COVID-19

A Review on Current Repurposing Drugs for the Treatment of COVID-19: Reality and Challenges

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Abstract

The coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic with a high growth rate of confirmed cases. Therefore, therapeutic options are desperately urgent to fight with this damning virus. As it may take years to develop a specific therapy of COVID-19, it is urgent to emphasize the repurposing of drugs used for other conditions. This study reviewed the most common drugs for COVID-19 based on available online literature representing the latest in vitro clinical trial database, rational of use, adverse effects, potential toxicities, and US National Institute of Health (NIH) recommendation to use for COVID-19. Based on the preliminary data from clinical trials and considering the NIH and FDA recommendation, remdesivir and convalescent blood products are the most promising potential for COVID-19 treatment. The use of chloroquine, hydroxychloroquine, favipiravir, ivermectin, and colchicine might also be effective. However, furthermore, in vivo investigations are needed in detail individually and in combination for possible benefits in humans. Besides, tocilizumab might be deemed as adjunctive therapy for patients with cytokine release syndrome. However, lopinavir-ritonavir, anakinra, and sarilumab had not proven their clinical efficacy. Eventually, sarilumab has been withdrawn from sponsored clinical trials based on the preliminary data. Baricitinib and ruxolitinib have the additive immunosuppressive effect. Consequently, all of these drugs are being evaluated with further studies. In addition, drug-drug interaction and safety concerns must be taken into account before the administration of the recommended drugs.

Keywords COVID-19 · Clinical trial · Convalescent plasma · Remdesivir · Chloroquine · Hydroxychloroquine

Introduction

A dangerous outbreak of atypical pneumonia of unknown origin was first identified in a group of patients in Wuhan city, China, at the end of December 2019 [1]. Chinese Centre for Disease Control identified a novel coronavirus, initially called 2019-nCoV, as a cause of this outbreak. Later, it was officially renamed to severe acute respiratory syndrome 2 (SARS-CoV-2) that is the causative factor of a disease known as coronavirus disease-19 (COVID-19) [2]. Due to its high transmission potential, the SARS-CoV-2 infection has become a global health threat within weeks [3]. Consequently, the World

Health Organization (WHO) declared the COVID-19 as a pandemic disease on 11 March 2020. As of 25 July 2020, about 15,802,717 confirmed cases and 639,228 deaths had been reported throughout the world in this ongoing pandemic [4]. The confirmed cases are heterogeneous and divided into mild (80%), severe (15%), and critical cases (5%) [5]. Notably, several clinical manifestations, such as fever, cough, dyspnea, and myalgia, with increased serum level of aspartate aminotransferase, creatinine, creatine kinase, and C-reactive protein were more frequently observed in the complicated COVID-19 patients than the uncomplicated group [6, 7]. Cytokine storm is only reported in critically ill patients and responsible for the development of complications leading to ultimate death associated with COVID-19 [8]. In addition, approximately 15% of COVID-19 patients will develop severe lung disease due to acute respiratory infection that is recognized in most cases after 7 to 14 days. The disease severity is characterized by systemic inflammation reactions associated with cytokine storm [9]. Unfortunately, no antiviral drug or standard treatment against COVID-19 is currently

available which results in the growing rate of morbidity and mortality. However, it may take years to develop and to evaluate the clinical studies of a specific, highly potent antiviral drug for SARS-CoV-2. Therefore, it is urgent to focus on previously used antiviral agents and immunomodulating drugs or other relevant agents to develop the new treatment or reduce the severity of the disease. The recovery rate of COVID-19 patients can be increased by repurposing the drugs that slow down the replication of SARS-CoV-2 and/or decrease disease symptoms. In addition, it could also reduce the pressure on intensive care units by shortening the time spent in these units that makes a chance for other patients to get services. Therefore, the quickest way to fight with this ongoing pandemic is to repurpose the currently available drugs that have been used clinically with a known safety profile. This article represents the old drugs with preliminary data of the latest clinical trial that could be potential against COVID-19 treatment.

Repurposing Drug Therapy Against COVID-19

Remdesivir

Remdesivir, an investigational nucleoside analog, is a broad-spectrum antiviral medication having in vitro activity against RNA viruses (belonging to Orthocoronavirinae, Filoviridae, Paramyxoviridae, and Pneumoviridae families) that is considered as the most promising drug against SARS-CoV-2. It inhibits the RNA-dependent RNA polymerases (RdRps) and competes with adenosine triphosphate for incorporation into the nascent viral RNA chains resulting in the premature termination of viral RNA transcription (Table 1) [10–12]. Though remdesivir is not an FDA-approved drug, however, FDA has issued an Emergency Use Authorization (EUA) to allow this drug intravenously for hospitalized COVID-19 patients with severe disease (SpO2 of 94% or less on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation) [13]. The NIH COVID-19 treatment guidelines also agree to this point; however, they recommend no clear statement about the patients with mild or moderate COVID-19 [14]. Notably, the drug is available through clinical trials for the treatment of children and pregnant women with COVID-19 infection [14]. Additionally, preliminary data from a phase 3 trial (Adaptive COVID-19 Treatment Trial (ACTT-1)) of a study demonstrated that remdesivir was better than the placebo in shortening the recovery time (11 vs. 15 days) of hospitalized adults with COVID-19 and lung involvement [15]. However, data from a randomized, open-label phase 3 clinical trial showed no significant difference between doses for 5 days and 10 days [16]. Another randomized, double-blind, placebo-controlled, multicenter trial evaluating efficacy and safety of remdesivir

