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Review

An overview of the safety, clinical application and antiviral research of the COVID-19 therapeutics

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ABSTRACT

Since a novel coronavirus pneumonia outbreak in late December 2019, coronavirus disease -19 (COVID-19) epidemic has gradually spread worldwide, becoming a major public health event. No specific antivirals are currently available for COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The treatments for COVID-19 are mainly based on the experiences of similar virus such SARS-CoV, MERS-CoV, HIV and influenza viruses. Scientists have taken great efforts to investigate the effective methods for the treatment of COVID-19. Up to now, there are over 1000 clinical studies for COVID-19 all over the world. In this article, we reviewed the current options for COVID-19 therapy including small molecules such as Remdesivir, Favipiravir, Lopinavir/Ritonavir etc, peptide inhibitors of ACE2, Traditional Chinese Medicines and Biologics such as SARS-CoV-2-specific neutralizing antibodies, mesenchymal stem cells and vaccines etc. Meanwhile, we systematically reviewed their clinical safety, clinical applications and progress of antiviral researches. The therapeutic effect of these antiviral drugs is summarized and compared, hoping to provide some ideas for clinical options of COVID-19 treatment and also provide experiences for the life-threatening virus diseases in the future.

Contents

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Introduction

Emerged in December 2019, a novel coronavirus (SARS-CoV-2) has caused an international outbreak of severe acute respiratory syndrome and spread rapidly to over 100 countries in the world. On January 21, 2020, the Chinese government regarded COVID-19 as the class B infectious diseases, and took prevention and control measures as class A infectious diseases. On February 11, 2020, the novel coronavirus pneumonia was named COVID-19 by WHO(World Health Organization). In late May 2020, the number of COVID-19 confirmed cases was over 5,000,000 worldwide, and the number of death was over 300,000 [1]. In fact, this is not the first time of a serious infectious disease caused by coronavirus. Both the SARS-CoV in 2003 and the MERS-CoV in 2012 belong to the *coronaviridae* family [2]. Due to the strong infectivity, high fatality rate and the absence of specific medicine for SARS-CoV, MERS-CoV and SARS-CoV-2, each outbreak of the coronavirus has brought heavy burden to the society.

Coronavirus is a positive strand RNA virus with enveloped structure which have the corona like protuberances on its envelope and look like a crown [3]. This kind of virus can be traced back to 80 years ago and isolated from chicken embryos [4]. Up to now, approximately 15 different coronavirus strains have been discovered and can infect a variety of mammals and birds [5]. Among these coronavirus strains, only SARS-CoV, MERS-CoV and SARS-CoV-2 can infect human and cause fatal pneumonia [5]. The clinical features of these three coronaviruses are similar and can range from asymptomatic or mild disease to severe pneumonia with acute respiratory distress syndrome (ARDS) and multi-organ failure [5].

Coronavirus mainly relies on its envelope structure to invade host cells. There are three kinds of proteins on its envelope, including spike protein(S protein), envelope protein and membrane protein [6]. S protein plays a key role in recognizing and binding to host cell surface receptors, and mediating the fusion of virus envelope with cell membrane [7]. The cleavage and activation of S protein of SARS-CoV-2 is mediated by transmembrane protease serine subfamily member 2 (TMPRSS2) [8]. The S protein of SARS-CoV and SARS-CoV-2 recognizes the same host receptor, namely, ACE2(angiotensin-converting enzyme 2) [8–10]. Thus, inhibitors of TMPRSS2 or ACE2 could have the potential for the treatment of SARS-CoV-2.

The virus enters the host cell via endocytosis, forms lysosomes and then releases virus RNA regulated by related protease and pH [11]. The endosomal acidification inhibitors such as Chloroquine and membrane fusion inhibitors such as Arbidol can also be used for the clinical study of COVID-19 therapy. Afterwards, the RNA completes the transcription and translation of virus proteins and RNA replication occurs in the cytoplasm. These processes can be blocked by the nucleoside analogues such as Remdesivir, protease inhibitors such Lopinavir/Ritonavir, SARS-CoV-2 3CLpro protease(for processing of polyproteins translated from the viral RNA) inhibitors such as pyridine-containing α-ketoamides [12–14]. Finally, the protein shells combine with RNA to generate new coronavirus particles, which are secreted to extracellular environment through Golgi apparatus and infect new cells [7].

