



An Update on Current Therapeutic Drugs Treating COVID-19

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Abstract

The current pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented unprecedented challenges to the healthcare systems in almost every country around the world. Currently, there are no proven effective vaccines or therapeutic agents against the virus. Current clinical management includes infection prevention and control measures and supportive care including supplemental oxygen and mechanical ventilatory support. Evolving research and clinical data regarding the virologic SARS-CoV-2 suggest a potential list of repurposed drugs with appropriate pharmacological effects and therapeutic efficacies in treating COVID-19 patients. In this review, we will update and summarize the most common and plausible drugs for the treatment of COVID-19 patients. These drugs and therapeutic agents include antiviral agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir), and supporting agents (Ascorbic acid, Azithromycin, Corticosteroids, Nitric oxide, IL-6 antagonists), among others. We hope that this review will provide useful and most updated therapeutic drugs to prevent, control, and treat COVID-19 patients until the approval of vaccines and specific drugs targeting SARS-CoV-2.

Keywords COVID-19 · SAR-CoV-2 · Remdesivir · Hydroxychloroquine · Chloroquine · Lopinavir · Umifenovir · Favipiravir · Oseltamivir · Azithromycin · Vitamin C · Methylprednisolone · Epoprostenol · Nitric oxide · Sirolimus · Sarilumab · Tocilizumab · Anakinra · Convalescent plasma · Traditional Chinese Medicine

Abbreviations

COVID-19 Coronavirus disease 2019
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

MERS-CoV Middle East respiratory syndrome coronavirus
ACE2 Angiotensin-converting enzyme 2
IFN Interferon
COPD Chronic obstructive pulmonary disease
ARDS Acute respiratory distress syndrome
BALF Bronchoalveolar lavage fluid
PBMC Peripheral blood mononuclear cells
SLE Systemic lupus erythematosus
RA Rheumatoid arthritis
HHV-8 Human herpesvirus 8
HCV Hepatitis C virus
iNO Inhaled nitric oxide
iEPO Inhaled epoprostenol
NSAID Nonsteroidal anti-inflammatory drug
CCoV Canine coronavirus
LAM Lymphangioleiomyomatosis
ALI Acute lung injury
TCM Traditional Chinese Medicine

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Introduction

The horrific pandemic outbreak of COVID-19 (coronavirus disease 2019) around the world caught the health care systems in every country by storm, most if not all were caught off guard without proper defense mechanisms to cope with and to control such a pandemic. COVID-19, caused by a new and novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), has recently been identified and characterized [1•]. Coronaviruses are named for their crown-like spikes on their surface and there are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta [1, 2]. SARS-CoV-2 belongs to the beta sub-grouping, and is one of the seventh coronavirus to date infecting humans [1•]. Some coronaviruses such as 229E alpha coronavirus [3], OC43 beta coronavirus [4], NL63 alpha coronavirus [5], and HKU1 beta coronavirus [6] were associated with mild clinical symptoms, whereas SARS-CoV beta coronavirus [7], Middle East respiratory syndrome coronavirus (MERS-CoV) beta coronavirus [8], and SARS-CoV-2 caused severe diseases [2].

SARS-CoV-2 is a positive-sense single-stranded RNA virus with 29,891 bases, 96% identical at the whole-genome level to a bat coronavirus, and shares 79.6% sequence identity to SARS-CoV [1•]. SARS-CoV-2 encodes spike S protein containing receptor binding domain (RBD) that binds to the human angiotensin-converting enzyme 2 (ACE2), and promotes membrane fusion and uptakes of the virus into human cells such as the lung by endocytosis [1, 9–11]. Upon entering the human cells, SARS-CoV-2, like other coronaviruses, will takeover or hijack the human cells' protein synthesis machinery to synthesize the viral proteins and assemble the proteins and subsequent viral replication [12•].

Once inside the human body, viruses in general will trigger a series of good versus bad host responses including autophagy, apoptosis, stress response, and innate immunity [13]. Fortunately, majority (more than 80%) of SARS-CoV-2-infected individuals are asymptomatic or have mild symptoms, most likely due to the activation of the good response. These good responders would likely activate the body's innate immune system by activating the body's antiviral defense mechanisms including natural killer cells and antiviral T cells, and induction of interferon (IFN) [13–16]. Unfortunately, in about 20% of SARS-CoV-2-infected individuals including the immune compromised, elderly, patients with underlying health conditions such as cardiovascular and pulmonary problems, diabetics, hypertension, obesity, chronic obstructive pulmonary disease (or COPD, such as emphysema), pulmonary fibrosis, asthma, and interstitial lung disease [17, 18] would encounter more severe disease characterized by significant respiratory symptoms leading to acute respiratory distress syndrome (ARDS) and even death. An important consideration to note is that ARDS occurs later in disease progression and is preceded by acute lung injury (ALI) [19]. This distinction may