in SARS-CoV-2-infected hospitalized adults (concurrent treatment with corticosteroids, interferons, and lopinavir-ritonavir) found no difference in the time of clinical improvement and similar mortality rate on day 28. A higher percentage of adverse events was reported in remdesivir patients (66%) compared with placebo patients (64%) [17]. A recent study involving 53 hospitalized COVID-19 severe patients from the USA ($n = 22$), Europe or Canada ($n = 22$), and Japan ($n = 9$), treated with remdesivir, has reported the clinical improvement of 68% patients and adverse effects including the abnormality of hepatic function (23%), diarrhea (9%), skin rash (8%), acute kidney injury (8%), etc. A course (10 days) of remdesivir (200 mg on day 1, followed by 100 mg daily) was administered intravenously among these patients. Nevertheless, the FDA suggested a dose of 200 mg IV once on day 1, followed by 100 mg IV once daily for 9 in the Emergency Use Authorization (EUA) statement [13, 14]. This dose is also being evaluated in multicenter randomized trials [14, 18, 27, 53]. Consequently, the authors suggest this therapy as a well-known potential for COVID-19 treatment as for now. However, remdesivir should be avoided in patients with hypersensitivity to remdesivir [13, 14] and in patients with drugs undergo interaction with remdesivir and safety caution must be taken with renal impairment, infusion-related reactions, and elevated hepatic enzyme (Table 2) [13, 33].

Favipiravir

Favipiravir is classified as an investigational broad-spectrum antiviral drug with in vitro activity against RNA viruses [19, 20]. It inhibits the RNA-dependent RNA polymerases (RdRps), resulting in the premature termination of viral RNA transcription and thus inhibits the viral RNA synthesis [19, 20] (Table 1). In March 2020, it was approved in China for marketing in the treatment of COVID-19 patients despite having no available pharmacokinetics data. However, a non-randomized, controlled, open-label trial has recently observed the efficacy of favipiravir (day 1: 1600 mg twice daily; days 2–14: 600 mg twice daily) in the treatment of COVID-19 patients compared against lopinavir-ritonavir (days 1–14: 400 mg/100 mg twice daily). Inhaled interferon-alpha (5 million U twice daily) was used with both treatments resulting from the shorten recovery time for favipiravir (median, 4 days; range, 2.5 to 9 days) than for lopinavir-ritonavir (median, 11 days; range 8 to 13 days; $p < 0.001$). Chest imaging improvement rate was also higher among favipiravir patients (91.43%) compared with that of lopinavir-ritonavir patients (62.22%) on day 14 of the treatment [21]. Therefore, this preliminary data may help the experts to ahead with further study and suggest this therapy when treatment is not feasible. Owing to early embryonic death and teratogenicity observed in animal studies, this should be avoided during pregnancy

Table 1 Summary of the mechanism of action, the latest output of clinical trials, and recommendation to use against COVID-19 of the most common drugs that are being evaluated against COVID-19

Drugs	Classification	Mechanism of action	The main output of clinical trial	Recommendation against COVID-19	References
Remdesivir	Investigational nucleoside analogue	Inhibits the viral RNA synthesis by inhibiting the RNA-dependent RNA polymerases (RdRps), competes with adenosine-triphosphate.	Superior effect to placebo, better clinical improvement	NIH and FDA recommends for hospitalized patients with severe COVID-19	[10–18]
Favipiravir	Investigational RNA-dependent RNA polymerase inhibitor	Inhibits the viral RNA synthesis by inhibiting the RNA-dependent RNA polymerases (RdRps)	Shortening the recovery time, improved chest image, better efficacy than lopinavir-ritonavir	Approved in China for marketing	[19–21]
Chloroquine and hydroxichloroquine	Antimalarial drug	Inhibits viral enzymes or processes, ACE2 cellular receptors acidifies the cell membrane surfaces and involves the immunomodulation of cytokine release	Active against SARS-CoV-2 inhibits the exacerbation of pneumonia, hydroxychloroquine is more potent than chloroquine	Used for whom clinical trial participation is not feasible	[10, 22–26]
Lopinavir-ritonavir	HIV protease inhibitor	Protease enzyme inhibitors bind to Mpro, a key enzyme for coronavirus replication	No favorable output was found, alone therapy has no clinical improvement	NIH recommends against the use of it outside the clinical trial.	[27–29]
Ivermectin	Anti-parasite	Inhibits the coupling of the SARS-CoV-2S-protein with the human ACE2 receptor, boosts the human immunity	Induces approximately 5000-fold reduction in the viral RNA of SARS-CoV-2 at 48 h	–	[30–32]
Baricitinib and ruxolitinib	Janus kinases inhibitor	Inhibits Janus kinases enzymes and alleviate the signal transmission due to cytokine storm	Improved clinical symptoms and respiratory parameters of baricitinib patients compared to control, no significant improvement between ruxolitinib and placebo	NIH recommends against the use of these drugs outside of clinical trials	[33–36]
Anakinra	Interleukin-1 inhibitor	Inhibits the binding of IL-1 to the interleukin-1 type 1 receptor (IL-1R1), controls the activation of caspase 1, balance the inflammatory cytokine	The better output of anakinra plus standard therapy compared to standard alone therapy	NIH did not give recommendations for or against the use of anakinra	[33, 37–39]
Canakinumab	Interleukin-1 inhibitor	Suppresses the free IL-1 beta	Several doses are being evaluated	NIH did not give recommendations for or against the use of anakinra	[40–43]
Siltuximab, tocilizumab, and sarilumab	Interleukin-6 inhibitor	Prevent the binding of IL-6 (a pro-inflammatory cytokine) to IL-6 receptors, stop the cytokine release syndrome	Tocilizumab plus standard therapy suggest the clinical benefit of tocilizumab as adjunctive therapy, tocilizumab improves the clinical symptoms, lymphocyte percentage, CT opacity changes, and CRP concentration, unexpected preliminary data of sarilumab	NIH did not give recommendations for or against the use, and sarilumab is being withdrawn from the manufacturer-sponsored trial	[18, 33, 44, 45]
Nitazoxanide	Antiviral	Affects the viral genome synthesis, preventing viral entry and interfering with the N-glycosylation	No clear safety data for patients with renal or hepatic impairment	No statement found	[46]
Colchicine	Antigout	Inhibits SARS-CoV-2 entry, transport, and replication by blocking microtubules polymerization	Give activity against flaviviruses but no precise safety data for COVID-19 patients.	NIH did not give recommendations for or against the use of this therapy	[8, 47]
Convalescent blood products	Blood products	Contain the antibodies to SARS-CoV-2	Temperature becomes normal, decrease virus load and became negative within 12 days, improve CT image, decreased symptoms	NIH did not give recommendations for or against the use of this therapy	[33, 48–50]
Fibrinolytic agents		Initiate the local fibrinolysis by converting plasminogen to plasmin on the surface of existing thrombi	Improvement of PaO2/FiO2 (P/F) ratio	–	[51, 52]

