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COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2)

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ABSTRACT

Currently, there is no approved therapy for coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) therefore endorses supportive care only. However, frontline clinicians and researchers have been experimenting with several virus-based and host-based therapeutics since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China. China's National Health Commission has issued the first COVID-19 treatment guidelines with therapy suggestions, which has inspired clinical studies worldwide. This review evaluates the major therapeutics. Key evidence from in vitro research, animal models and clinical research in emerging coronaviruses is examined. The antiviral therapies remdesivir, lopinavir/ritonavir and umifenovir, if considered, should be initiated before the peak of viral replication for an optimal outcome. Ribavirin may be beneficial as an add-on therapy but is ineffective as monotherapy. Corticosteroid use should be limited to specific co-morbidities. Intravenous immunoglobulin (IVIg) is not recommended owing to lack of data in COVID-19. The traditional Chinese medicine Xuebijing may benefit patients with complications of bacterial pneumonia or sepsis. The efficacy of interferon is unclear owing to conflicting outcomes in coronavirus studies. Chloroquine and hydroxychloroquine have shown in vitro inhibition of SARS-CoV-2, but studies on their clinical efficacy and whether the benefits outweigh the risk of dysrhythmias remain inconclusive. For patients who develop cytokine release syndrome, interleukin-6 inhibitors may be beneficial.

1. Introduction

On 31 December 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 named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. On 11 March 2020, the WHO declared the COVID-19 outbreak a pandemic [2]. According to the Johns Hopkins University COVID-19 global case dashboard, by 23 June 2020 there were 9 157 320 confirmed cases and 473 849 total deaths worldwide [3]. At present, there is no treatment specific for SARS-CoV-2 infection with proven efficacy in randomised controlled trials (RCTs). However, given the scale and rapid spread of this infectious disease, it is obligatory to take a deeper look at therapies that have been experimented by frontline clinicians and to examine the clinical and laboratory evidence behind them.

2. Methods

The selection of treatments in this review is based on the 7th edition of the '*COVID-19 diagnosis and treatment guideline*' issued by the National Health Commission (NHC) of the People's Republic of China [4] (Table 1) and relevant clinical studies. Although there are few published RCTs on SARS-CoV-2, the novel coronavirus is found to share 79% genome sequence identity with severe acute respiratory syndrome coronavirus (SARS-CoV) and ~50% identity with Middle East respiratory syndrome coronavirus (MERS-CoV) while manifesting overlapping pathogenesis [5,6]. Relevant in vitro studies, animal models and clinical evidence on all coronaviruses were reviewed up to 23 June 2020 to gain insights on the potential

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

3. Results

3.1. Remdesivir

Remdesivir (GS-5734) is an investigational drug first developed for the treatment of Ebola virus [7,8]. As an adenosine analogue prodrug, it putatively disrupts viral RNA transcription and is viewed as a broad-spectrum antiviral agent [9–12]. Profoundly, remdesivir has exhibited mechanisms to overcome drug resistance and genetic mutations in coronavirus [12]. Remdesivir is not recommended in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73] or severe liver disease [13–15]. Remdesivir is generally well tolerated, with possible adverse effects of nausea, liver enzyme elevation, hypotension and respiratory failure [7,8,14,15].

In a mouse SARS-CoV model, remdesivir efficiently reduced viral burden and lung pathology. 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 [16]. In February 2020, results of remdesivir in the first non-human primate model of MERS became available, revealing successful reduction of clinical signs, lung lesions and viral replication [17]. The regimen was started 12 h post-inoculation, again signalling the importance of early initiation of therapy [17].