inform treatment strategy in terms of drugs directed towards cytokine storm and thrombosis which is described in this manuscript. A study on SARS-CoV and MERS-CoV has found that these two coronaviruses appear to have evolved mechanisms to attenuate or delay IFN production, resulting in enhanced inflammatory host responses and severe lung injury [12, 13, 20–22]. This aberrant host immune response with the production of powerful inflammatory cytokines, known as “cytokine storm” found in SARS-CoV- and MERS-CoV-infected patients, would correlate with disease severity and poor prognosis [13, 16, 20–23]. Severe COVID-19 patients exhibit profound inflammatory response [24, 25]. Transcriptomic RNA-seq analysis of COVID-19 patients has revealed that several immune pathways and pro-inflammatory cytokines CXCL, CCL2, CXCL2, CCL8, IL33, and CCL3L1 in bronchoalveolar lavage fluid (BALF) and TNFSF10, CXCL10, IL10, TIMP1, C5, IL18, AREG, and NRG1 in peripheral blood mononuclear cells (PBMC) were induced by SARS-CoV-2 infection, suggesting a sustained inflammation and cytokine storm [26]. Importantly, SARS-CoV-2 infection-induced excessive cytokine release correlates with lung tissue injury and COVID-19 pathogenesis [26]. This estimated 20% of patients developing more severe disease with SARS-CoV-2 infection are most likely due to genetics, epigenetics, and or other factors, with dampened innate immune response to fight the virus coupled with enhanced viral load leading to cytokine storm, severe inflammatory/oxidative stress response, and severe lung injury secondary to ARDS. While there is clear understanding that the respiratory system is dramatically impacted in COVID-19 patients, evidence suggests that other organ systems are also affected. Emerging data show that SARS-CoV-2 may lead to damage to other organs including the heart and brain. Nearly 20% of hospitalized patients with COVID-19 have indication of cardiac damage [17]. Furthermore, neurologic symptoms have been reported in patients and infection of SARS-CoV-2 has been found in the brainstem of both humans and experimental animals [18, 19].

Currently, there is no vaccine and/or specific therapeutic drugs targeting the SARS-CoV-2. Hence, it remains a major challenge to decide what potential therapeutic regimens to prevent and treat the severely sick COVID-19 patients. Effective vaccines are essential to combat against the extremely contagious SARS-CoV-2. At present, a lot of research efforts have been invested to develop vaccines around the world. Until we have specific vaccines or therapeutic drugs targeting SARS-CoV-2, “repurposed” drugs that have been approved by the FDA in the USA for other indications have been used to treat COVID-19 patients. This review will summarize the most current pharmacotherapeutics prescribed in the treatment of severe cases of COVID-19 patients. These include antiviral therapy, antibiotics, systemic corticosteroids and anti-inflammatory drugs (including anti-arthritis drugs),

neuraminidase inhibitors, RNA synthesis inhibitors, convalescent plasma, and traditional herbal medicines.

Current Therapeutics Drugs in Treating COVID-19

In the absence of definitive and specific treatment regimens, strategies including early diagnosis, timely reporting, isolation, and supportive treatments are important line of actions against COVID-19 infections. Current social practices including timely release of epidemic information and maintenance of social orders and personal practices such as improving personal hygiene, wearing facial coverings or masks, adequate rest, and keeping rooms well ventilated remain some of first line of actions against COVID-19 pandemic.

At present, the treatments of patients with SARS-CoV-2 infection are mainly repurposing the available therapeutic drugs and based on symptomatic conditions. Considering ARDS, followed by secondary infections, antibiotics, antiviral therapy, systemic corticosteroids, and anti-inflammatory drugs (including anti-arthritis drugs) are often used in the treatment regimens. In addition to antiviral interferers and antibiotics, neuraminidase inhibitors, RNA synthesis inhibitors, convalescent plasma, and traditional herbal medicines have also been utilized in the treatment of COVID-19 [27]. Nevertheless, the efficacy of these treatment regimens remains to be verified by appropriately designed clinical trials.

Antiviral Agents

Remdesivir

Remdesivir is a potential drug for treatment of COVID-19. It is a phosphoramidate prodrug of an adenosine C-nucleoside and a broad-spectrum antiviral agent synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection [28]. Remdesivir is metabolized into its active form, GS-441524, that obscures viral RNA polymerase and evades proofreading by viral exonuclease, causing a decrease in viral RNA production. The antiviral mechanism of remdesivir is a delayed chain cessation of nascent viral RNA.

Animal experiments indicate that remdesivir can effectively reduce the viral load in lung tissue of mice infected with MERS-CoV, improve lung function, and alleviate pathological damage to lung tissue [29]. Wang et al. found that remdesivir potently blocks SARS-CoV-2 infection at low range of micromolar concentrations and has a high selectivity index (half-maximal effective concentration (EC₅₀), 0.77 μ M; half-cytotoxic concentration (CC₅₀) > 100 μ M; SI > 129.87) [30]. Holshue et al. reported that IV administration of remdesivir yielded promising results in the treatment of a patient with COVID-19 recovering from pneumonia in the

USA [31]. In order to evaluate the efficacy and safety of the drug in patients with COVID-19, a randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial was launched on February 5, 2020 in China. Patients in the experimental group received an initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days via intravenous infusion in addition to routine treatment. Patients in the control group received same dose of placebo treatment. The trial is expected to conclude by the end of April 2020. The number of cases planned to be enrolled is 308 and 452, respectively [32, 33]. Current recommendation for remdesivir includes a 10-day regimen of remdesivir treatment: 200 mg loading dose on day 1, followed by 100 mg once-daily maintenance doses for 9 days in both studies. This regimen of remdesivir therapy is similar to that of former randomized clinical trial against the Ebola virus [32, 33]. In a summary of subjects receiving remdesivir via compassionate use in the USA, nearly 70% of patients had improvement in terms of oxygen requirements and many patients that were mechanically ventilated were extubated. This report did not include a control group; therefore, extrapolating these results is difficult. It is too early to conclude the direct antiviral effect of remdesivir on the enhanced clearing of viral loads in the respiratory tract, but it indeed suggests a promising therapeutic effect of remdesivir [34].

