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TITLE PAGE

COVID-19 Treatment: Close to a Cure?
– A Rapid Review of Pharmacotherapies for the Novel Coronavirus

1. Yang Song, PharmD, BCPS
Department of Pharmacy Services
CHI Franciscan Health-St. Joseph Medical Center
Tacoma, WA 98405
songx298@gmail.com

2. Min Zhang, PharmD, BCPS
Department of Pharmacy Services
Boston Medical Center
Boston, MA 02118

3. Ling Yin, PharmD, PhD, BCPS, BCOP
Department of Pharmacy Services
AdventHealth Celebration Cancer Institute
Celebration, FL 34747

4. Kunkun Wang, PharmD
Department of Pharmacy Services
Fairbanks Memorial Hospital
Fairbanks, AK 99701

5. Yiyi Zhou, PharmD
Department of Pharmacy Services
Beijing United Family Hospital
Beijing, China 100016

6. Mi Zhou, MM
Department of Pharmacy Services
Children's Hospital of Soochow University
Suzhou, China 215000

7. Yun Lu, PharmD, MS
Associate Clinical Professor, University of Minnesota
Department of Pharmacy Services
Hennepin County Medical Center
Minneapolis, MN 55415

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Abstract

Currently, there is no specific treatment for COVID-19 proven by clinical trials. WHO and CDC guidelines therefore endorse supportive care only. However, frontline clinicians have been applying several virus-based and host-based therapeutics in order to combat SARS-CoV-2. Medications from COVID-19 case reports, observational studies and the COVID-19 Treatment Guideline issued by the China's National Health Commission *(7th edition published March 3rd, 2020. Edited translation attached)* are evaluated in this review. Key evidence from relevant *in vitro* researches, animal models and clinical studies in SARS-CoV-2, SARS-CoV and MERS-CoV are examined. Antiviral therapies remdesivir, lopinavir/ritonavir and umifenovir, if considered, could be initiated before the peak of viral replication for optimal outcomes. Ribavirin may be beneficial as an add-on therapy and is ineffective as a monotherapy. Corticosteroids use should be limited without indicating comorbidities. IVIG is not recommended due to lack of data in COVID-19. Xuebijing may benefit patients with complications of bacterial pneumonia or sepsis. The efficacy of interferon is unclear due to conflicting outcomes in SARS and MERS studies. Chloroquine and hydroxychloroquine have shown *in vitro* inhibition of SARS-CoV-2 and may be beneficial as both prophylactic and treatment therapy. For patients who developed cytokine release syndrome, interleukin-6 inhibitors may be beneficial. Given the rapid disease spread and increasing mortality, active treatment with readily available medications may be considered timely prior to disease progression.

Keywords

China's COVID-19 Guide; Remdesivir; Xuebijing; Hydroxychloroquine; IL6 inhibitors; COVID-19

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Introduction

On December 31st, 2019, several pneumonia cases linked to a seafood market in Wuhan, China were reported to the World Health Organization (WHO). The fast-spreading infection, now known as coronavirus disease 2019 (COVID-19), is caused by a novel coronavirus (SARS-CoV-2) [1]. On March 12th, 2020, WHO declared COVID-19 outbreak a pandemic [2]. According to Johns Hopkins' COVID-19 global case dashboard, by March 24th, 2020, there were 417,582 confirmed cases and 18,612 total deaths worldwide [3]. At present, there is no treatment specific for SARS-CoV-2 with efficacy proven by randomized controlled trials (RCT). However, given the scale and rapid spread of this infectious disease, it is obligatory to take a deeper look at medication therapies that have been applied or suggested by frontline clinicians and examine the clinical and laboratory evidence behind them.