In February 2020, it was reported that remdesivir demonstrated high efficacy against SARS-CoV-2 in vitro, with a half maximal effective concentration (EC_{50}) of 0.77 μM, a 50% cytotoxic concentration (CC_{50}) of >100 μM and a selectivity index (SI) of >129.87] [10]. The first COVID-19 case in the USA was treated with intravenous (i.v.) remdesivir [18]. Within 24 h of remdesivir initiation, the patient became afebrile, was weaned off nasal cannula, and chest rales resolved. However, the viral load had been trending downward even before remdesivir treatment. Therefore, it cannot be determined whether the further viral load decrease and clinical improvement were a direct result of remdesivir. A case series of remdesivir compassionate use ($n = 53$) reported 68% of patients with improved oxygenation, 47% of patients discharged and 13% died [13]. The study was weakened by many factors, including most significantly the lack of a paired control group [13]. A double-blinded RCT in China ($n = 237$) revealed no superiority of remdesivir over placebo in time to clinical recovery, 28-day mortality or viral clearance [14]. On average, remdesivir was initiated 11 days post-symptom onset, likely past the peak of viral replication. As the COVID-19 surge passed in China, the trial only recruited 50% of the target sample size, reducing its statistical power. SIMPLE, a phase 3 open-label RCT, demonstrated that remdesivir 5-day vs. 10-day regimens of 200 mg once followed by 100 mg i.v. daily produced similar outcomes. The group that started remdesivir early (<10 days of symptoms onset) had a higher discharge rate on Day 14 (62% vs. 49%) [15]. The US National Institutes of Health (NIH) recently released preliminary result analysis of the Adaptive COVID-19 Treatment Trial (ACTT) ($n = 1063$) [19]. In this RCT, the remdesivir arm had a 31% faster time to recovery than the placebo group ($P < 0.001$). The mortality rate was also reduced in the remdesivir group but not statistically significantly (8.0% vs. 11.6%; $P = 0.059$). The forthcoming full publication might reveal whether the promising outcomes were associated with early administration of remdesivir, as suggested by previous studies.

Certainly, remdesivir has not shown a significant mortality benefit. When initiated early, remdesivir appears to expedite recovery.

Table 1
National Health Commission of the People's Republic of China: the *COVID-19 Diagnosis and Treatment Guide 7th Edition* (treatment session only, translated) [4].

1. **Standard treatment**
I. Bed rest, supportive care, ensure calorie intake; maintain fluid and electrolyte balance, haemostasis; monitor closely vitals and oxygen saturation.
II. Monitor the complete blood count (CBC), comprehensive metabolic panel (CMP), arterial blood gas (ABG), urinalysis, C-reactive protein (CRP), cardiac enzymes, coagulation, chest imaging, and other applicable laboratory parameters. 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 nebulisation twice a day, prepare with sterile water 2 mL.
• 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, diarrhoea, 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 weighing 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 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 (*summarised*): determine proper support from nasal cannula, face mask to mechanical ventilation and prone positioning. For severe acute respiratory distress syndrome (ARDS), ECMO should be considered.
III. Circulation support: optimise fluid resuscitation first, consider vasoactive therapy to ensure circulation and organ perfusion. Apply haemodynamic monitoring if indicated.
IV. Convalescent plasma transfusion: appropriate for severe or critical cases.
V. Plasmapheresis: may consider for cytokine storm management.
VI. Immunotherapy: tocilizumab 4–8 mg/kg or 400 mg standard dose IV once can be considered for elevated interleukin-6. May repeat a dose in 12 hours without exceeding a total dose of 800 mg.
VII. Other measures:
• Based on respiratory distress and chest imaging, may consider glucocorticoids equivalent to methylprednisolone 1–2 mg/kg/day for 3–5 days or less. Note that large-dose glucocorticoids suppress the immune system and could delay clearance of SARS-CoV-2.
• May consider Xuebijing 100 mL 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 breaths/minute, oxygen saturation ≤93%, $PaO_2/FiO_2 \leq 300$ 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.

IV, intravenous; ECMO, extracorporeal membrane oxygenation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit.

As an investigative drug on incomplete trials, remdesivir is neither recommended nor disapproved by China's NHC and the WHO [4,20]. Currently, remdesivir is recommended by the NIH for hospitalised severe COVID-19 cases as defined by oxygenation requirement [21].