Hydroxychloroquine and Chloroquine

Chloroquine and hydroxychloroquine are drugs with a long history of clinical use with similar chemical structures often used in the treatment of lupus erythematosus, rheumatoid arthritis, and malaria [35]. Compared with chloroquine, hydroxychloroquine has a hydroxyl group, which makes it less toxic while maintaining similar activity. One mechanism of action of chloroquine and hydroxychloroquine is targeting lysosome which may be useful to control graft-versus-host disease in humans [36]. With the accumulation of chloroquine in lysosomes, the pH of lysosomes is significantly changed and the activity of proteases in lysosomes is directly affected, thus affecting the degradation of proteins and glycosaminoglycan [36, 37]. Chloroquine can inhibit the entry of SARS-CoV-2 and prevent virus-cell fusion by interfering with glycosylation of ACE2 receptor and its binding with spike protein, suggesting that chloroquine treatment might be more effective in the early stage of infection, before COVID-19 reduces ACE2 expression and activity [30, 38, 39]. Hydroxychloroquine possesses anti-inflammatory effect on Th17-related cytokines (IL-6, IL-17, and IL-22) in healthy individuals, and systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients [40]. There is some evidence that chloroquine and hydroxychloroquine can reduce cytokine storm. According to one analysis, the main cause of death of COVID-19 patients is related to the triggering of

the cytokine storm, which contributed to acute respiratory distress [41]. It has been reported that hydroxychloroquine is effective in inhibiting SARS-CoV-2 infection in vitro [1, 39, 42]. Zinc inhibits SARS-CoV and retrovirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture [43]. There is also evidence that zinc enhances chloroquine intracellular uptake [44]. As such, combining zinc with chloroquine or hydroxychloroquine is intriguing and is currently under investigation. Overall, more clinical trials are underway to evaluate the safety and efficacy of hydroxychloroquine as a prophylactic and treatment for COVID-19. The US FDA has issued emergency authorization for the use of chloroquine and hydroxychloroquine for the treatment of COVID-19. A recent study by Tang et al. reported that hydroxychloroquine did not lead to higher negative conversion rates, but had reduced clinical symptoms through the anti-inflammatory properties and recovery of lymphopenia [45]. It has also been reported that high doses of chloroquine (600 mg twice daily for 10 days or total dose of 12 g) may be associated with significant cardiac risks and should not be recommended for treating COVID-19 [46]. There is still a lack of evidence regarding the safety and effectiveness of these agents in treating COVID-19. In this regard, clinicians and patients should be made aware of the risk versus benefit profile of these medications [47].

Lopinavir-Ritonavir

Lopinavir is a protease inhibitor with high specificity for HIV-1 protease. Lopinavir is marketed and administered exclusively in combination with ritonavir. This combination was first marketed by Abbott under the brand name Kaletra in 2000 [48]. Due to lopinavir's poor oral bioavailability and extensive biotransformation, it is co-formulated with ritonavir to enhance its exposure. Ritonavir is a potent inhibitor of the enzymes that are responsible for lopinavir metabolism, and its co-administration "boosts" lopinavir exposure and improves antiviral activity [48]. Lopinavir is a peptidomimetic molecule, containing a hydroxyethylene scaffold that mimics the peptide linkage typically targeted by the HIV-1 protease enzyme but which by itself cannot be cleaved, thus preventing the activity of the HIV-1 protease [49].

Lopinavir-ritonavir was investigated in an open-label, individually randomized, controlled trial, where patients with COVID-19 received either lopinavir-ritonavir 400 mg/100 mg, orally twice daily plus standard of care, or standard of care alone. No benefit was observed with lopinavir-ritonavir treatment beyond standard care. Diarrhea, nausea, and asthenia were the most frequently reported adverse effects in patients receiving lopinavir-ritonavir-based regimen [50]. Interestingly, in a report from Korea, lopinavir-ritonavir administration significantly decreased coronavirus titers with no or little coronavirus titers were observed in the follow-up

study. However, the analysis included a single patient in the initial phase of outbreak in Korea [51].

Umifenovir (Arbidol)

Umifenovir (branded as Arbidol), a derivative of indole carboxylic acids, was first developed in 1988 in Russia and has since been approved in Russia and China for treating prophylaxis and infections associated with influenza A and B, and other arbovirus [52]. Later on, umifenovir demonstrated in vitro antiviral efficacy in widely spreading virus strains such as the Ebola virus, human herpesvirus 8 (HHV-8), hepatitis C virus (HCV), and Tacaribe arenavirus [53]. Its major mechanism of action is to block the virus-cell membrane fusion as well as virus-endosome fusion through incorporation into cell membranes and interference with the hydrogen bonding network of phospholipids [54]. In influenza virus, it has been shown to directly interact with virus particles to stabilize hemagglutinin (HA), reducing the likelihood of reaching the low pH threshold required for conformational transition into functional fusogenic HA [55]. Blaising et al. reported the in vitro activity of umifenovir against SARS-CoV-1 and SARS-CoV-2 [56, 57]. A retrospective cohort study has reported that compared with lopinavir-ritonavir (LPV-RTV) only group, combination of umifenovir and LPV-RTV has shown increased negative conversion rate of SARS-CoV-2 and improved chest CT scan results [58]. However, another prospective study (ChiCTR200030254) has shown that compared with favipiravir, umifenovir has inferior outcome in clinical recovery rate and relief of fever and cough [59]. There are two randomized and open-label trials ongoing in China, investigating the efficacy and safety of umifenovir against COVID-19. The effect of umifenovir plus standard treatment versus LPV-RTV plus standard treatment will be evaluated in NCT04252885, and the effect of umifenovir plus standard treatment versus standard treatment will be tested in NCT04260594.