Methods

This review focuses on potential medication therapies for SARS-CoV-2. The selection of medications in this review is based on case reports, observational studies and the 7th edition of COVID-19 diagnosis and treatment guideline issued by the National Health Commission (NHC) of the People's Republic of China (*Table 2*). Although there are few controlled clinical studies on SARS-CoV-2, the novel virus is found to share 79% genome sequence with severe acute respiratory syndrome coronavirus (SARS-CoV) and about 50% with Middle East respiratory syndrome coronavirus (MERS-CoV) while manifesting overlapping pathogenesis [4,5]. Relevant *in vitro* researches, animal models and clinical evidence in SARS-CoV-2, SARS-CoV and MERS-CoV are searched and reviewed by March 24th 2020, in order to gain insights on

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the potential role of these medication therapies in combating COVID-19. Data for this review were identified by searches of PubMed and references from relevant articles using the search terms "[medication name]" and "SARS-CoV-2", "MERS", "SARS", "COVID-19". Only articles published in English and Chinese (speaking languages of the authors) were included. Patients-based clinical data, when available, were given priority over *in vitro* and *in vivo* data. Randomized controlled trials, when available, were given priority over other studies.

Results

Remdesivir

Remdesivir (GS-5734) is an investigational drug first developed for the treatment of Ebola [6,7]. As an adenosine analogue prodrug, it putatively disrupts viral RNA transcription and is viewed as a broad-spectrum antiviral agent [8,9,10,11]. Previous safety data suggested that hypotension might occur and that liver enzymes that need to be closely monitored [6,7].

Remdesivir has shown *in vitro* inhibition on coronaviruses MERS-CoV and SARS-CoV [8,9,10]. One genomic study found a remarkable 96% sequence similarity of RNA-dependent RNA polymerase (RdRp), the supposed drug target site for remdesivir, between SARS-CoV-2 and SARS-CoV [10]. Profoundly, an *in vivo* research has shown that remdesivir overcomes drug resistance induced by exoribonuclease and genetic mutations in SARS-CoV RdRp [11]. Based on the above, remdesivir is a potential treatment for SARS-CoV-2 and future emerging coronaviruses.

In a mouse SARS-CoV model, remdesivir reduced viral burden and lung pathology efficiently. Notably, when remdesivir was given after the peak of viral replication and airway epithelium damage, it no longer increased survival or reserved pulmonary function significantly [12]. This finding indicates that remdesivir should be initiated promptly before patients become critically ill. In February 2020, results of

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remdesivir in the first nonhuman primate model of MERS-CoV became available, revealing successful reduction of clinical signs, lung lesions, and viral replication [13]. The regimen was started 12 hours post-inoculation, again signaling the importance of early initiation of therapy [13].

In February 2020, remdesivir produced high efficacy against SARS-CoV-2 *in vitro* (half maximal effective concentration EC_{50} = 0.77 μM; the 50% cytotoxic concentration CC_{50} > 100 μM; the selectivity index SI > 129.87) [9]. The first COVID-19 case in the United States was also the first COVID-19 treated with remdesivir intravenously (IV) [14]. The medication was started for compassionate use without any adverse drug effects observed. Within 24 hours of remdesivir initiation, the patient became afebrile, off nasal cannulae, with chest rales resolved. However, the reverse transcription polymerase chain reaction (RT-PCR) series showed downward-trending viral loads even before remdesivir treatment. It therefore cannot be determined if further viral load decrease and clinical improvement were a direct result of remdesivir. Although promising, the outcome from a single case cannot be generalized to a larger population.

Two phase III RCTs have started in China to evaluate remdesivir for SARS-CoV-2 from February to April 2020. The regimen is 200 mg IV on day 1, followed by 100 mg IV once daily for 9 days. Patients with severe renal impairment (eGFR< 30 mL/min/1.73) or severe liver disease are excluded [15,16]. The trials will provide insights on the clinical efficacy and safety of remdesivir in COVID-19. As an investigative drug, remdesivir is not recommended by China's NHC [17].

Lopinavir/ritonavir

Lopinavir/ritonavir (LPV/r) is a combination protease inhibitor approved for the treatment of human immunodeficiency virus (HIV) infection [18]. Lopinavir binds to viral protease and prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles. Ritonavir

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increases the plasma concentration of lopinavir by inhibiting cytochrome P450 3A (CYP3A) metabolism. Short-term side effects of LPV/r include nausea, diarrhea, abdominal pain, elevation of liver enzyme and prolongation of QT and PR interval. Potential drug interactions exist with CYP3A or P-glycoprotein (P-gp) substrates, inducers and inhibitors [18].