3.2. Lopinavir/ritonavir (LPV/r)

LPV/r is a combination protease inhibitor approved for the treatment of human immunodeficiency virus (HIV) infection [22]. Lopinavir binds to viral protease and prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature non-infectious virus particles. Ritonavir increases the plasma concentration of lopinavir by inhibiting cytochrome P450 3A (CYP3A) metabolism. Short-term side effects of LPV/r include nausea, diarrhoea, abdominal pain, elevation of liver enzymes, and prolongation of QT and PR intervals [22].

Lopinavir showed an in vitro cytopathic effect against SARS-CoV at 4 μg/mL [23]. Although the trough concentration of lopinavir (5.5 μg/mL) can reach >4 μg/mL, the free drug concentration would likely be below the inhibitory threshold in the setting of high protein binding (98–99%). Unfavourable pharmacodynamics are also likely to limit the efficacy of LPV/r in COVID-19.

During the severe acute respiratory syndrome (SARS) outbreak in 2003, it appeared that LPV/r conferred clinical benefit in the early phase of the disease to reduce peak viral load before progression to acute respiratory distress syndrome (ARDS). 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%, and 0% vs. 11.0%, respectively; $P < 0.05$) in a multicentre retrospective cohort study [24]. A Hong Kong study retrospectively evaluated the efficacy of LPV/r in 152 patients with SARS. Patients from the historical control arm received ribavirin, whilst those in the second arm received LPV/r in addition to ribavirin. The second group showed lower rates of 21-day adverse outcomes (ARDS or death) compared with the historical controls (2.4% vs. 28.8%; $P < 0.001$) [23].

In a cohort study of 18 patients with COVID-19 in Singapore, 5 of 6 patients with hypoxaemia started LPV/r [200 mg/100 mg twice daily (b.i.d.)] [25]. Two patients deteriorated and required admission to the intensive care unit (ICU); both patients had persistent nasopharyngeal viral loads during their ICU stay. Limitations of the study include statistical underpowering, a suboptimal dose of LPV/r, and delay in initiation of therapy or absence of combination therapy with ribavirin [25]. The ELACOI trial, a single-blind RCT, included 44 patients with mild-to-moderate COVID-19 symptoms [26]. There were no differences in the primary outcome of time to negative pharyngeal reverse transcription (RT)-PCR test between the LPV/r, umifenovir and control groups (8.5, 7 and 4 days, respectively). There were no differences in pyrexia, cough or lung computed tomography (CT) findings on days 7 and 14. Five patients in the LPV/r group experienced adverse events, including gastrointestinal symptoms and worsening liver function [26].

In March 2020, the results of the first COVID-19 clinical trial of LPV/r were published [27]. Unfortunately, LPV/r did not show superiority over standard of care for time to achieve clinical improvement, 28-day mortality or viral clearance [27]. In the trial, LPV/r shortened ICU stay by a median of 5 days [95% confidence interval (CI) −9 to 0 days]. 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.

LPV/r is suggested presumptively as an antiviral option by China's NHC (Table 1) [4] but is recommended against by the NIH owing to unfavourable pharmacodynamics and lack of proven clinical efficacy [21].

3.3. Ribavirin

Ribavirin is a nucleoside analogue with antiviral activity against multiple RNA viruses, including respiratory syncytial virus, SARS-CoV and MERS-CoV, by interfering with RNA polymerase and viral protein synthesis [28,29]. The most severe adverse effects are haemolytic anaemia and leukopenia. Other adverse effects include fatigue, pruritus, rash and gout. Ribavirin is a notorious teratogenic drug and is contraindicated in pregnancy [28,29].

Ribavirin, with or without concomitant use of steroids, was used extensively during the 2003 SARS outbreak. In vitro tests showed that ribavirin inhibited a β-coronavirus at relatively high concentrations [30]. However, when using ribavirin with interferon-α2b combined, lower concentrations of ribavirin inhibited viral replication in Vero cell lines [30].