Favipiravir (Avigan)

Favipiravir (branded as Avigan) has been developed by Fujifilm Toyama Chemical in 2014 in Japan for the treatment of avian influenza or novel influenza resistant to neuraminidase inhibitors. It is a guanine analogue with pyrazinecarboxamide structure, and its antiviral activity is decreased at the presence of purine nucleosides due to the competition [60]. The prodrug favipiravir first enters the infected cells through endocytosis and is then transformed into active favipiravir ribofuranosyl phosphates through phosphoribosylation and phosphorylation [60, 61]. The antiviral activity is exhibited through selectively targeting conservative catalytic domain of RNA-dependent RNA polymerase (RdRp), interrupting the nucleotide incorporation process

during viral RNA replication [60]. The dysregulation in viral RNA replication results in increased number and frequency of transition mutations including replacement of guanine (G) by adenine (A) and cytosine (C) by thymine (T) or C by Uracil (U) which induces destructive mutagenesis in RNA viruses [60]. Favipiravir has been used in the treatment of infectious diseases caused by RNA viruses such as influenza, Ebola, and norovirus [62]. Recent *in vitro* and human studies have repurposed favipiravir as an experimental agent against enveloped, positive-sense, single-strand RNA virus SARS-CoV-2. An *in vitro* research has investigated seven potential anti-SARS-CoV-2 medicines including ribavirin, penciclovir, favipiravir, nafamostat, nitazoxanide, remdesivir, and chloroquine, showing that remdesivir and chloroquine have favorable selectivity index [30]. In addition, the study showed favipiravir has exerted efficacy in Vero E6 cells infected with SARS-CoV-2 with half-maximal effective concentration (EC₅₀) of 61.88 μM and half-cytotoxic concentration (CC₅₀) at over 400 μM , implying the high concentration is needed for safe and effective treatment [30]. Clinical trials testing favipiravir against COVID-19 have been carried out vigorously in various countries including China and Japan. A randomized control trial (ChiCTR200030254) has shown that COVID-19 patients treated with favipiravir have superior recovery rate (71.43%) than that treated with umifenovir (55.86%), and the duration of fever and cough relief time are significantly shorter in favipiravir group than in umifenovir group [59]. Up to mid-April 2020, there are eight ongoing clinical trials in China and two in Japan examining the anti-SARS-CoV-2 potential of favipiravir. These trials include non-randomized and randomized controlled trials evaluating the efficacy and safety of favipiravir alone (ChiCTR2000030113, JPRN-jRCTs031190226, JPRN-jRCTs041190120) or in conjunction with interferon- α (ChiCTR2000029600), baloxavir marboxil (ChiCTR2000029544, ChiCTR2000029548), tocilizumab (ChiCTR2000030894, NCT04310228), or chloroquine phosphate (ChiCTR2000030987, NCT04319900).

Oseltamivir (Tamiflu)

Oseltamivir (branded as Tamiflu) is a drug approved for treatment of influenza A and B. Oseltamivir targets the neuraminidase distributed on the surface of the influenza virus to inhibit the spread of the influenza virus in the human body [63, 64]. A study in Wuhan reported that no positive outcomes were observed after receiving antiviral treatment with oseltamivir [65]. Several clinical trials are still evaluating the effectiveness of oseltamivir in treating SARS-CoV-2 infection. Oseltamivir is also used in clinical trials in several combinations, such as with chloroquine and favipiravir [66].

Supporting Agents

In the absence of vaccine or specific antiviral drugs been proven against SARS-CoV-2, many adjunctive therapies are used as supportive care for COVID-19 patients. The adjunctive therapies including azithromycin, ascorbic acid, corticosteroids, epoprostenol, sirolimus, tocilizumab, sarilumab, and anakinra are highlighted below. Several of these therapies (i.e., tocilizumab and other interleukin-directed therapies) are administered in an effort to blunt the cytokine storm often seen in progressing disease. The optimal timing of administration is yet to be identified. Conceptually, blocking cytokine production before it progresses to an exaggerated level would seem to be the most mechanistically sound idea. Elevated serum concentration of IL-6 is associated with worse outcome in COVID-19 and blocking the activity of this pro-inflammatory mediator with directed therapies may be a key target [67]. Other adjuncts are directed at viral replication, viral entry, or through some other alternative mechanisms.

Azithromycin

Azithromycin is an antibiotic that can be used to fight many different types of infections caused by susceptible bacteria, such as respiratory infections, skin infections, and sexually transmitted diseases [68]. Moreover, it has been proven to be active *in vitro* against Zika and Ebola viruses and to prevent severe respiratory tract infections when treated to patients suffering viral infection [69–71]. For the mechanism of action, azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA [72]. Previously, azithromycin has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza) [73, 74]. Currently, many trials are testing the effect of azithromycin conjunction with hydroxychloroquine on the course of disease in people with SARS-CoV-2. For example, Pfizer has announced positive data for the use of its azithromycin (Zithromax) drug, along with hydroxychloroquine, in a COVID-19 clinical trial that was performed in France. In brief, the clinical trial was conducted to assess hydroxychloroquine in 20 patients, 6 of which were co-administered with azithromycin. Compared with 16 controls and 14 hydroxychloroquine alone group, the 6 patients treated with hydroxychloroquine + azithromycin presented with highest virologic cure rate following 6-day treatment [73]. Three other clinical studies used azithromycin (500 mg on day 1, then 250 mg daily on days 2–5) co-treated with 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label non-randomized study in France (6 pts) [73], open-label uncontrolled study in France (11 pts) [75], and

uncontrolled observational study in France (80 pts) [76]. Specifically, Gautret et al. reported a 100% viral clearance in nasopharyngeal swabs in their 6 patients after co-treated of hydroxychloroquine and azithromycin [73]. But the findings reported by Molina et al. stand in contrast with those reported by Gautret. Molina et al. repeated the experiments, thought the rapid and full viral clearance was quite unexpected and found 8 of 11 patients had significant comorbidities [75]. Based on those results, data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in patients with COVID-19 [76]. Furthermore, one must consider the additive cardiac toxicity of hydroxychloroquine and azithromycin. Both agents are known to prolong the QT interval and may potentiate the risk for cardiac events in a population known to have cardiac-related comorbidities.