Table 2 List of common interacting agents and their effect; adverse effect and safety concerns of most promising drugs against COVID-19

Drugs (US trade name)	Dosage forms and strength	Common interacting agents	Effects of interaction	Adverse effects	Safety concerns	Reference
Remdesivir	100 mg powder for injection; 5 mg/mL solution for injection	Atropine, scopolamine, belladonna alkaloid, chloroquine, hydroxychloroquine, isoniazid, rifampin, phenytoin, phenobarbital, dexamethasone, amoxicillin, etc.	Reduce the systemic exposure of remdesivir, and thus reduce its antiviral activity	Anaphylactoid reactions, angioedema, nausea, vomiting, fever, headache, diarrhea, skin rash, hypotension, tachycardia, bradycardia, elevated hepatic enzymes. etc.	Infusion-related reactions, the risk for elevated hepatic enzymes, renal impairment	[13, 17]
Favipiravir	200 mg tablet	Warfarin, acetyldigoxin, acyclovir, adefovir dipivoxil, afatinib, allopurinol, almotriptan, alprostadil, ambrisentan, etc.	Decrease metabolism of or excretion of the respective drug	Decreases red blood cell production and increases the liver function parameters such as aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and total bilirubin, and increased vacuolization in hepatocytes	Pregnancy owing to early embryonic death and teratogenicity effect	[21]
Chloroquine (Aralen) and hydroxychloroquine (Plaquenil)	Chloroquine phosphate 250 mg tablet; 50 mg/mL solution for injection and hydroxychloroquine sulfate 200 mg tablet	Amiodarone, acarbose, acetohexamide, metformin, sitagliptin, tolbutamide, insulin, albuterol, ipratropium, azithromycin, ciprofloxacin, fluconazole, ketoconazole, tamoxifen, tetracycline trametinib, vigabatrin, interferon, antacid, etc.	Severe hypoglycemia, QT prolongation retinal damage.	Agranulocytosis, anaphylactic shock, anaphylactoid reactions, Blurred vision, confusion, dyskinesia, elevated hepatic enzymes, QT prolongation, thrombocytopenia, retinal damage.	Cardiac arrhythmia, diabetes, ratinal demage, G6PD deficiency, significant drug interaction, etc.	[19–21, 23]
Lopinavir/ritonavir (Kaletra)	100 mg/25 mg tablet; 200 mg/50 mg tablet; (400 mg/100 mg)/5 mL oral solution	Alfuzosin, triazolam, lovastin, simvastin, rifampin, ergot alkaloids, fluconazole, meperidine, cisapride, naloxegol, apalutamide, sirolimus, tacrolimus, fentanyl, cyclosporine, warfarin, phenytoin, phenobarbital, ketoconazole, itraconazole, amiodarone, methadone, etc.	Severe hypoglycemia, QT prolongation, etc.	Allergic reaction, irregular heartbeat, nausea, vomiting, abdominal pain, redness erectile dysfunction, libido decrease, menorrhagia, feeling faint, headache, heartburn, etc.	Cardiac arrhythmia, diabetes	[54, 55]
Ivermectin (Stromectol)	3 mg tablet; 6 mg tablet	Warfarin, 4-hydroxycoumarin, abemaciclib, abiraterone, acalabrutinib, afatinib, aminophylline, amiodarone, cabazitaxel, zolpidem.	Alteration the metabolism of or excretion of the respective drug	Abdominal pain, asthenia, hypotension, edema, tachycardia, dizziness, headache, hyperthermia, insomnia, depression, ataxia, psychosis, confusion, seizure, sommolence, vertigo, pruritus, rash, urticaria, diarrhea, nausea, vomiting, eosinophilia, leukopenia, myalgia, blurred vision, mild conjunctivitis, punctate opacity, fever, lymphadenopathy.	Hypersensitivity	[30–32]
Baricitinib (Olumiant)	1 mg tablet; 2 mg tablet	Azathioprine, abatacept, adalimumab, anakinra, sarilumab, infliximab, cyclosporine, probenecid, etc.	Additive immune suppressive effect	allergic reaction, severe infection, liver injury, anemia, nausea, runny nose.	Thrombosis, risk GI perforation, cancer, neutropenia, lymphopenia, and anemia and	[34]

Table 2 (continued)