A prospective, uncontrolled study evaluated clinical outcomes of ribavirin and corticosteroids in 132 patients with suspected SARS when fever was not resolved after 48 h of hospital admission [31]. Twenty-five patients (18.1%) responded to ribavirin and corticosteroids and two of those patients received i.v. ribavirin [31]. Approximately 49–59% of patients treated with ribavirin had a reduction in haemoglobin of greater than 2 g/dL from baseline, 36–76% had evidence of haemolytic anaemia and 40% experienced elevation of liver transaminases [31,32].

In a phase 2, open-label COVID-19 trial that enrolled 127 patients from six Hong Kong hospitals, Hung et al. compared triple therapy (LPV/r 400/100 mg oral every 12 h, ribavirin 400 mg oral every 12 h and interferon β-1b 8 million IU subcutaneous on alternative days) with a control group of LPV/r [33]. The median time from symptom onset to start of treatment was 5 days. In an intent-to-treat analysis, the triple therapy group had a significantly shorter median time to negative RT-PCR test (hazard ratio = 4.37, 95% CI 1.86–10.24; $P = 0.0010$), shorter clinical improvement and time to complete alleviation of symptoms (4 days vs. 8 days) and shorter median hospital stay (9 days vs. 14.5 days). There was no difference in the incidence of adverse events, serious adverse events or duration of nausea/vomiting. Limitations of the study include the open-label study design, the absence of critically ill patients and the confounding factor of a subgroup omitting concurrent interferon β-1b if the time of symptom onset was ≥7 days.

Intravenous ribavirin is suggested by China's NHC for COVID-19 only as an add-on therapy to LPV/r or interferon (Table 1) [4]. It has not been evaluated by the NIH [21].

3.4. Interferon (IFN)

IFN induces several parallel antiviral pathways by triggering viral RNA degradation, RNA transcription alteration, protein synthesis inhibition and apoptosis [34]. Common side effects include flu-like symptoms and mood changes [35]. It is contraindicated in patients with decompensated liver disease, severe autoimmune diseases, worsening psychiatric conditions, cytopenia and uncontrolled seizures [35].

IFN regimens for coronaviruses are summarised in Table 2.

During the SARS and MERS outbreaks, IFN was widely used for its antiviral effects after showing in vitro efficacy [36,37]. 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 with corticosteroids alone [38]. Similarly, a randomised, four-arm, open-label, retrospective study on SARS in Guangzhou, China, demonstrated that IFN plus high-dose steroid therapy achieved respiratory improvement, faster resolution of pulmonary infiltrates and less need for mechanical ventilation [39]. However, IFN combined with ribavirin was not correlated with either a faster vi-

ral clearance or an improved survival rate in older (>50 years) critically-ill patients with co-morbidities [40,41,43].

In vitro data of IFN activity against SARS-CoV-2 suggested that the EC_{50} values in Vero cells of IFN-α and IFN-β treatment are 1.35 IU/mL and 0.76 IU/mL, respectively [44]. These data may provide some evidence for clinical application of IFN therapy in COVID-19. Considering the risk of spreading infectious aerosols, the uncertainty of pharmacokinetics in nebulisation and lack of clinical data, it is difficult to justify IFN inhalation therapy for treatment of COVID-19 at this point. RCTs on IFN are required to evaluate its efficacy in COVID-19.

China's NHC recommended IFN nebulisation as an antiviral option for COVID-19 presumptively at the beginning of the pandemic (Table 1) [4]. The NIH recommends against the use of IFN [21].

Table 2
Interferon (IFN) regimens for coronaviruses.