With a better understanding of the structure, the infection mechanisms of SARS-CoV-2 and the clinical symptoms of COVID-19 patients, many drugs had been used for the clinical practice of COVID-19. Up to now, the therapeutic options for COVID-19 can

Table 1
Potential options for the treatment of COVID-19.

Antiviral mechanism		Drug	Applications	Dosage for COVID-19	Clinical Trials
Protease inhibitors	Nucleoside analogue	Remdesivir	Not approved, clinical practice for Ebola virus, COVID-19	200 mg/time on the 1 st day, then 100 mg/time maintenance dose every day for 9 days	COVID-19
		Ribavirin	Approved for Hepatitis C, human respiratory syncytial virus (RSV) and some hemorrhagic fevers	500 mg/time, 2∼3 times per day for 10 days	COVID-19
		Favipiravir	Approved for new or recurrent influenza and COVID-19	1200 mg/time on the 1 st day, twice a day and 400 mg/time from the 2nd to 5th days, twice a day	COVID-19
	HIV protease	Lopinavir/ Ritonavir	Approved for AIDS, clinical practice for SARS, MERS and COVID-19	Lopinavir 400 mg/time, Ritonavir 100 mg/time, twice a day for no less than 10 days.	COVID-19
	TMPRSS2 serine protease	Camostat	Approved for chronic pancreatitis, cellular study for COVID-19	No	No
	SARS-CoV-2 Mpro (3Clpro) protease	Pyridine containing α-ketoamides	New compound screened for *in vivo* study of COVID-19 therapy	No	No
Endosomal acidification inhibitors		Chloroquine/ Hydroxychloroq-uine	Approved for malaria and autoimmune diseases, clinical practice for COVID-19	Patients >50 kg, 500 mg/time, twice a day for 7 days; patients ≤ 50 kg, 500 mg/time, twice a day for the first and second days, 500 mg/time, once a day for the third to seventh days	COVID-19
Immunoregulant		Interferon	Approved for malignant tumors and various virus, clinical practice for COVID-19	adults is 5 million U, twice a day	COVID-19
Membrane fusion inhibitor		Arbidol	Approved for influenza, clinical practice for covid-19	0.2 g/time, 3 times a day for 10 days	COVID-19
ACE2 inhibitors		Peptide inhibitor based on phase display	New compounds for *in vitro* study of COVID-19 therapy	No	No
Chinese Traditional Medicine		Lianhua Qingwen Capsule	Approved for influenza	4 capsules/time, third a day	COVID-19
		SARS-CoV-2-specific neutralizing antibodies	Clinical practice for COVID-19	——	COVID-19
	Biologics				
	Tocilizumab	Approved for rheumatoid arthritis, clinical practice for COVID-19	For adults, 4∼8 mg/kg, total 2 times	COVID-19	
	Mesenchymal Stem Cells	Clinical practice for COVID-19	——	COVID-19	
	Vaccines	Clinical practice for COVID-19	——	COVID-19	

be classified into small molecules, peptide inhibitors, Traditional Chinese Medicines and biologics summarized in Table 1. In late May, 2020, over 1600 clinical trials have been registered to find the effective treatments for COVID-19 from clinical trial registry platforms (http://clinicaltrials.gov/ and http://www.chictr.org.cn/). The most widely used therapeutic drugs include Abidol, Ribavirin, Favipiravir, Interferon-α, Chloroquine/Hydroxychloroquine, Kaletra(Lopinavir/Ritonavir), Remdesivir (GS-5734), SARS-CoV-2-specific neutralizing antibodies and so on. Besides, the newly discovered small drugs, peptides and vaccine are also under preclinical or clinical researches. In this paper, we systematically introduced the safety, clinical efficacy, and the progress of antiviral researches of these drugs, hoping to provide some ideas for the therapeutic options of COVID-19 worldwide and better understand the antiviral strategies prepared for the life-threaten virus diseases in the future.