Vitamin C (Ascorbic Acid)

Vitamin C is an essential nutrient and plays significant roles within the human body. It can neutralize free radicals and assist to prevent or reverse cellular damage as a potent antioxidant agent. It is also involved in some biological processes, many of which are associated with immune health [77]. Moreover, vitamin C appears to be effective as an antiviral agent, especially against influenza viruses [78]. Many studies showed that vitamin C positively affects the development and maturation of T lymphocytes and NK (natural killer) cells involved in the immune response to viral agents. It also contributes to the inhibition of reactive oxygen species (ROS) production and to the remodulation of the cytokine network typical of systemic inflammatory syndrome [79]. Given this background, a phase II clinical trial (NCT04264533) is initiated in China to evaluate high-dose IV vitamin C in ICU patients with severe COVID-19-associated pneumonia [80]. Some hospitals have reported giving infected patients 1500 mg of vitamin C as supportive treatment. High-dose IV vitamin C has been given in the treatment of 50 moderate to severe COVID-19 patients in China [81]. The doses varied between 2 and 10 g per day, given over a period of 8–10-h IV infusion. The oxygenation index was improved in real time and all the patients eventually recovered and were discharged [81]. Moreover, high-dose (1.5 mg/kg body weight) vitamin C has been used for several decades clinically and an NIH panel also documented clearly that this dose regimen is safe and has no major side effects [81, 82].

Corticosteroids

As a potent anti-inflammatory and anti-fibrotic drug, low doses of methylprednisolone (DEPO-Medrol or SOLU-Medrol) have the potential to prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [83, 84]. Recently, many

medical researchers believe that corticosteroids, especially methylprednisolone, may improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase blood pressure when it is low [85]. Specifically, in a retrospective cohort study, 201 patients with confirmed COVID-19 who developed ARDS were treated with methylprednisolone (1–2 mg/kg daily IV for 5–7 days) and the results showed that treatment with methylprednisolone may be beneficial for patients who develop ARDS in the reduction of the risk of death. Briefly, of those patients with ARDS who received methylprednisolone treatment, 23 of 50 (46%) patients died, while those who did not receive methylprednisolone, 21 of 34 (61.8%) died [86]. In another study, 46 patients with severe COVID-19 that progressed to acute respiratory failure, use of methylprednisolone was associated with improvement in clinical symptoms (i.e., fever, hypoxia) and a shortened disease course in patients who received the drug compared with those who did not [87]. Moreover, according to expert consensus statement from Chinese Thoracic Society, dosage regimen of methylprednisolone should be low to moderate (i.e., ≤ 0.5 to 1 mg/kg daily or equivalent) [88] and the most common regimens of methylprednisolone applied in China were typically 40–80 mg IV daily for a course of 3–6 days [89]. The appropriate dosage (low dose versus high dose), place in therapy (early versus late), and role for corticosteroids (cytokine storm or comorbidity management) require additional clarity. There is concern that the use of corticosteroids may have deleterious effects (i.e., inhibition of immune response and pathogen clearance) in patients with COVID-19 [83]. One study reported no effect on mortality and decreased viral clearance with the use of corticosteroids [24]. Furthermore, the Infectious Diseases Society of American recommends against the routine use of corticosteroids in COVID-19. However, they do recommend the use of corticosteroids in the setting of ARDS in the context of a clinical trial [90]. Similarly, the Surviving Sepsis Campaign recommends against corticosteroids in mechanically ventilated patients with acute lung injury in the absence of ARDS [91]. However, they provide a recommendation for the use of corticosteroids in patients with ARDS acknowledging the weak level of evidence. Dexamethasone has demonstrated utility on ARDS by decreasing ventilator days and mortality on severe ARDS in patients without COVID-19 [92]. Whether the use of corticosteroids provides similar benefit in patients with COVID-19 and ARDS remains to be seen. Ultimately, the clinical utilization of corticosteroids still needs to be established and should be considered on a case by case basis.

Nitric Oxide and Epoprostenol

Since patients with pre-existing pulmonary conditions are at higher risk of COVID-19 and should be closely monitored