The molecular dynamic simulations demonstrated binding affinities of LPV/r to SARS-CoV's main protease enzyme $3CL^{pro}$ [19]. An *in vitro* susceptibility test showed that the cytopathic effect of lopinavir against SARS-CoV was 4 μg/mL [20]. Although the peak (9.6 μg/mL) and trough (5.5 μg/mL) concentrations of lopinavir were above the threshold for SARS inhibition (4 μg/mL), the free drug concentration for pharmacodynamic effect would likely be below the inhibitory threshold in the setting of high protein binding (98-99%).

During the Middle East respiratory syndrome coronavirus (MERS) outbreak, LPV/r showed modest improvement on clinical, radiological, pathological and viral-load outcomes in common marmosets with severe infection when compared to untreated animals [21]. However LPV/r-based triple therapy with ribavirin and interferon showed conflicting results in two published case reports [22,23].

During the severe acute respiratory syndrome (SARS) outbreak, it appeared that LPV/r conferred clinical benefit in an early phase of the disease to reduce peak viral load before progression to acute respiratory distress syndrome (ARDS). A multicenter retrospective cohort study compared the outcomes of SARS patients treated with LPV/r with a matched cohort who received the standard treatment of ribavirin and corticosteroids [24]. When LPV/r was added to ribavirin and corticosteroids as initial treatment, the mortality and intubation rates were lower than among those who received it as rescue therapy (2.3% vs. 15.6%, 0% vs. 110% respectively, $p<0.05$) [24]. Another study group from Hong Kong retrospectively evaluated the efficacy of LPV/r in 152 patients with SARS [20]. Patients from the

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historical control arm received ribavirin while those in the second group received LPV/r in addition to ribavirin. The second group showed lower rates of 21 days adverse outcomes (ARDS or death) when compared to the historical controls (2.4% vs. 28.8%, p<0.001) [20]. However, the historical nature of the control arm from a different study period and variations in baseline characteristics did not allow for a valid estimate of efficacy [5]. Given the limitations of the study design, caution should be used when evaluating the efficacy of LPV/r-based regimens against coronavirus.

On March 18th, the results of the first COVID-19 clinical trial of LPV/r were published. Unfortunately, LPV/r did not show superiority over standard care for time to achieve clinical improvement, 28-day mortality and viral clearance [25]. In the trial, LPV/r shortened the intensive care unit (ICU) stay by a median of 5 days (95% CI, −9 to 0). The authors made valuable points that the study size is small and the antiviral medication might have been initiated too late in the course of infection. An open-label phase IV RCT has started in China to evaluate the efficacy of LPV/r plus umifenovir (arbidol) for treating patients with COVID-19 since January 2020. The results will provide evidence for the treatment of SARS-CoV-2 with LPV/r [26]. LPV/r is recommended by China's NHC (*table 2*) [17].

Ribavirin

Ribavirin is a nucleoside analog which has antiviral activity against multiple RNA viruses, including respiratory syncytial virus (RSV), SARS-CoV and MERS-CoV by interfering with RNA polymerase and viral protein synthesis [27,28]. The most severe adverse effects associated with ribavirin use are hemolytic anemia and leukopenia. Other adverse effects include fatigue, pruritus, rash, and gout. Ribavirin is a notorious teratogenic drug and is contraindicated in pregnancy [27,28].

Ribavirin, with or without the concomitant use of steroids, was used extensively during the 2013 SARS outbreak. *In vitro* tests showed that ribavirin inhibited a β coronavirus at relatively high concentration [29]. However, when using ribavirin with interferon-α2b combined, lower concentrations

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of ribavirin inhibited viral replication in Vero cell lines [29]. More than 24 studies with 10 to 100 patients described ribavirin-based regimens with interferon or corticosteroids. However, the findings were inconclusive given various methodological issues and the presence of confounding variables [30].

A retrospective case series on 144 patients with SARS reported that 88% of patients received ribavirin [31]. Approximately 91% of those individuals received ribavirin within the first 48 hours of hospital admission. About 40% of patients also received corticosteroids. Twenty-one day mortality was 6.5%, and 20% in patients transferred to ICU with and without mechanical ventilation (MV) [31]. A prospective, uncontrolled study evaluated clinical outcomes of ribavirin and corticosteroids in 132 patients with suspected SARS when fever was not resolved after 48 hours of hospital admission. 25 patients (18.1%) responded to ribavirin and corticosteroids and two of those patients received ribavirin IV [32]. Approximately 49% to 59% of patients treated with ribavirin had a reduction in hemoglobin of more than 2 g/dL from baseline, 36% to 76% had evidence of hemolytic anemia and 40% experienced elevation of transaminases.[32,33] In view of substantial adverse events, and also the lack of *in vitro* efficacy, ribavirin-based therapy for SARS is still in question [31,32,33,34].