Drugs (US trade name)	Dosage forms and strength	Common interacting agents	Effects of interaction	Adverse effects	Safety concerns	Reference
					elevated liver function	
Ruxolitinib (Jakafi)	5, 10, 15, 20, and 25 mg tablet	Fluconazole, agmatine, alclofenac, benserazide, bevacizumab, ketoconazole, erythromycin, rifampin, etc.	Reduce or interrupt the effect of the respective drug	Anemia, balance impairment, dizziness, headache, labyrinthitis, Meniere's disease, neutropenia, thrombocytopenia, vertigo, and orthostatic dizziness	Thrombocytopenia, anemia and neutropenia.	[33, 36]
Anakinra (kineret)	100 mg per 0.67 ml solution for injection	Abatacept, adalimumab, baricitinib, ruxolitinib, sarilumab, tocilizumab, tofactinib	Additive immune suppressive effect	Allergic reactions, breathing problems, severe infection, nausea, vomiting, diarrhea, headache, joint pain, etc.	Infusion-related reaction, thrombocytopenia, neutropenia	[33, 37]
Canakinumab (Ilaris)	150 mg/ml powder for injection or solution for injection	Abatacept, adalimumab, baricitinib, ruxolitinib, etc.	Additive immune suppressive effect	Allergic reaction, severe infection, diarrhea, nausea, and gastroenteritis.	Hypersensitivity, severe infection, renal and hepatic impairment, thrombocytopenia, neutropenia, etc.	[43]
Siltuximab (Sylvant) and tocilizumab (Actemra)	Siltuximab 100 mg powder for injection, 400 mg powder for injection and tocilizumab 200 mg/10 ml solution for injection, 400 mg/20 ml solution for injection	Abatacept, adalimumab, baricitinib, ruxolitinib, atorvastin, cyclosporine, lovastin, warfarin, etc.	Additive immune suppressive effect	Allergic reaction, back pain, breathing problems, stomach pain, dizziness, facial flushing, irregular heartbeat, headache, nausea, vomiting, angioedema, GI perforation, hepatotoxicity, visual problems	Risk of GI perforation, risk of hepatotoxicity, thrombocytopenia, neutropenia, infusion-related reactions	[44, 56]
Colchicine (Colcrys)	0.6 mg tablet; 0.6 mg capsule; 0.6 mg/5 ml oral solution	Abacavir, alogliptin, ampicillin, tianeptine, sulindac, ritonavir, vilanterol, zaleplon, etc.	Alteration the metabolism of or excretion of the respective drug	Alopecia, diarrhea, vomiting, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia, myopathy, elevated CPK, myotonia, muscle weakness, rhabdomyolysis	Risk of GI perforation, renal impairment, hepatic impairment.	[57]

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[21]. Additional data are being evaluated regarding clinical efficacy for COVID-19 (Table 2).

Chloroquine, Hydroxychloroquine, and Azithromycin

Chloroquine, the antiprotozoal agent, is indicated for the treatment of malaria, autoimmune diseases, and extraintestinal amebiasis. It influences the hemoglobin digestion by increasing intravascular pH in malarial parasite cells and interferes with the nucleoprotein synthesis of the patients [22]. Notably, chloroquine has shown the activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by inhibiting viral enzymes or processes such as viral DNA and RNA polymerase, virus assembly, viral protein glycosylation, new virus particle transport, and virus release. It also inhibits ACE2 cellular receptor, acidifies the surface of the cell membrane that leads to the inhibition of the fusion of virus, and involves in the immunomodulation of cytokine release in COVID-19 patients [10, 22–24]. However, due to the potential for severe adverse events and drug interactions, it is not used for treating COVID-19 patients outside of clinical trials. (Table 2) [58]. However, due to having a clinical benefit in the treatment of COVID-19 due to SARS-CoV-2, chloroquine is recommended to treat the hospitalized COVID-19 patients (50 kg or more) for whom clinical trial participation is not feasible [25]. Additionally, in vitro preclinical data suggest that chloroquine has activity against SARS-CoV-2 [13, 59]. There have also been reports of potential benefit in inhibiting the exacerbation of SARS-CoV-2 infection in patients with pneumonia; however, specific data are not available [55]. It should be administered orally with a meal at the recommended dose for COVID-19 patients (1000 mg PO on day 1, then 500 mg PO once daily for 4 to 7 days) [25]. Moreover, chloroquine should be avoided during pregnancy, and necessary cautions should be taken during administration to breastfeeding women as it is excreted into breast milk. Hydroxychloroquine, an oral disease-modifying antirheumatic drug (DMARD), is an important drug to treat rheumatoid arthritis, malaria, and systemic lupus erythematosus. Outside of clinical trials, the NIH COVID-19 treatment guidelines do not recommend the hydroxychloroquine to use for COVID-19 patients. However, it is used to treat hospitalized COVID-19 patients when clinical trial participation is difficult [26]. Notably, an in vitro analysis observed the hydroxychloroquine as a more potent drug than chloroquine (EC50 values, 0.72 and 5.47 μM, respectively) for COVID-19 treatment. In addition, hydroxychloroquine shows fewer drug-drug interactions (Table 2) than chloroquine with having the ability to control the cytokine storm and shorten the clinical recovery time among the SARS-CoV-2-infected patients [23]. Consequently, the US Centers for Diseases Control and Prevention approved the hydroxychloroquine in treating adult and adolescent COVID-19 patients for severe cases on 28 March 2020. It was administrated as a loading dose of 400 mg twice daily, followed by a maintenance dose of 200 mg twice daily for 4 days, which showed the superior effect to chloroquine (500 mg twice daily) in inhibiting SARS-CoV-2 [23]. This superior effect in shortening the recovery time was also confirmed by a randomized controlled trial in Wuhan, China. This parallel-group, randomized clinical trial of hydroxychloroquine with non-severe COVID-19 patients demonstrated the shortened of cough (3.1 days vs 2 days) and fever (3.2 days vs. 2.2 days) recovery time compared to the standard therapy [60]. Nevertheless, a non-randomized clinical trial confirmed the significantly greater proportion of PCR-negative patients treated with hydroxychloroquine (70%) compared to the control group (12.5%) on day 6 [61]. Also, a multicenter, parallel, open-label, randomized trial in 150 adults hospitalized patients found no significant difference in negative viral conversion rate, symptoms alleviation rate, and adverse events rate between hydroxychloroquine and control group [62]. An observational trial reported that hydroxychloroquine was not associated with a significantly higher or lower risk of intubation or death [63]. Azithromycin, a macrolide antibiotic, is used in combination with hydroxychloroquine to enhance the efficacy of hydroxychloroquine. Notably, a study involving 20 severe COVID-19 patients observed the reinforcement of the efficacy of hydroxychloroquine when it was administrated with azithromycin as a loading dose of 500 mg on the first day followed by 250 mg once for 2–5 days. After the administration of this combination therapy, a positive clinical outcome was obtained from these COVID-19 patients attributing an outstanding efficiency in virus elimination [61]. Moreover, a retrospective analysis found the lower rate of death and ventilation among patients with combination therapy compared to the individual therapy of hydroxychloroquine [64]. As a result, hydroxychloroquine plus azithromycin therapy might be a useful alternative to remdisivir for the treatment of patients infected with SARS-CoV-2.