and cared, pulmonary vasodilator agents have been used in some patients for hypoxemia refractory to conventional treatments, but no study has been performed specifically on COVID-19 patients. The Surviving Sepsis Campaign suggested a trial of inhaled pulmonary vasodilator method as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies. Inhaled nitric oxide (iNO) and inhaled epoprostenol (iEPO, a naturally occurring prostaglandin) are two common pulmonary vasodilators that have been widely studied [93–95]. Experience in patients with ARDS indicates that iNO can substantially reduce mean pulmonary artery pressure and improve oxygenation in such patients. Furthermore, in vitro evidence of direct antiviral activity against SARS-CoV was studied and the genetic similarity between SARS-CoV and SARS-CoV-2 suggests their potential effectiveness against SARS-CoV-2 [96]. For iEPO, dosages up to 50 ng/kg per minute have been used [93, 94, 97, 98]. Previous studies reported that to provide a clinically important increase in PaO₂ and reduction in pulmonary artery pressure, the most effective and safe dosage appears to be 20–30 ng/kg per minute in adults and 30 ng/kg per minute in pediatric patients [98]. For iNO, therapy was given for ≥ 3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, then weaned on day 4) in a pilot study on SARS-CoV [99]. Additionally, clinical trials evaluating iNO for treatment or prevention of COVID-19 are planned or underway (NCT04305457, NCT04306393, NCT04312243) [100, 101]. And on March 20, 2020, FDA granted emergency expanded access allowing its iNO delivery system (INOpulse®) to be immediately used for the treatment of COVID-19. Finally, additional studies are needed to evaluate the potential role of iEPO and iNO in the treatment of COVID-19 patients.

Sirolimus

Sirolimus, also known as rapamycin, is an immunosuppressant that is used to prevent organ transplant rejection and to treat lymphangioleiomyomatosis (LAM) by inhibiting mammalian target of rapamycin (mTOR) kinase. It was originally isolated from the bacterium *Streptomyces hygroscopicus* found on Easter Island (Rapa Nui) [102] and is commercially available as Rapamune (Pfizer). mTOR, and more specifically a protein complex mTORC1 formed by mTOR, plays a key role in viral replication. In an in vitro experiment, sirolimus has been shown to affect PI3K/AKT/mTOR pathway which inhibited MERS-CoV activity [103]. A new randomized double-blind placebo-controlled clinical trial (SCOPE) by University of Cincinnati is planned to be conducted between April and September 2020 to test the effect of sirolimus on progression of patients hospitalized with COVID-19 to advanced respiratory support [104]. Studies of patients

hospitalized with influenza can further shed light on the antiviral effect of sirolimus. In a randomized clinical trial conducted on 38 patients with confirmed H1N1 pneumonia and on mechanical ventilator support, a group treated with corticosteroids and 2 mg/day of sirolimus for 14 days ($N = 19$) showed significantly better clinical outcomes compared with the group treated with corticosteroids only, including shorter median duration of ventilator used [105]. Delayed oseltamivir plus sirolimus treatment in pH1N1-infected mouse model further suggested a significant association between the sirolimus treatment and improved outcomes [106]. Additionally, a new trial by the Chinese University of Hong Kong is planned to begin in August 2020 to investigate the effect of sirolimus and oseltamivir on normalization of respiratory status and changes in biomarkers (viral RNA concentration, 10 cytokines/chemokines and pro-inflammatory mediators) and several other clinical endpoints in influenza patients [107]. At least one in silico study identified sirolimus as one of the 16 potential candidates for treating COVID-19 patients based on data from other human coronavirus infections using network-based drug repurposing model [108].

Tocilizumab

Tocilizumab (branded as Actemra) is a humanized mAb developed by Roche and Chugai Pharmaceutical for treating RA and systemic juvenile idiopathic arthritis patients. At the time of publishing this article, [ClinicalTrials.gov](https://clinicaltrials.gov) listed 20 planned studies that included tocilizumab treatment arm, all of them at the recruiting stage or earlier. A study published in April 2020 reported that 21 severe or critical COVID-19 patients in China were treated with the compound, with 20 of them recovered at the time of publication and 1 on the way to recovery (but still in ICU). Encouraged by these results, a larger multicenter clinical trial was launched (ChiCTR2000029765) and had about 500 patients treated with tocilizumab already enrolled [109, 110].

Sarilumab

Sarilumab, (branded as Kefraza), a humanized mAb, was developed by Regeneron Pharmaceuticals and Sanofi for treatment of rheumatoid arthritis (RA). A phase 2/3 randomized double-blind placebo-controlled clinical trial was planned by Regeneron Pharmaceuticals and Sanofi (and in partnership with Northwell Health's Feinstein Institutes for Medical Research) for March 2020 targeting to enroll 400 COVID-19 patients, measuring percent change in C-protein (Phase 2 only) and time to improvement on a 7-point scale (based on death and type of hospitalization) in patients with serum IL-6 level above a threshold as primary endpoints. As of the time of this publication, the results of this study have not been made public [111].

Anakinra

Anakinra (branded as Kineret by Swedish Orphan Biovitrum) is a modified human IL-1 receptor antagonist (IL-1RA) approved in 2001 in the USA and in 2002 in Europe for use in RA patients. IL-1 family of receptors triggers innate immune response and was associated with damaging inflammation [112]. Out of 5 approved clinical trials involving anakinra treatment, 2 also have tocilizumab as a comparison: one multicenter open-label non-randomized trial in Greece with estimated enrollment of 20 patients [113], and another multicenter randomized open-label trial in Belgium with estimated 342 patients has been enrolled to date [114].