Currently, ribavirin's efficacy against SARS-CoV-2 has not been evaluated in animal, *in vitro* or clinical studies. Ribavirin 500mg IV 2 to 3 times daily is suggested by China's NHC for COVID-19 as an add-on therapy to lopinavir/ritonavir or interferon *(table 2)* [17].

Interferon

Interferon (IFN) can induce several parallel antiviral pathways by triggering viral RNA degradation, RNA transcription alteration, protein synthesis inhibition, and apoptosis [35]. The common side effects include flu-like symptoms and mood changes [36]. It is contraindicated in patients with decompensated liver disease, severe autoimmune disease, worsening psychiatric conditions, cytopenia and uncontrolled

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seizures [36]. Peginterferon α-2a is FDA-approved for the treatment of hepatitis B and C. However, it is no longer the standard therapy for hepatitis C given serious adverse effects and lower efficacy compared to newer antiviral agents [37].

Table 1 Interferon regimens for coronaviruses

Indication	**IFN Type & Suggested Regimen**
SARS	Alfacon-1®(IFN-α): 9 μg/day subcutaneous (SQ) for at least 2days and increased to 15 μg/day if no responses [38] rIFN-α: 3,000,000 U/day intramuscular (IM) [39]
MERS	IFN-α-2b: 100 μg to 144 μg SQ weekly [40] PEG-Intron® (rIFN-α-2b): 1.5μg/kg SQ weekly for 2 weeks [41] Pegasys® (Pegylated IFN-α-2a): 180 μg SQ weekly [22, 41, 42, 43] Rebif® (rIFN-β-1a): 44 mg SQ three times a week [41, 43]
COVID-19	IFN-α 5 million unit or equivalent dose in 2 mL sterile water via nebulization twice a day [17]

The *in vitro* data and animal studies of interferon have shown promising activity against SARS-CoV and MERS-CoV. The EC_{50} of IFN-β-1a and IFN-α were 8 U/mL and 30 U/mL respectively in an assay of a prototype SARS-CoV cell line [44]. Another *in vitro* study of MERS-CoV showed that Rebif® (rIFN-β-1a) achieved 100% MERS-CoV plaque reduction at 62,500 IU/mL with an EC_{50} of 480.54 ± 183.85 IU/mL [45].

During the SARS and MERS outbreaks, interferon was widely used for its antiviral effects. An open-label uncontrolled retrospective study on SARS showed that the addition of Alfacon-1® (IFN-α) to corticosteroids was associated with faster lung recovery and shorter intubation time compared to corticosteroids alone [38]. Similarly, a randomized, 4-arm, open-label, retrospective study on SARS in

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Guangzhou, China demonstrated that IFN plus high dose steroid therapy achieved respiratory improvement, faster resolution of pulmonary infiltrates, and less need for MV [39]. Since the MERS outbreak, several studies have been conducted to evaluate the antiviral therapies used. One retrospective cohort study found that the combined regimen of ribavirin and IFN was associated with higher 14-day survival rates, but did not improve the long-term survival rate [42]. Moreover, IFN combined with ribavirin was correlated with neither a faster viral clearance, nor an improved survival rate in older (>50 years old) critically-ill patients with comorbidities [37,40,41,43].

To date, both *in vitro* and clinical data of IFN against SARS-CoV-2 are limited. Thus, the role of INF in the treatment of COVID-19 remains unclear. Considering the risk of spreading infectious aerosol, uncertainty of pharmacokinetics in nebulization, and lack of clinical data, it is difficult to justify inhalation therapy for the treatment of COVID-19 at this point. RCTs on IFN are required to evaluate its efficacy against SARS-CoV-2. China's NHC recommended IFN nebulization as one of the antiviral options for COVID-19 (*table 2*) [17].