However, hydroxychloroquine shows drug-drug interaction (Table 2) with azithromycin resulting in the prolongation of QTc that must be cautiously considered [33]. In addition, an observational study of 1438 in-patients found no difference in mortality among the patients treated with the individual therapy or combination therapy compared with no use of these agents (adjusted OR 0.84; 95% CI 0.47–1.51; $p = 0.56$) [65]. Consequently, the authors suggest the individual therapy of hydroxychloroquine for COVID-19 infection to reduce the cardiac toxicities.

Lopinavir-Ritonavir and Ribavirin

Protease enzyme, such as papain-like protease and 3 C-like proteases, is crucial for the survival of virus from Orthocoronavirinae family. So protease inhibitors (PIs), like

lopinavir-ritonavir, are used to target these protease enzymes (Table 1) [28]. These are indicated for the treatment of HIV-1 infections in adults and pediatric patients in combination with other antiretroviral medications. However, the antiviral activity of lopinavir-ritonavir therapy against the treatment of MERS-CoV is controversial in the tissue culture model [66]. Available data of this therapy regarding the treatment of COVID-19 due to SARS-CoV-2 are also limited and indecisive. In addition, pharmacodynamics and clinical trial data of this therapy are not favorable leading to the recommendation of NIH COVID-19 treatment guidelines against the use of lopinavir-ritonavir outside of clinical trials [33]. A study, involving hospitalized patients with confirmed SARS-CoV-2 infection ($n = 199$), did not find any difference in clinical improvement with lopinavir-ritonavir therapy compared with the standard care. Individual therapy of lopinavir-ritonavir (400/100 mg administered orally twice daily for 14 days) also failed to show the clinical improvement and reduce the RNA virus load in patients with severe SARS-CoV-2 [29]. However, it is administrated orally as a tablet or solution at the conventional dose for the treatment of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and should be taken with food to minimize the pharmacokinetics variabilities. The oral solution must be avoided during pregnancy due to containing alcohol and propylene glycol [67]. Therapeutic monitoring is necessary when administrating to patients with hepatic impairment leading to an increase in the concentration of drugs [54]. It is also necessary to monitor the several parameters (such as blood glucose, CBC with differential, serum bilirubin (total and direct), serum cholesterol, serum lipid profile, urinalysis) when lopinavir-ritonavir is concurrently used with other agents leading to the drug-drug interactions (Table 2) [54, 55]. Notably, authors are not being confirmed to use this drug for COVID-19, and further study may be introduced to evaluate this therapy during pregnancy. In addition, the National Health Commission and State Administration of Traditional Chinese Medicine recommended ribavirin (a guanosine analog) for COVID-19 treatment [68]. The effectiveness of this drug in combination with lopinavir-ritonavir was also proven against SARS-CoV in patients and tissue culture [69]. The estimated concentration ribavirin against SARS-CoV was up to 50 µg/mL [66].

Ivermectin

Ivermectin is a semisynthetic broad-spectrum anti-parasitic FDA-approved drug that acts on parasite by potentiating GABA-mediated neurotransmission and by binding to glutamate-gated chloride channels [70]. Besides, it boosts human immunity by increasing the IL-1 production and other cytokines, activating superoxide anion production, and enhancing the lymphocyte response to mitogens [30]. It blocks the HIV replication by inhibiting the interaction between the HIV-1 integrase protein (IN) and α/β1 heterodimer of the importin. Additionally, ivermectin has also been shown the activity to control the disease caused by several RNA viruses such as dengue, influenza, RSV, and rabies [31]. However, its broad-spectrum antiviral activity depends on IMPα/β1 during infection. Recently, a molecular modeling study has claimed the inhibition of the coupling of the SARS-CoV-2S-protein with the human ACE2 receptor through the binding of ivermectin in the RBD region [32]. A recent study with COVID-19 patients demonstrated the induction of ivermectin in the reduction of viral RNA of SARS-CoV-2. In a Vero-hSLAM cell culture model, a single dose of ivermectin induced approximately 5000-fold reduction in the viral RNA of SARS-CoV-2 at 48 h [31]. The huge fold of viral reduction within 48 h attracts the expert's attention to recommending it against COVID-19. However, the antiviral concentration of ivermectin was obtained only after a large dose. Notably, the drug could penetrate the blood-brain barrier and affect GABA-ergic transmission at large doses [71]. Consequently, human overdose has been associated with several adverse effects, including depression, ataxia, psychosis, confusion, and seizure (Table 2) [72]. The safety of ivermectin for human therapy is only obtained at the conventional dose (≤ 200 µg/kg) [73].