Miscellaneous Agents and Therapies

Angiotensin-Converting Enzyme 2 Receptor

Angiotensin-converting enzyme 2 (ACE2) receptor is regarded as an important target in the pathogenesis of COVID-19. Studies reveal that frequently observed comorbidities, including hypertension and diabetes in patients infected with SARS-CoV-2, are under medication with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) [115–118] that result in overexpression of ACE2. It is speculated that SARS-CoV and SARS-CoV-2 bind to human cells via interaction with ACE2 receptors [118, 119]. The opposing physiological actions of ACE and ACE2 in the renin-angiotensin system are reviewed to determine the therapeutic efficacy of ACE2 inhibitors or ARBs [120, 121]. In hypertensive patients, chronic treatment with angiotensin II type 1 receptor (AT1R) antagonists like losartan, lisinopril, or olmesartan facilitates cardiac and renal ACE2 overexpression according to some *in vivo* studies [120, 122]. In contrast, SAR viral RNA following entry into respiratory epithelial cells downregulates the activity of ACE2, thereby increasing the levels of angiotensin 2. This may potentially cause severe lung damage [121, 123]. Continued treatment with these drugs may be essential for the survival to attenuate the cardiac stress of advancing COVID-19 infection and limit the vasoconstriction and profibrotic effects of angiotensin 2 in alveolar capillaries.

Ibuprofen

Some of the anti-inflammatory drugs such as ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), are activators of ACE2 receptors, same as ACE inhibitors or ARBs. Their usage can lead to increased risk of contracting COVID-19 [118]. Since fatal lung failure induced by SARS-CoV infections may be controlled by blocking renin-angiotensin pathway [123], ibuprofen may not be harmful. However, there is no strong evidence, suggesting a link between intake of an

NSAID and worsening symptoms due to infection caused by SARS-CoV-2. The FDA considers ibuprofen and the likes as a potentially promising therapeutic agent against COVID-19 [124].

Thiazolidinediones

Studies have demonstrated that thiazolidinedione and its derivatives, which are type 2 diabetes mellitus drugs, show efficacious effect against pulmonary disease induced by respiratory syncytial virus (RSV) or H1N1 influenza infection [125, 126]. But their role as a therapeutic drug against coronavirus is not yet explored. Interestingly, it is known that thiazolidinediones may have the potential to upregulate ACE2 receptor, which is identified as a binding target for SARS-CoV-2 in host cells [118]. However, lack of clinical evidence makes it uncertain to determine its therapeutic efficacy against coronavirus infections.

Indomethacin

Amici et al. have demonstrated that indomethacin, a well-known NSAID and a potential cyclooxygenase (COX) inhibitor, exhibits antiviral activity against SARS-CoV and canine coronavirus (CCoV). *In vitro* studies suggest that indomethacin exhibits dose-dependent response in Canine A72 cell monolayers infected with CCoV with an IC₅₀ of 5 μ M after 24 h of exposure. Also, remarkable inhibition against SARS-CoV-infected Vero cells by more than 99% at concentrations that were non-toxic for uninfected cells is also observed. In addition, indomethacin significantly blocks viral RNA synthesis in dogs infected with CCoV following oral administration of the drug (1 mg/kg) [127]. This suggests probable efficacy of indomethacin against SARS-CoV-2 [127].

Colchicine

Colchicine is an anti-inflammatory drug commonly used for gout management and a variety of other conditions sharing similar pathophysiology. Its mechanisms of action are related to interfering with migration of neutrophils to sites of inflammation and blocking the inflammasome complex in both neutrophils and monocytes, thus reducing IL-1 β activation [128]. Colchicine also has inhibitory effects on macrophages via the inhibition of the NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome and pore formation activated by purinergic receptors P2X7 and P2X2. There may also be beneficial effects on endothelial function due to colchicine's antifibrotic activities. Some patients with COVID-19 present with myopathies and colchicine has been shown to reduce inflammation in the cardiac myocytes [129]. There are several ongoing studies investigating colchicine for cytokine storm (NCT04326790, NCT04322682, NCT04322565).

Niclosamide and Ivermectin

Niclosamide, an anthelmintic drug, has been shown to be an effective SARS-CoV virus replication inhibitor at dose concentration of 1.56 μM or higher in Vero E6 cells without interfering with binding of corona virus onto the cells [130]. Another study reveals the efficacy of niclosamide in inhibiting MERS-CoV replication in VeroB4 cells via reduction of SKP2 regulated BECN1 ubiquitination and enhancement of autophagic flux and its IC_{50} value is determined to be 0.3 μM [131]. Thus, the possibility of niclosamide to inhibit SARS-CoV-2 cannot be neglected. Ivermectin, a potent anthelmintic drug, was first discovered to inhibit interaction between integrase (IN) molecule of human immunodeficiency virus (HIV)-1 and its nuclear transport receptor importin α/β [132]. Further studies exhibit its potential to prevent viral replication of a broad spectrum of viruses, including dengue virus, flavivirus, and influenza [133–135]. Very recently, ivermectin has shown inhibition against SARS-CoV-2 up to 5000-fold at 48 h in vitro. Inhibition of IMP α/β 1-mediated nuclear import of viral proteins is suggested as the probable cause of its antiviral activity [136]. It will be interesting to know its inhibition effect against SARS-CoV-2 in vivo.

Nitazoxanide and Tizoxanide

Both nitazoxanide and its metabolite and tizoxanide have shown inhibitory effects against MERS-CoV in LLC-MK2 cells. Besides, inhibition of other corona virus strains, including murine corona virus, mouse hepatitis virus strain A59 (MHV-A59), bovine corona virus strain L9 (BCoV-L9), and human enteric corona virus 4408 (HECoV-4408) by nitazoxanide is reported via suppression of viral N protein [137]. Nitazoxanide is found to suppress pro-inflammatory cytokines in peripheral blood mononuclear cells (PBMCs) and IL-6 in vivo. However, the relevance of this information is currently unknown [138].