Corticosteroids:

Corticosteroids are a type of anti-inflammatory medication that is effective in treatment of a variety of conditions such as asthma, allergic conditions, autoimmune diseases, septic shock, and cancers [46]. Corticosteroids are a double-edged sword since while these agents inhibit inflammation, they also impair immune response and increase the risk of infection. The adverse effects vary depending on the dosage and duration of therapy. These side effects include hyperglycemia, abdominal obesity, infection, mood swing, osteoporosis, growth retardation, glaucoma and hypertension [46].

A systematic review of steroids administered to patients with SARS reported no survival benefit and possible harm including avascular necrosis, psychosis, diabetes, and delayed viral clearance [30].

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Another study of patients receiving corticosteroids for MERS found no benefit in mortality but delayed lower respiratory tract clearance of MERS-CoV [47].

Since the outbreak of COVID-19 in China, corticosteroid treatment has been used in up to 45% of patients infected with SARS-CoV-2 [48, 49]. One retrospective observational study showed 72% of the ICU patients with COVID-19 received glucocorticoid therapy [48]. However, the existing evidence regarding the use of steroids in this specific patient population remains inconclusive due to methodological limitations. Based on the previous data on other clades of coronavirus, such as SARS-CoV and MERS-CoV, the WHO and the Centers of Disease Control and Prevention (CDC) generally recommend glucocorticoids not be used in COVID-19 pneumonia unless there are other indications (e.g., exacerbation of chronic obstructive pulmonary disease) [50,51]. In line with current WHO and CDC guidelines, Russell and his colleagues suggest that corticosteroids should not be used for the treatment of COVID-19-induced lung injury or shock outside of the setting of clinical trials [52]. However, some front-line physicians in China have a different perspective. They recommend short courses (≤7 days) of corticosteroids at low-to-moderate doses (≤0.5-1mg/kg per day methylprednisolone or equivalent) be used judiciously for critically ill patients with COVID-19 pneumonia [53,54]. According to China's NHC, systemic glucocorticoids should be used with caution and the routine use should be avoided [17]. Short-term methylprednisolone can be administered for patients with rapid disease progression or severe illness, and the recommended dose should not exceed 1-2mg/kg/day. Notably, the guideline states that high doses of corticosteroids may delay viral clearance due to their inhibitory effects on the immune system. The benefits and risks should be carefully evaluated before administration of corticosteroids. For patients with hypoxemia or who take corticosteroids regularly for chronic diseases, corticosteroids should be used cautiously [54]. As of now, the use of corticosteroids to reduce cytokine-related pulmonary damage in patients with COVID-19 pneumonia is controversial. Robust evidence from well-

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designed clinical trials is needed for the recommendation of corticosteroid treatment in patients with COVID-19.

Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulin (IVIG) is a product of human immunoglobulins derived from plasma, indicated for various immunodeficiencies, autoimmune and inflammatory disorders [55, 56]. IVIG has potent immune replacement and immune modulating effects via complex pathways [56]. In addition, IVIG has anti-inflammatory properties and can neutralize bacterial toxins [57]. The most common adverse reactions of IVIG are headache, fever and tachycardia [56].

Several animal studies found that equine and bovine-produced human immune antibodies can reduce viral titers and accelerate viral clearance of MERS-CoV in mouse models [58]. These studies implied that immunoglobulin may have a potential to prevent and treat MERS.

During the 2013 SARS epidemic, observational studies and case reports described IVIG for the treatment of critically ill patients in combination with antiviral therapies. In a clinical review of different treatment protocols for SARS, IVIG was used with interferon in all critically ill patients (n=120). The authors concluded that there was no significant benefit [38]. In another prospective observational study, IVIG was used in SARS patients with severe leukopenia or thrombocytopenia, and it appeared to be effective for controlling cytopenia by increasing leukocyte and platelet counts. However, without a control group, IVIG's role in SARS treatment remains undetermined [59]. Currently, there is no solid clinical evidence to support the use of IVIG in SARS or MERS.