Indication	IFN type and suggested regimen
SARS	Alfacon-1® (IFN-α): 9 μg/day SC for ≥2 days and increased to 15 μg/day if no response [36]
	rIFN-α: 3 000 000 U/day intramuscular [37]
MERS	IFN-α-2b: 100–144 μg SC weekly [38]
	PEG-Intron® (rIFN-α-2b): 1.5 μg/kg SC weekly for 2 weeks [39]
	Pegasys® (pegylated IFN-α-2a): 180 μg SC weekly [39,41,42]
	Rebif® (rIFN-β-1a): 44 mg SC three times a week [39,41]
COVID-19	IFN-α 5 million units or equivalent dose in 2 mL of sterile water via nebulisation twice a day [4]

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; COVID-19, coronavirus disease 2019; SC, subcutaneous; rIFN, recombinant interferon.

3.5. Corticosteroids

Corticosteroids are a type of anti-inflammatory medication that is effective in the treatment of a variety of conditions such as asthma, allergic conditions, autoimmune diseases, septic shock and cancer [45]. Corticosteroids are a double-edged sword since while these agents inhibit inflammation, they also impair the immune response and increase the risk of infection. Adverse effects vary depending on the dosage and duration of therapy. Side effects include hyperglycaemia, abdominal obesity, infection, mood swing, osteoporosis, growth retardation, glaucoma and hypertension [45].

A systematic review of steroid administration to patients with SARS reported no survival benefit and possible harm including avascular necrosis, psychosis, diabetes and delayed viral clearance [46]. Another study of patients receiving corticosteroids for MERS found no benefit in mortality but delayed lower respiratory tract clearance of the virus [47].

Since the outbreak of COVID-19, corticosteroid treatment has been used in up to 45% of infected patients in China [48,49]. One retrospective observational study showed that 72% of ICU patients with COVID-19 received glucocorticoid therapy [48]. In COVID-19 patients with ARDS, treatment with steroids is associated with a decreased risk of death compared with patients who do not receive steroids (46% vs. 61.8%) [50]. However, existing evidence regarding the use of steroids in this specific patient population remains inconclusive due to methodological limitations.

Based on previous data on other clades of coronavirus, the WHO and NIH generally recommend glucocorticoids not to be used in COVID-19 pneumonia unless there are other indications (e.g. exacerbation of chronic obstructive pulmonary disease or ARDS) [20,21]. However, some front-line physicians in China have a different perspective. They recommend short courses (≤7 days) of corticosteroids at low to moderate doses (≤0.5–1 mg/kg per day methylprednisolone or equivalent) be used judiciously for critically ill patients with COVID-19 pneumonia [51,52]. According to China's NHC, systemic glucocorticoids should be used with caution and their routine use should be avoided [4]. Short-term methylprednisolone can be administered for patients with rapid disease progression or severe illness, and the recommended dose should not exceed 1–2 mg/kg per day. Notably, the guideline mentions that high doses of corticosteroids may delay viral clearance owing to their inhibitory effects on the immune system. The benefits and risks should be carefully evaluated. For patients with hypoxaemia or who take corticosteroids regularly for chronic diseases, corticosteroids should be used cautiously [52]. The Society of Critical Care Medicine (SCCM) suggests using low-dose corticosteroid therapy for COVID-19 patients with refractory shock. In mechanically ventilated patients with COVID-19 and respiratory failure (without ARDS), the SCCM recommends against the routine use of systemic corticosteroids [53].

As of now, use of corticosteroids to reduce cytokine-related pulmonary damage in patients with COVID-19 pneumonia is controversial. Robust evidence from well-designed clinical trials is needed for the recommendation of corticosteroid treatment in COVID-19 patients who have developed different complications.

3.6. Intravenous immunoglobulin (IVIg)

IVIg is a product of human immunoglobulins derived from plasma that is indicated for various immunodeficiencies and autoimmune and inflammatory disorders [54,55]. IVIg has potent immune replacement and immunomodulating effects via complex pathways [55]. In addition, IVIg has anti-inflammatory properties and can neutralise bacterial toxins [56]. The most common adverse reactions to IVIg are headache, fever and tachycardia [55].