Baricitinib and Ruxolitinib

Janus kinases (JAK), intracellular enzymes, are associated with the signal transmission arising from cytokine interactions on the cellular membrane and thus influence cellular processes of immune cell function. Baricitinib and ruxolitinib show their activity by inhibiting these enzymes to alleviate the signal transmission due to cytokine storm. They are originally indicated for the treatment of rheumatoid arthritis when tumor necrosis factor (TNF) inhibitors fail to produce a response [34]. As JAK inhibitors can alleviate the cytokine storm (maybe a component of severe COVID-19), they are (including Baricitinib, ruxolitinib) currently being studied for the treatment of patients with COVID-19-associated cytokine storm based on the preliminary data of a study involving an immunomodulator (an IL-6 receptor antibody) [74]. A non-randomized, open-label trial involving 12 patients with moderate COVID-19 compared the safety and efficacy of baricitinib plus lopinavir-ritonavir against a control group treated with hydroxychloroquine plus lopinavir-ritonavir [35]. All clinical symptoms and respiratory parameters were improved in baricitinib patients, while no significant changes were reported in the control group [35]. However, 1 patient from the investigation group stopped after 10 days due to an increased liver function test. The oral administration of baricitinib (2 mg PO once daily for 10–14 days and 4 mg PO daily for 7–14 days) is being evaluated in combination with antiviral therapy [75, 76]. It can be administrated with or without food.

About three-fourth of the administered dose is eliminated in the urine, and only one-fifth of the dose is eliminated in the feces. It is largely excreted through urine (69%) as unchanged drug and feces (15%). Sufficient data are not available on the placental transfer of the drug to the fetus during pregnancy or the presence of drugs in breast milk [34]. Concomitant use of baricitinib with biologic DMARDs, immunosuppressive agents, Virus Vaccine, OAT3 inhibitors, etc. is not recommended due to having the additive immunosuppressive effect and increasing the infection risk (Table 2) [34].

Additionally, the efficacy and safety of ruxolitinib were evaluated in a randomized, multicenter, placebo-controlled, phase 2 trial in hospitalized patients with severe COVID-19 [36]. Though there was no significant difference in the clinical improvement between ruxolitinib and the placebo group, the median time of clinical improvement was higher for ruxolitinib. Adverse events were observed among 80% of ruxolitinib compared to 71.4% of placebo patients [36]. Notably, due to having a broad immunosuppressive effect, they are recommended against the use of JAK inhibitors outside of clinical trials by the NIH COVID-19 treatment guidelines [33]. Therapeutic monitoring is needed in patients with anemia, lymphopenia, neutropenia, serious infection, and lipid elevations.

Anakinra

Anakinra is an interleukin-1 receptor antagonist (IL-1Ra). Recombinant DNA technology using an *Escherichia coli* bacterium is applied to produce the drug [37]. It competitively inhibits the binding to the interleukin-1 type 1 receptor (IL-1R1) and thus blocks the effects of IL-1, specifically IL-1alpha and IL-1beta in the inflammatory system. It maintains the balance effects of inflammatory cytokines by reducing the IL-1, known as primary pro-inflammatory cytokines, associated with rheumatoid arthritis [37]. It is indicated for the treatment of familial cold autoinflammatory syndrome associated with the inhibition of IL-1beta, IL-6, and IL-8 in affected skin. It also inhibits the increased IL-6 serum concentrations after cold exposure [77]. It controls the activation of caspase 1, leading to the deduction of active interleukin derivatives involving IL-1 beta and IL-18. However, the NIH COVID-19 treatment panels did not give any recommendations for or against the use of anakinra due to the lack of available clinical data [33]. Depending on preliminary data from other anti-interleukin medications, researchers have introduced several studies to evaluate the use of anakinra for COVID-19 treatment [38, 39]. A study is evaluating the dose 200 mg IV every 8 h for 7 days (that is to be reduced to 100 mg for 15 days in patients with renal impairment), in patients with macrophage activation syndrome (MAS) infected with SARS-CoV-2, or immune dysregulation. For patients with COVID-19, 100 mg IV infusion every 6 h for 15 days is currently being

investigated. Use of 5 mg/kg infused over 60 min twice daily was investigated in 29 COVID-19 patients with moderate-to-severe acute respiratory distress and hyper inflammation resulting higher survival rate for patients receiving anakinra plus standard therapy (90%) compared with that of patients receiving standard therapy alone (50%) on day 21 [38, 39]. A dose of 100 mg SC injection once daily for 28 days or until hospital discharge is also being evaluated [78]. After checking the patient's neutrophil count, Anakinra should be administrated monthly for the first 3 months of therapy, and then quarterly for up to 1 year [79]. It is associated with the increased risk of various infections, hematologic side effects, headache and arthralgia, increased risk of cancer, hypersensitivity reactions including anaphylactoid reactions, angioedema, urticaria, rash (unspecified), and pruritus, etc. (Table 2) [37]. However, the reaction at the injection site is the most common adverse reaction of anakinra subcutaneous administration [37]. Concomitant use of anakinra with biologic DMARDs, immunosuppressive agents, Virus Vaccine, OAT3 inhibitors, etc. is not recommended due to having the additive immunosuppressive effect and increasing the infection risk [37]. Due to a lack of sufficient available data on anakinra use during pregnancy and on breastfeeding, it should be avoided if possible [37].

Canakinumab

Canakinumab, a human monoclonal antibody, binds with the interleukin (IL)-1 beta and blocks its interaction with the IL-1b receptor leading to the reduction of biologically active IL-1b. Unbound IL-1 beta in tissue increases the probability of a disease flare by stimulating serum amyloid A protein (SAA) and C-reactive protein (CRP) production. Canakinumab suppresses the free IL-1 beta by binding with it that reduces the IL-1 beta production to the rate found in normal subjects [40, 41]. It is indicated for the treatment of IL-1 beta-induced inflammatory diseases, such as cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS) [80]. The NIH COVID-19 treatment guidelines did not give any recommendations for or against the use of canakinumab for the treatment of IL-1 beta-induced COVID-19 due to having a lack of clinical data [33]. As preliminary data are available from other anti-interleukin medications, experts have started several studies based on these data to evaluate the use of canakinumab for COVID-19 [42, 81]. The dosing regimens having under investigation for COVID-19 therapy are included 4 mg/kg and 8 mg/kg IV once for patients with 40 kg or less; 300 mg and 600 mg IV once for more than 40 kg patients; 450 mg IV once for patients with 40 to 59 kg body weight; 600 mg IV once for patients with 60 to 80 kg and 750 mg IV once for patients with more than 80 kg. All doses are to be infused over 2 h after diluting in 250 mL of 5%