Since the outbreak of COVID-19 in Wuhan, China, clinicians have used IVIG in patients infected with SARS-CoV-2 by extrapolating the IVIG data from SARS and MERS. In a descriptive study of COVID-19, 27% of 99 patients received IVIG, but the efficacy and safety of IVIG in this patient population were

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not addressed in this study [47]. Given the lack of data on IVIG in treatment of COVID-19 patients, clinicians and researchers have proposed a number of clinical trials to evaluate the efficacy of IVIG for severe COVID-19 as compared to standard care [60]. Another interesting trial is aiming to separate immunoglobulin from recovered COVID-19 patients and evaluate the safety and efficacy of the immunoglobulin as a therapy. This study may provide a new strategy to treat patients with COVID-19 by using specific antibodies against virus antigen [61]. Neither China's NHC nor WHO guideline for diagnosis and treatment of COVID-19 currently provides any recommendations on the use of IVIG [17,48].

Xuebijing (XBJ)

Xuebijing (XBJ) is a widely used traditional herbal medicine in China for its anti-inflammatory and anti-endotoxin effects [62,63]. It is a five-herbal combination (carthamus tinctorius, radix paeoniae rubra, ligusticum wallichii, salvia miltirrhiza and angelica sinensis). The common side effects include infusion reactions of rash, tachycardia, hypotension and GI discomforts including nausea, vomiting, abdominal pain and/or diarrhea.

In a meta-analysis of case-control studies on sepsis, XBJ significantly reduced 28-day mortality and improved clinical parameters including the Acute Physiology and Chronic Health Evaluation II score (APACHE II), WBC, C-reactive protein (CRP), procalcitonin and body temperature [62]. That being said, the efficacy of XBJ in sepsis needs to be confirmed in a RCT. The current clinical data on XBJ in ARDS are inconsistent. One RCT showed reduction in duration of MV, ICU stay and Murray score, while the other RCT revealed no difference in these clinical outcomes [64,65]. However, neither of the ARDS studies proved significant 28-day mortality benefit. Further well-designed RCT with larger sample size is warranted to conclude on XBJ in ARDS. In a multicenter RCT on critically-ill patients with severe community-acquired pneumonia (CAP), XBJ significantly improved pneumonia severity index, 28-day mortality, duration of MV, and ICU stay [66]. Based on the clinical evidence on XBJ in sepsis, bacterial

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pneumonia and ARDS, three common complications in COVID-19, China's NHC has recommended XBJ 100mL in 250 mL normal saline IV twice a day as one of the treatment options in COVID-19 patients presenting with cytokine release syndrome and/or multi-organ failure (*table 2*) [17].

Umifenovir (arbidol)

Umifenovir is a synthetic antiviral drug marketed in Russia and China for treating seasonal influenza. It has shown broad-spectrum antiviral activity against other viruses including SARS-CoV [67]. In a COVID-19 case series study, the combination of umifenovir, lopinavir/ritonavir and traditional Chinese medicine alleviated pneumonia symptoms in all four patients and decreased viral load to undetectable in two [68]. Umifenovir is a new addition to China's NHC guide on COVID-19.

Chloroquine (CQ) / hydroxychloroquine (HCQ)

Chloroquine (CQ) is a classic antimalarial drug. Its well-known effect of neutralizing acidic endosomal pH supports broad-spectrum antiviral usage by blocking endosome-mediated viral entry [69,70]. It also exhibits anti-inflammatory and immunomodulatory benefits in viral infections. HCQ is a less toxic metabolite of CQ. Both could be toxic and even fatal if overdosed [71,72]. The adverse effects include retinopathy, arrhythmia, liver enzyme elevation, blood counts change and mood change. It is important to monitor drug interactions with other QTc-prolonging agents [71,72].

During the SARS outbreak, CQ was found to inhibit SARS-CoV *in vitro*, showing potential as both prophylactic and therapeutic treatment [70]. Since the COVID-19 outbreak, CQ showed potent antiviral effect on SARS-CoV-2 *in vitro*, with the 90% effective concentration (EC_{90}) of 6.90 µM, which is clinically achievable [9]. HCQ is even more potent *in vitro* (EC_{50}=0.72 µM) against SARS-CoV-2 and a pharmacokinetic model found that a regimen of 400 mg twice a day orally followed by 200 mg twice a day orally for four days would achieve therapeutic level [73].