Currently, there is no solid clinical evidence to support the use of IVIg in coronavirus infections. Several animal studies found that equine- and bovine-produced human immune antibodies can reduce viral titres and accelerate viral clearance of MERS-CoV in mouse models [57]. During the 2003 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 on SARS, IVIg was used with IFN 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 in controlling cytopenia by increasing leukocyte and platelet counts. However, without a control group, the role of IVIg in SARS treatment remains undetermined [58].

Since the outbreak of COVID-19 in China, clinicians have used IVIg in patients infected with SARS-CoV-2 based on extrapolated 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 was not addressed in this study [47]. Several observational case reports suggest that high-dose IVIg at the early stage of clinical deterioration may improve clinical outcomes in patients with severe symptoms [59,60]. The small number of patients with heterogeneous clinical status and the use of other medications or therapies with unapproved efficacy leads to inconclusive results. There are several ongoing trials initiated to evaluate the efficacy and safety of IVIg for treatment of COVID-19. To date, there is no completed RCT demonstrating its efficacy.

China's NHC does not provide any recommendations on the use of IVIg [4]. The NIH COVID-19 Treatment Guidelines Panel recommends against the use of non-SARS-CoV-2-specific IVIg for the treatment of COVID-19, except in the context of a clinical trial or indicated complications [21].

3.7. Xuebijing (XBJ)

XBJ is a widely used traditional herbal medicine in China for its anti-inflammatory and anti-endotoxin effects [61,62]. It is a five-herb combination (*Carthamus tinctorius*, *radix paeoniae rubra*, *Ligusticum wallichii, Salvia miltiorrhiza* and *Angelica sinensis*). Common side effects include infusion reactions of rash, tachycardia, hypotension and gastrointestinal discomfort including nausea, vomiting, abdominal pain and/or diarrhoea [61,62].

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 (APACHE II) score, white blood cell count, C-reactive protein (CRP) and procalcitonin levels, and body temperature [61]. That being said, the efficacy of XBJ in sepsis needs to be confirmed in a RCT. Current clinical data on XBJ in ARDS are inconsistent. One RCT showed a reduction in duration of mechanical ventilation, ICU stay and Murray score, whilst the other RCT revealed no difference in these clinical outcomes [63,64]. However, neither of the ARDS studies demonstrated a significant 28-day mortality benefit. Further well-designed RCTs with larger sample sizes are warranted to conclude on the use of XBJ in ARDS. In a multicentre RCT on critically-ill patients with severe community-acquired pneumonia, XBJ significantly improved the pneumonia severity index, 28-day mortality, duration of mechanical ventilation and duration of ICU stay [65].

Based on the clinical evidence on XBJ in sepsis, bacterial pneumonia and ARDS, which are three common complications in COVID-19, China's NHC has recommended i.v. XBJ as one of the treatment options in COVID-19 patients presenting with cytokine release syndrome and/or multi-organ failure (Table 1) [4].

3.8. Umifenovir (Arbidol)

Umifenovir is a synthetic antiviral drug marketed in Russia and China for the treatment of seasonal influenza. It has shown broad-spectrum antiviral activity against other viruses including SARS-CoV [66] and is generally well tolerated.

Umifenovir has been used alone or in combination with other antiviral treatments in a few COVID-19 clinical studies. In one trial, a total of 81 non-ICU COVID-19 patients were assigned to either a umifenovir group or a control group. The median time from onset of symptoms to SARS-CoV-2-negative RT-PCR was similar in the two groups. No clinical differences were reported, and the umifenovir group had slightly longer hospital stay (13 days vs. 11 days) [67]. In a COVID-19 case series, the combination of umifenovir, LPV/r and traditional Chinese medicine alleviated pneumonia symptoms in all four patients and decreased the viral load to undetectable in two patients [68]. A retrospective cohort study on non-ventilated COVID-19 patients ($n = 33$) compared LPV/r plus umifenovir and LPV/r monotherapy over 5–21 days of treatment [69]. The LPV/r plus umifenovir combination group had a higher negative viral detection rate on Days 7 and 14, with significantly improved chest CT scans on Day 7. However, inflammation markers were not compared at baseline. The LPV/r monotherapy group had significantly higher corticosteroids usage, which could delay viral clearance.