Convalescent Plasma

This treatment option refers to transfusion of plasma loaded with antibodies from individuals after resolution from a specific pathogen. This technique has been used for decades [139]. Transfusion can offer a short-term, immediate immunity for individuals. Convalescent plasma can be used prophylactically and for already infected patients to attenuate clinical severity [140, 141]. Mechanism of action is through binding of the transfused antibodies to the pathogen, resulting in cellular cytotoxicity, phagocytosis, or direct neutralization of the pathogen [142, 143]. Previously, convalescent plasma was used for two coronaviruses, SARS-CoV and MERS [144]. One large study in Hong Kong involving 80 patients with SARS-CoV supported early administration of antibodies for

optimal clinical effect compared to later administration [145]. Limited data from Taiwan and South Korea showed clinical benefits in severe cases of SARS-CoV and MERS [146, 147]. Reported dosage varied widely in terms of the amount of plasma transfused and antibody titer [148]. Limited data on COVID-19 patients from China illustrated clinical benefits [149, 150]. Pilot study reported clinical improvement in terms of fever, cough, tightness of breath, and chest pain while no serious side effects were reported [150].

Anticoagulation

There has been considerable attention placed on the role of hypercoagulable state leading to micro- and macro-vascular thrombosis in COVID-19. Disseminated intravascular coagulation and elevated d-dimer level were identified as predictors of worse outcomes in a cohort study of patients with COVID-19 [151]. Patients receiving anticoagulants had a decreased mortality [152]. Heparin has anti-inflammatory properties and may also inhibit viral attachment via conformational changes to the SARS-CoV-2 surface receptor (Spike) S1 [153]. Low molecular weight heparin in patients hospitalized with COVID-19 was associated with lower serum IL-6 concentrations, suggesting that there may be an added mechanism besides prevention/treatment of thrombosis [154]. Based on available evidence, it is reasonable to administer venous thromboembolism prophylaxis with either a low molecular weight or unfractionated heparin in hospitalized patients. In patients with rapidly progressing respiratory deterioration or where clinical judgment suggests thrombosis, treatment doses of anticoagulants may be considered.

Traditional Herbal Medicines

Historically, traditional herbal medicines have been used in the past to control and to treat epidemic outbreaks [155] including the past epidemic outbreaks, such as SARS and H1N1 influenza [156, 157]. To date, China and South Korea have issued traditional medicinal treatment guidelines on the prevention and treatment of COVID-19 [158]. It is reported that greater than 85% of SARS-CoV-2-infected patients in China had received some forms of Traditional Chinese Medicine (TCM) treatments [159]. Similar to SARS-CoV, SARS-CoV-2 uses host receptor ACE2 for the cellular entrance; it appears that some traditional medicines may have the capacity to target ACE2 and these show some promises to prevent the infection of SARS-CoV-2 [160, 161]. Due to the high similarity in epidemiologic, genomics, and pathogenesis between SARS-CoV-2 and SARS-CoV, some herbal medicinal products were used for the treatment of patients with infection of SARS-CoV-2 in China and Korea [162, 163]. The top 10 most commonly used TCM herbal medicinal products in China to treat COVID-19 patients include *Astragalus membranaceus*,

Glycyrrhiza uralensis, *Saposhnikovia divaricata*, *Rhizoma Atractylodis Macrocephalae*, *Lonicerae Japonicae Flos*, *Fructus forsythia*, *Atractylodis Rhizoma*, *Radix platycodonis*, *Agastache rugosa*, and *Cyrtomium fortunei* J. Sm [164]. In addition, some TCM herbal products, such as *Shen Fu Injection* and *Re Du Ning Injection*, could manifest potential immunosuppressive effects and thereby decrease the level of TNF- α , IL-1 β , IL-6, IL-8, IL-10, and other cytokines, resulting in inhibition of lung inflammation or acute lung injury [159, 165–167].

As discussed above, cytokine storm/inflammatory responses may contribute to the deaths of many COVID-19 patients. Thus, anti-inflammatory agents presumably could reduce the severity and mortality rate [24, 168, 169]. It is reported that *Qingfei Paidu* decoction could inhibit and alleviate excessive immune response and eliminate inflammation by regulating immune-related pathway and cytokine action-related pathway. The herbal formula *Qingfei Paidu* decoction was recommended by both Chinese and Korean guidelines. According to a recent publication, this herbal formula increases immunity and reduces inflammation by targeting the lung and spleen in COVID-19 patients [170]. Li et al. reported that *Lianhuaqingwen* (LH), a TCM formula, significantly inhibited SARS-CoV-2 replication in Vero E6 cells and markedly reduced pro-inflammatory cytokine (TNF- α , IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) production at the mRNA levels [171]. *Sangju Yin* and *Yinqiao San* are commonly used in clinical treatment to clear “lung heat,” expel phlegm, relieve cough, regulate the patient’s lungs, and restore normal lung function [172]. Similarly, *Yinqiao San* may have antibacterial and antiviral functions [172]. Several clinical studies showed that TCM may bring new hope for the prevention and control of COVID-19 [173–175]. In general, it appears that TCM products were commonly used in COVID-19 patients with mild symptoms to severe symptoms and could prevent or block the diseases progression. Although the precise molecular mechanisms currently are unknown, the potential role of anti-inflammatory/antioxidative stress, improving hypoxemia/hypoxia and antiviral activities, among others, could be some of the major drivers. Further investigations in the future are needed to uncover the molecular mechanisms.

Conclusion The COVID-19 pandemic represents the greatest global public health crisis in the past 100 years. Hopefully vaccines and or specific therapeutic drugs targeting SARS-CoV-2 will be made available in the next few months or years. With the speed and volume of basic and clinical COVID-19/SARS-CoV-2 research to develop potential drugs and therapies for this disease, our hope will be on the horizon.

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