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An open-label non-randomized clinical trial in France studied HCQ regimen of 200 mg three times a day orally with and without azithromycin. The study reported 100% viral clearance on day 6 in HCQ plus azithromycin group vs. 57.1% in HCQ monotherapy group vs. 12.5% in control group [74]. While this trial resulted in promising data, it has a few limitations. The size of 42 participants was too small. It was not randomized and the HCQ group had higher viral load at baseline. Clinical outcomes of patients were not studied in this trial. The correlation of clinical outcomes with viral clearance can not be determined without further study.

A controlled pilot study in Shanghai presented hydroxychloroquine as ineffective for expediting viral clearance, recovery from fever and CT image improvement ($P > 0.05$) [75]. However, the study had a very small sample size (n=30). It is not a treatment vs. placebo study. Both HCQ group and control group were treated with IFN and most patients also received LPV/r or arbidol. The study design is questionable, especially when there are no conclusions on the effect of IFN and antivirals in COVID-19 yet. More trials with improved sample size and study design are needed to address the efficacy of CQ and HCQ against SARS-CoV-2. China's NHC recommends CQ 500 mg twice a day orally for 7 days for COVID-19 with some exceptions (*table 2*) [17].

Interleukin-6 (IL-6) inhibitors

Tocilizumab (Actemra®), known as a humanized interleukin-6 (IL-6) receptor antagonist, is currently approved for rheumatoid arthritis, and cytokine release syndrome (CRS) due to chimeric antigen receptor T cell (CART) therapy [76]. The common side effects of tocilizumab include hypersensitivity reaction and infection [76].

In COVID-19 patients with CRS, patients were found to have elevated levels of cytokines such as IL-2, 6, 8, 10 and TNFα that indicate inflammation and immunological diseases. In addition, CRS was

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revealed to be associated with the severity of COVID-19 [77, 78, 79]. These data suggest that the IL-6 pathway may play an important role in the overactive inflammatory response in the lungs of COVID-19 patients. Therefore, it could be a potential target for immunotherapy of COVID-19. Based on these clinical evidence, the FDA has given fast track approval to a phase III clinical trial to evaluate the safety and efficacy of tocilizumab plus standard of therapy in hospitalized adults with severe COVID-19 pneumonia. Another multicenter RCT for the safety and efficacy of tocilizumab in the treatment of COVID-19 is also ongoing in China [80] . The 7th edition of China NHC guideline on COVID-19 has included tocilizumab as one of treatment options for COVID-19 patients who show severe lung damage and elevated level of IL-6 (*table 2*) [17]. The recommended dose is 400 mg as the initial dose. Additional dose of 400 mg can be given if clinical improvement does not occur 12 hours after the first dose.

Sarilumab (Kevzara®) is another fully-human monoclonal antibody that inhibits the IL-6 pathway by binding and blocking the IL-6 receptor. It has been approved for the treatment of rheumatoid arthritis [81]. The common toxicities include neutropenia, thrombocytopenia, infusion reaction and infection [81]. The global clinical trials of sarilumab in COVID-19 treatment have been initiated to evaluate the clinical outcomes such as fever, the need for supplemental oxygen, mortality, MV, ICU stay and hospitalization [82].

Siltuximab (Sylvant®) approved in the US to treat patients with multicentric Castleman disease is the third potential IL-6 targeted therapy for COVID-19 trials [83]. Similar to other IL-6 antagonists, the common adverse effects of siltuximab are cytopenia, infection and hypersensitivity reaction [83]. An observational case-control study of siltuximab in ARDS patients secondary to SARS-CoV2 infection is underway to evaluate the need of invasive ventilation and mortality reduction in Italy [84]. All these trials will help determine whether IL-6 inhibition with these IL-6 antagonists will provide clinical benefit in COVID-19 patients.

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Table 2. National Health Commission of the People's Republic of China: the COVID-19 Diagnosis and Treatment Guide 7th Edition (Treatment Session Only, Translated) [17]

1. Standard treatment

I. Bed rest, supportive care, ensure calories intake; maintain fluid and electrolyte balance, hemostasis; monitor closely vitals and oxygen saturation.

II. Monitor the complete blood count (CBC), comprehensive metabolic panel (CMP), arterial blood gas (ABG), urinalysis, CRP, cardiac enzymes, coagulation, chest imaging, and other applicable labs. If available, check cytokine panel.