All available clinical studies on umifenovir have significant limitations in study design and sample size. It appears that umifenovir monotherapy is ineffective. The combination of umifenovir with other antivirals might benefit viral clearance and chest CT improvement. Whether the positive outcome is achieved by using an antiviral combination strategy or by adding umifenovir remains to be studied. All of these studies should be treated as hypothesis-generating and should be interpreted with great caution. Umifenovir is a newly added antiviral option in China's NHC guide on COVID-19 (Table 1) [4].

3.9. Chloroquine (CQ) and hydroxychloroquine (HCQ)

CQ is a classic antimalarial drug. Its well-known effect of neutralising the acidic endosomal pH supports broad-spectrum antiviral usage by blocking endosome-mediated viral entry [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]. Adverse effects include retinopathy, liver enzyme elevation, blood count changes and alterations in mood. It is important to monitor drug interactions with other QTc-prolonging agents [71,72].

Since the COVID-19 outbreak, CQ has shown an antiviral effect on SARS-CoV-2 in vitro, with a 90% effective concentration (EC_{90}) of 6.90 μM, which is clinically achievable [10]. 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 orally b.i.d. followed by 200 mg orally b.i.d. for 4 days would achieve therapeutic levels [73].

An open-label, non-randomised clinical trial in France studied a HCQ regimen of 200 mg three times a day orally with and without azithromycin (AZM). The study reported 100% viral clearance on Day 6 in the HCQ plus AZM group versus 57.1% in the HCQ monotherapy group and 12.5% in the control group [74]. However, the small trial ($n = 42$) was not randomised. The HCQ group had higher viral loads at baseline and the control group had younger patients. Six patients were excluded in the results reporting, and clinical outcomes were not studied.

The first published RCT assessing HCQ in COVID-19 was conducted in China ($n = 150$) [75]. The primary endpoint of negative COVID-19 test by Day 28 showed HCQ plus standard-of-care (SOC) to be non-superior to SOC alone (85.4% vs. 81.3%, respectively; 95% CI of difference between groups, −10.3 to 18.5%) [75]. However, only two patients were severely sick. The endpoint by Day 28 may not be clinically relevant in mild-to-moderate illness as viral clearance is expected to occur much sooner. It is worth noting that the SOC arm is not a placebo. More than 50% patients in both arms received other antivirals. This introduces a great confounder, especially when there are not yet any conclusions on the effect of antivirals in COVID-19. Another small-size HCQ trial in Shanghai with similar outcomes had the same issue [76]. The RCT also reported higher adverse effect in the HCQ vs. SOC group (30% vs. 9%). This could be due to the high-dose regimen of HCQ 800–1200 mg daily [76].

In June 2020, a retrospective multicentre study ($n = 807$) in American veterans with COVID-19 showed HCQ as ineffective and potentially harmful [77]. HCQ with or without AZM did not decrease mortality, the mechanical ventilation rate or length of hospitalisation. The HCQ group, but not the HCQ + AZM group, even had a higher risk of death. However, the study subjects were not randomised. Naturally, patients with severe disease were more likely to start HCQ treatment. In fact, both HCQ and HCQ + AZM groups had more patients with elevated liver enzymes and inflammation markers, which are confounders that could affect study outcomes [77]. A New York hospital reported QTc prolongation associated with HCQ + AZM ($n = 84$) [78]. QTc increased from a baseline of 435 ± 24 ms to a maximum value of 463 ± 32 ms ($P < 0.001$) on Day 3.6 ± 1.6 of therapy. No torsades de pointes events were observed.