dextrose [42, 81]. Diarrhea (20%), nausea (14%), and gastro-enteritis (11%) are the most commonly reported adverse reactions associated with canakinumab. This therapy should be avoided for the patients with a confirmed hypersensitivity to canakinumab, need to take caution in patients with hepatic disease or renal impairment. If canakinumab is needed to use in patients with infection, therapeutic monitoring must be required to maintain the immunosuppressive effect [43]. Concomitant use of canakinumab with biologic DMARDs, immunosuppressive agents, Virus Vaccine, OAT3 inhibitors, etc. results in an additive immunosuppressive effect and increased infection risk (Table 2). So, co-administration of canakinumab with this agent must be avoided if feasible. Canakinumab crossed the placenta following a linear fashion as pregnancy progresses, increasing the potential fetal risk during the second and third trimesters. But data are not sufficient regarding the presence of canakinumab in breast milk or its effects on milk production and breast-fed infant [43].

Siltuximab, Tocilizumab, and Sarilumab

Interleukin-6 (IL-6) antagonists prevent the binding of IL-6 (a pro-inflammatory cytokine) to IL-6 receptors. They are classified as antineoplastic and immunomodulating monoclonal antibody (interleukin-6 inhibitors) that block the binding of IL-6 with both soluble and membrane-bound IL-6 receptors resulting in the prevention of T cell activation, induction of immunoglobulin secretion, initiation of hepatic acute-phase protein synthesis, and proliferation, differentiation, and stimulation of hematopoietic precursor cell [44]. They may be used in COVID-19 patients to stop the cytokine release syndrome [44, 45, 82]. Notably, due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give any recommendations for or against the use of IL-6 receptor inhibitors, such as siltuximab, tocilizumab, and sarilumab[33].

Several studies have begun to evaluate the efficacy of siltuximab in COVID-19 treatment based on the preliminary data from a study with another IL-6 receptor antibody [72, 73, 78]. A siltuximab single dose of 11 mg/kg via intravenous infusion over 1 h is being evaluated for COVID-19 treatment [72, 73, 78]. A retrospective study involving 21 patients with COVID-19 induced pneumonia/ARDS, who received siltuximab therapy, found an outcome of 33% patients for condition improved with reduced need for ventilation; 43% for condition stabilized; 24% for condition worsened and required intubation [73]. Moreover, preliminary data of a retrospective review involving 21 patients treated with tocilizumab plus standard COVID-19 therapy suggest the clinical benefit of tocilizumab as adjunctive therapy [45]. This therapy improves the clinical symptoms, CT opacity changes, lymphocyte percentage, and CRP concentrations in patients leading to the addition of tocilizumab in some protocols for use. Consequently, the

dosage regiment, 4 to 8 mg/kg/dose (usual dose: 400 mg; maximum dose: 800 mg) IV once, is evaluated in combination with antiviral therapy followed by the second dose administration in patients with no clinical response 8 to 12 h after the first infusion. If required, the third dose would administrate16 to 24 h after the first dose [45]. On the other hand, the 200 mg dose of sarilumab, used intravenously in severe hospitalized patients, is being withdrawn from manufacturer-sponsored trials based on preliminary data; however, the 400 mg IV dose used to treat critical hospitalized patients is still being evaluated [83]. Both doses are being studied outside of manufacturer-sponsored trials [84, 85]. Besides, the subcutaneous administration of either 200 or 400 mg once is being studied in combination with antiviral therapy [18, 85]. Additional clinical efficacy data for COVID-19 are being evaluated. All of these drugs show several adverse events such as dermatologic, hematologic, gastrointestinal (GI), metabolic adverse events, infections, edema. In addition, this therapy should be monitored carefully with caution in patients who are receiving a CYP3A4 substrate (e.g., oral contraceptives, lovastatin, atorvastatin), due to having drug-drug interactions (Table 2) [44, 56]. Cautions should be concerned with the risk of GI perforation, hepatotoxicity, and patients with thrombocytopenia and neutropenia [56]. Due to its teratogenic effect and potential for serious adverse reactions in the breast-fed infant, siltuximab is not recommended during pregnancy and breastfeeding [44]. In addition, tocilizumab and sarilumab may affect labor and obstetric delivery [44, 56].

Nitazoxanide

Nitazoxanide, an antiprotozoal drug, has previously been shown the broad spectrum of antiviral activity against human and animal coronaviruses [86]. It shows its antiviral activity by affecting viral genome synthesis, preventing viral entry, and interfering with the *N*-glycosylation [46]. Notably, nitazoxanide acts on the SARS-CoV-2 by interfering with its spike protein that is highly *N*-glycosylated [87]. This drug also potentiates the production of type 1 interferons [46]. After the administration of nitazoxanide, it rapidly produces the metabolite named tizoxanide in humans that is being evaluated against SARS-CoV-2 infection. Tizoxanide has also demonstrated similar activities to nitazoxanide for viruses and other pathogens [88]. Though the safety of nitazoxanide is well understood, it has no precise safety data for patients with renal or hepatic impairment. Additionally, based on the existing data, the antiviral activity of nitazoxanide for SARS-CoV-2 requires further study.