III. Provide oxygen therapy in time via nasal cannula (low to high flow) and face mask.

IV. Antiviral treatment (adult dosing): assess clinical response. Concurrent use of 3 or more antiviral agents is not recommended.

- Interferon-α 5 million units nebulization twice a day, prepare with sterile water 2ml.
- Lopinavir / ritonavir 2 capsules (200 mg/ 50 mg per capsule) twice a day orally for no more than 10 days. Monitor closely for nausea, vomiting, diarrhea, hepatotoxicity, other side effects. Screen for drug interactions.
- Ribavirin 500 mg IV 2-3 times a day for no more than 10 days. Use in combination with lopinavir/ritonavir or INF-α.
- Chloroquine 500 mg twice a day orally for 7 days. For patients less than 50 kg, reduce dose to 500 mg once daily from day 3 through day 7. Avoid use in patients with cardiovascular disease.
- Umifenovir (arbidol) 200 mg 3 times a day orally for no more than 10 days.

V. Antimicrobial therapies: avoid unnecessary or inappropriate prescribing of antimicrobial medications, especially the broad- spectrum therapies.

2. Treatment for severe and critical cases*

I. Principle: Besides standard treatment, actively prevent and treat complications, manage patients' chronic medical diseases, prevent secondary infections, support multiple organ functions.

II. Respiratory support (*summarized*): determine proper support from nasal cannula, face mask to mechanical ventilation and proning. For severe acute respiratory distress syndrome, ECMO should be considered.

III. Circulation support: optimize fluid resuscitation first, consider vasoactive therapy to ensure circulation and organ perfusion. Apply hemodynamic monitoring if indicated.

IV. Convalescent plasma transfusion: appropriate for severe or critical cases.

V. Plasmapheresis: may consider for cytokine storm management

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VI. Immunotherapy: tocilizumab 4-8 mg/kg or 400mg standard dose IV once can be considered for elevated Interleukin-6. May repeat a dose in 12 hours without exceeding a total dose of 800mg.
VII. Other measures: ▪ Based on respiratory distress and chest imaging, may consider glucocorticoid that is equivalent to methylprednisolone 1-2 mg/kg/day for 3-5 days or less. Note that large-dose glucocorticoid suppresses immune system and could delay clearance of SARS-CoV-2. ▪ May consider Xuebijing 100ml IV twice a day. ▪ May use microecological preparation to maintain intestinal flora balance and prevent secondary infection. ▪ Provide psychotherapy for patients who develop high level of anxiety.
3. Traditional Chinese medicine
I. Practice syndrome differentiation and dialectics-based medicine.
II. General recommendations of traditional therapies are made for each stage of clinical course from initial, severe, critical to recovery stage. *(Note: Please refer to the original guide for details.)*
***Severity of illness definition**
Severe case: respiratory rate ≥ 30 per minutes, oxygen saturation ≤ 93%, PaO2/FiO2 ≤ 300 mmHg, or significant disease progression in 24-48 hours per chest imaging **Critical case:** ARDS requiring mechanical ventilation, shock, or organ failure requiring ICU care

Conclusion

Currently the guidance from WHO and CDC focuses on supportive care and the management of complications per general guidelines [50,51]. Remdesivir is viewed as potentially promising for treating COVID-19. The COVID-19 diagnosis and treatment guideline issued by China's NHC provides several medication therapy recommendations (*table 2*). All these therapeutics are discussed in this review.

This review does not include darunavir/cobicistat, nitazoxanide, angiotensin II receptor blockers and other medications that have been suggested for SARS-CoV-2, awaiting evidence. This review does

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not discuss any oral-route traditional Chinese medications, the prescribing of which follows dialectics-based medicine.

In conclusion, supportive care remains the cornerstone of COVID-19 management. Complications should be managed according to general guidelines. However, the rapid disease spread and increasing mortality call for a progressive approach. When safety is ensured, active treatment might be considered promptly prior to disease progression. Timely clinical data sharing from the frontline should be encouraged to further evaluate the efficacy of medication therapies. For the medication agents discussed in the review, well-designed controlled clinical trials in SARS-CoV-2 are warranted before final conclusions on efficacy can be made.

Declarations of interest

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