So far, studies present conflicting outcomes of CQ and HCQ. More RCTs with improved study designs are needed to examine the efficacy and whether the clinical benefits of CQ/HCQ are greater than the risks. China's NHC suggests low-dose CQ 500 mg b.i.d. for 7 days with some exceptions (Table 1) [4]. Currently,

the NIH recommends against CQ/HCQ and HCQ + AZM as treatment for COVID-19, except in clinical trials; the organisation recommends against high-dose CQ 600 mg b.i.d. for 10 days in all settings due to potential toxicity [21].

3.10. Interleukin-6 (IL-6) inhibitors

Tocilizumab (Actemra®), known as a humanised IL-6 receptor antagonist, is currently approved for rheumatoid arthritis and cytokine release syndrome (CRS) due to chimeric antigen receptor T-cell (CART) therapy [79]. Common side effects of tocilizumab include hypersensitivity reaction and infection [79].

In COVID-19 patients with CRS, patients were found to have elevated levels of cytokines such as IL-2 receptor, IL-6, IL-8, IL-10 and tumour necrosis factor-alpha (TNFα) that indicate inflammation and immunological disease. In addition, CRS was revealed to be associated with the severity of COVID-19 [80,81]. 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.

A recent single-group, multicentre study showed that within a few days of administration of tocilizumab, temperature curve was normalised and oxygen intake was lowered in 75% of patients with severe or critical COVID-19 [82]. They also observed a significant improvement in CT imaging, abnormally elevated CRP, and lymphopenia. No obvious adverse reactions were identified in this study [82]. This suggests that tocilizumab may be a new therapeutic strategy for treatment of severe or critical COVID-19 patients, however further data from large RCTs are required to justify the efficacy and safety of tocilizumab.

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 [83]. Common toxicities include neutropenia, thrombocytopenia, infusion reaction and infection [83]. Global clinical trials of sarilumab in COVID-19 treatment have been initiated to evaluate clinical outcomes such as fever, the need for supplemental oxygen, mortality, mechanical ventilation, ICU stay and hospitalisation [84].

Siltuximab (Sylvant®), approved in the USA to treat patients with multicentric Castleman disease, is the third potential IL-6-targeted therapy for COVID-19 trials [84]. Similar to other IL-6 antagonists, common adverse effects of siltuximab are cytopenia, infection and hypersensitivity reaction [85]. Recently, an Italian clinical team reported that among 21 COVID-19 patients with ARDS who received siltuximab (700–1200 mg, median 900 mg), the serum CRP level was reduced in 16 patients. Moreover, 33% of patients were observed to have clinical improvement, 43% remained stable and 24% deteriorated. Thirty-day mortality is not complete to be reported yet [86]. The efficacy and safety of siltuximab in the treatment of COVID-19 patients need to be addressed in large sample-size RCTs.

More robust clinical evidence is required to determine whether IL-6 antagonists can provide clinical benefit in COVID-19 patients. The 7th edition of China's NHC guideline on COVID-19 has included tocilizumab as one of treatment options for patients with severe lung damage and elevated level of IL-6 (Table 1) [4]. The NIH recommends neither for nor against the use of IL-6 inhibitors in COVID-19 [21].

4. Conclusions

Currently, guidance from the WHO focuses on supportive care and the management of complications per general guidelines [20]. Remdesivir is moderately recommended by the NIH for hospitalised severe cases [21]. The COVID-19 diagnosis and treatment guideline issued by China's NHC provides several medication therapy recommendations (Table 1) [4]. All of these therapeutics have been 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 that are awaiting evidence, nor does it 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. When safety is ensured, remdesivir might be considered early in the course of illness prior to disease progression for potential clinical recovery. For the other medication agents discussed in the review, outcomes from case reports and case series cannot be generalised for a larger population. More well-designed RCTs in COVID-19 therapies are warranted before final conclusions on efficacy can be made.

Declaration of Competing Interest

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