Colchicine

Colchicine derived from *autumn crocus* has both anti-inflammatory and antiviral properties [8, 47]. Now, this drug is already used for Mediterranean fever, gout, Behcet's

disease, and pericarditis [89]. Colchicine might be preventing cytokine storm and decrease COVID-19 severity. Colchicine inhibits microtubules polymerization that is essential for SARS-CoV-2 entry, transport, and replication [90]. Besides, this drug modulates several pro- and anti-inflammatory pathways. It has been reported that colchicine significantly decreases virus replication in flaviviruses, such as dengue and Zika viruses, hepatitis virus and HIV viral load [47]. A study on 4745 patients was reported that colchicine significantly decreased cardiovascular risk and pneumonia [79]. Treatment with 1 mg of colchicine on day 8 and then 0.5 mg/day was reported to be beneficial found in a case report of a COVID-19-infected patient [91]. The absorption of colchicine occurs in the jejunum and ileum and accumulates in tissues that is metabolized in the liver and the intestine by cytochrome P (CYP) 450 3A4 and P-glycoprotein (P-gp) [47]. Overdose of colchicine has been associated with several adverse effects, including diarrhea, GIT adverse event, headache, fever, and myopathy [57].

Convalescent Blood Products

Convalescent blood products are obtained from the serum or whole blood of patients who have recovered from the COVID-19 infections that may contain the antibodies to SARS-CoV-2. This product may be of various forms, including convalescent serum or whole blood, pooled human immunoglobulin, high titer immunoglobulin, and polyclonal or monoclonal antibodies [48]. Centrifugation or membrane filtration are the two different ways for plasma therapies [92]. However, owing to a lack of clinical data, the NIH COVID-19 treatment panels do not give any suggestions for or against the use of a convalescent plasma [33]. Clinical trials are being investigated to justify the use of convalescent blood products against the COVID-19 infection. A randomized, open-label, multicenter trial for evaluating the safety and efficacy of this therapy against severe and life-threatening COVID-19 found no significant difference of clinical improvement and mortality on 28 days between patients with convalescent blood products plus and slandered therapy (51.9% and 15.7%) and patients with standard therapy alone (43.1% and 24%). However, both groups experienced with transfusion-related adverse events [21]. In a case series of 5 patients confirmed with COVID-19 and ARDS having several criteria, such as high viral load after antiviral treatment, PAO2/FIO2 less than 300 and mechanical ventilation, two consecutive transfusions of 200 mL–250 mL convalescent plasma (total dose: 400 mL) are given to the selected patients. Notably, after plasma infusion, body temperature became normal within 3 days in 4 to 5 patients; virus load decreased and became negative within 12 days; ARDS resolved in 4 patients by day 12 and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment [49]. Three infected health workers in Taiwan received plasma therapy and resulted in a significantly reduced viral load with increased anti-SARS-CoV IgM and IgG [92]. Another case series study was conducted among 6 patients of confirmed COVID-19 with abnormalities on chest CT where patients received at least 1 cycle (range, 1 to 3 cycles, 200 ml per cycle) of convalescent plasma over 30 min [23]. All patients had recovered from abnormal chest CT, decreased symptoms, and released from the hospital. Nevertheless, safety data were also collected from 5000 hospitalized patients with severe and life-threatening COVID-19 infection, who received 200 mL to 500 mL convalescent plasma, which demonstrated only 35 serious adverse events (SAEs) within 4 h of transfusion, 15 deaths and 21 non-lethal SAEs. The 7-day mortality rate was only 14.9% [93]. Therefore, the convalescent plasma may become a promising and potential therapy in the treatment of severe COVID-19 infection.

Fibrinolytic Agents

Central line thrombosis, pulmonary congestion with microvascular thrombosis, coagulopathy, and occlusion are observed in severe COVID-19 infection. ARDS is developed by fibrin deposition in the pulmonary microvasculature [94]. Notably, fibrinolytic agents initiate the local fibrinolysis by converting plasminogen to plasmin on the surface of existing thrombi. A case series study was conducted with 3 critically ill patients with ARDS and respiratory failure where patients received alteplase intravenously, leading to the improvement of the PaO2/FiO2 (P/F) ratio by 11% to 100% in all the 3 patients. Bleeding problems make this agent limited to use [94].

However, the improvements were transient. Efficacy data of other fibrinolytic agents, including defibrotide, are being investigated for the treatment of COVID-19 [92, 93].

Conclusion

COVID-19 has become a pandemic with a high growth rate of confirmed and death cases. Unfortunately, no specific therapy has been approved against this deadly virus as for now. So it is important to focus on the repurposing drugs that may show their activity against COVID-19. In addition, there may have numerous drugs with potentially good in vitro efficacy against COVID-19. Hence, clinicians should have rapid access to information from the clinical trial. Also, the clinical trial and the reports of these trials should be of high quality and out of bias as these reports will guide the clinician to make decision on which drug to use, their dosage regimens, and the inclusion-exclusion criteria. Thus, clinical trials should be designed with care to get robust results. Clear scientific in vitro and preclinical in vivo evidence is needed to select the

therapies for specific treatment. Based on the preliminary clinical data of safety and efficacy, we have identified some drugs for COVID-19 that has been validated to have acceptable safety and pharmacokinetics profile. Apart from them, remdesivir and convalescent blood products are the most promising potential for COVID-19 treatment as a well mentionable clinical improvement was found in their clinical output. Eventually, the evidence of a negative load of the virus was observed in convalescent blood plasma therapy. In addition, the US NIH recommends the use of remdesivir against severe COVID-19 patients. The use of chloroquine, hydroxychloroquine, favipiravir, tocilizumab, ivermectin, and colchicine might also be effective as a treatment option for COVID-19 but need more investigation for recommendation. Notably, favipiravir was approved for marketing on 28 March 2020 for the treatment of COVID-19. In addition, tocilizumab might be deemed as adjunctive therapy for patients with cytokine release syndrome. However, some drugs, such as lopinavir-ritonavir, have not proven their clinical efficacy against COVID-19. Sarilumab has been withdrawn from the sponsored clinical trials based on the preliminary data. Anakinra, Janus Kinase inhibitors (baricitinib and ruxolitinib) are not recommended due to having an additive immunosuppressive effect. Therefore, it is necessary to choose the treatment option by evaluating their clinical efficacy, adverse effects, drug-drug interaction, and safety concern before administration of the treatment.

Compliance with Ethical Standards

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