Methods

This review was conducted according to the studies which were randomized controlled trials (RCTs), prospective cohort, retrospective cohort studies and so on; performed among adult patients with COVID-19 and evaluated the efficacy and safety of anti-coronavirus agents. The studies were excluded if they lacked a control group or target quantitative outcomes. The primary outcomes included mortality, virological eradication, and clinical improvement. The secondary outcomes included improvement of symptoms, time to become afebrile, improvement of chest radiography results, utilization of mechanical ventilation, intensive care unit admission, and adverse events. All the date was searched from PubMed, EMBASE, China National Knowledge Infrastructure (CNKI) and WANFANG DATA was performed without language restriction. Unpublished trials were also identified from clinical trial registry platforms (http://clinicaltrials.gov/ and http://www.chictr.org.cn/). Preprint articles were retrieved from the websites MedRxiv (https://www.medrxiv.org) and BioRxiv (https://www.biorxiv.org).

The drug candidates for treatment of COVID-19

Nucleoside analogues

Remdesivir

Remdesivir (GS-5734) is a novel prodrug of an adenosine analogue and effective against a broad spectrum of human and pre-epidemic zoonotic CoVs [15]. Remdesivir can be triphosphorylated in cells and act as a substrate of virus RNA-dependent RNA polymerase (RdRp) and penetrate into the virus newly synthesized RNA strand, thus interrupting the synthesis of the virus genome [12].

Safety

In the phase I clinical trial of Remdesivir, 3−225 mg intravenous injection of single dose hill climb test was conducted. The subjects showed good tolerance, and all the adverse reactions were grade 1 or grade 2 with aspartic transaminase (AST) or alamine aminotransferase (ALT) increasing, but no abnormality in total bilirubin, alkaline phosphatase (ALP) or albumin, and no effect on renal function [16]. According to a recently Randomised Clinical Trial (RCT) of COVID-19, 66% (102/155)adverse events of Remdesivir treatment were observed compared to the 64%(50/78) in placebo treatment [17].

Clinical application

Remdesivir has not yet been approved for antiviral therapy and is currently used for the phase III clinical trial of COVID-19 in China. The dosage form of Remdesivir used in clinical trials is freeze-dried powder injection and the designed administration mode is as follows: on the 1 st day, 200 mg loading dose of Remdesivir was provided by intravenous dripping, and then 100 mg maintenance dose of the drug was provided by intravenous dripping every day for 9 days, from “International Clinical Trials Registry Platform:WHO ICTRP”.

Antiviral research

Remdesivir had previously shown inhibitory effect on coronaviruses, such as SARS-CoV, MERS-CoV and COVID-19 in vitro or in vivo [18–20]. The cell-based experiments showed that Remdesivir can inhibit intracellular replication of COVID-19 with EC50 of 0.77 μM [20], indicating that Remdesivir may be a promising candidate for the treatment of COVID-19. Since the first American COVID-19 patient treated with Remdesivir got obvious clinical benefits, numbers of clinical trials of Remdesivir were preformed to investigate the efficacy and safety in patients with COVID-19 [21]. A short-term study with 53 COVID-19 patients showed that, after 18 days' Remdsivir treatment, 47% patients (25/53) had been discharged from hospital, total mortality was 13%, overall clinical improvement was 68%. However this uncontrolled respective study makes outcomes lack strong evidence [22]. In this situation, the first double-blind, randomized clinical trial of Remdesivir was conducted in severe COVID-19 patients in Wuhan, China. The results indicated that Remdesivir treatment had clinical improvement in severe COVID-19 patients with symptom duration no more than 10 days [17]. The outcomes of another multicenter RCT of Remdesivir in COVID-19 patients has present a significant shorten in duration of discharge from hospital without significant difference in mortality [17]. According to these studies, we still do not know the benefit or harm of Remdesivir treatment in severe COVID-19 patients. However, further studies of Remdesivir in patients with COVID-19 in higher dosage or combination with other antivirals agents might help us to better understand its potential mechanism and clinical efficacy.

Ribavirin

Ribavirin is a guanosine analogue with broad-spectrum antiviral activity against RNA viruses. The antiviral mechanisms of Ribavirin includes fatal mutagenesis, specific or non-specific chain termination and inhibition of nucleotide biosynthesis etc [23,24].

Safety

The reproductive toxicity and the hemolytic anemia is the most serious side effects of Ribavirin. Some cohort studies of Ribavirin showed that patients on therapy with loading dose of Ribavirin experience significant toxic and side effects, such as hemolytic anemia [25]. In another retrospective study, among the 126 patients who received loading dose of Ribavirin(2000 mg) treatment, the mainly adverse drug reactions included hemolytic bleeding, bradyarrhythmia(14%) and elevated transaminase(40%) [26]. Thus, the dose of Ribavirin need to be carefully adjusted to treat patients with COVID-19.

