *Pharmacol Rep.* 2021;73(3):736-749.
27. Bryant A, Lawrie TA, Dowswell T, et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. *Am J Ther.* 2021;28(4):434-460.
28. Padhi S, Pati A, Panda AK. Effect of ivermectin in the treatment of COVID-19: A trial sequential analysis highlighted the requirement of additional randomized controlled trials. *Clin Infect Dis.* 2021;692.
29. Banno M, Tsujimoto Y, Ishikane M. Need for more randomized controlled trials with rigorous methodology to confirm that ivermectin is not a viable option for the treatment of coronavirus disease. *Clin Infect Dis.* 2021;689.
30. Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med.* 2020;383(21):2030-2040.
31. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med.* 2020;382(25):2411-2418.
32. Tocilizumab. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. http://micromedex.com/. Updated 2021. Accessed August 7, 2021.
33. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2021;397(10285):1637-1645.
34. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med.* 2021;384(16):1491-1502.
35. Baricitinib. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. http://micromedex.com/. Updated 2021. Accessed August 7, 2021.
36. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med.* 2021;384(9):795-807.
37. Romanou V, Koukaki E, Chantziara V, et al. Dexamethasone in the Treatment of COVID-19: Primus Inter Pares? *J Pers Med.* 2021;11(6):556.
38. Johns M, George S, Taburyanskaya M, Poon YK. A Review of the Evidence for Corticosteroids in COVID-19. *J Pharm Pract.* 2021;897190021998502.
39. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest.* 2007;131(4):954-963.
40. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med.* 2016;42(5):829-840.

41. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care.* 2016;20(1):329.
42. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med.* 2020;8(3):267-276.
43. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med.* 2021;384(8): 693-704.
44. Sterne JAC, Murthy S, Diaz JV, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA.* 2020;324(13):1330-1341.
45. Mishra GP, Mulani J. Corticosteroids for COVID-19: the search for an optimum duration of therapy. *Lancet Respir Med.* 2021;9(1):8.