Clinical application

Ribavirin is only approved by FDA for Hepatitis C, human respiratory syncytial virus (RSV) and some hemorrhagic fevers in combination with pegylated interferon. In China, Ribavirin is used for the patients with COVID-19, which is mentioned in“*Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme(Trial Edition Fifth)*” issued by the Chinese government [27]. It is recommended to use Ribavirin in combination with Interferon or Lopinavir/Ritonavir, the dosage for adults is 500 mg per time, 2∼3 times per day by intravenous infusion, and the course of treatment is no longer than 10 days.

Antiviral research

The clinical studies in Hong Kong have shown that Ribavirin couldn't improve clinical outcome of patients with SARS-CoV [28]. In 20 MERS-CoV infected patients, a combination treatment of Ribavirin and IFN-α showed significantly improved survival at 14 days but not at 28 days [29]. Although Ribavirin has shown a certain effect on MERS-CoV, it is still controversial [30,31]. In China, Ribavirin was chosen for patients with COVID-19 in combination with IFN or Lopinavir/Ritonavir according to the clinical guidelines [27]. A clinical trial showed the significantly antiviral effect of combination treatment of Ribavirin and IFN-α on patients with MERS-CoV [32]. But the adverse reaction of decreasing hemoglobin in infected patients reduces its potential antiviral agent against COVID-19. Take consideration of limited efficacy of Ribavirin against coronaviruses and toxicity in vivo, some medical team stop Ribavirin treatment and related studies.

Favipiravir

Favipiravir is a nucleoside analogue that can be triphosphorylated in cells and act as a substrate of virus RNA-dependent RNA polymerase (RdRp) [33].

Safety

The most serious side effect of Favipiravir is teratogenicity. In the phase III of a Japanese and international multi-center clinical trial with 501 patients, the main adverse reactions including rising uric acid(24 cases, 4.79%), diarrhea(24 cases, 4.79%), neutropenia(9 cases, 1.80%), increased AST(9 cases, 1.80%) and increased ALT(8 cases, 1.60%) [34]. In a randomized clinical trial of Favipiravir with 240 patients with COVID-19, the most common adverse events were liver enzyme abnormalities, psychiatric, gastrointestinal symptoms and serum uric acid elevations.0001) [35]. The overall adverse reactions were mild symptoms, but pregnant woman should not be treated with Favipiravir.

Clinical application

Favipiravir is approved in Japan for treatment of new or recurrent influenza. Favipiravir was approved for treatment of COVID-19 on February 15, 2020 in China and also became the first approved drug for COVID-19. The recommended mode of administration in China is 1200 mg/400 mg, with 1200 mg every time on the first day, twice a day, and 400 mg every time from the second to fifth days, twice a day.

Antiviral research

In 2014, Favipiravir was urgently used to treat Ebola virus and achieved good results [36,37]. In 2020, Favipiravir showed cytotoxicity in Vero E6 cells infected with SARS-CoV-2 at EC50 of 61.88 μM [20]. A recent randomized clinical trial revealed that Favipiravir had a clinical recovery rate of day 7 and led to shorter latencies to relief for both pyrexia (difference: 1.70 days, $P < 0.0001$) and cough (difference:1.75 days, $P < 0.0001$) compared to Arbidol [35]. An open-label control study to evaluate the safety and efficacy of Favipiravir in the treatment of COVID-19 was conducted with 80 patients [38]. The Favipiravir arm had a shorter viral clearance time versus the control arm (median 4 days vs. 11 days, $p < 0.001$), and also had a higher rate of improvement in chest imaging (91.43% vs. 62%, $p < 0.001$). In addition, patients with COVID-19 have been recruited to evaluate the efficacy of Favipiravir plus interferon-α(ChiCTR2000029600, ChiCTR (Chinese Clinical Trial Register), Favipiravir plus baloxavir marboxil (ChiCTR2000029544), Favipiravir plus tocilizumab(ChiCTR2000030894) and Favipiravir plus Chloroquine Phosphate(ChiCTR2000030987) etc. The clinical trials registered indicate that the combination therapy of Favipiravir with other drugs may be a promising option for COVID-19 patients.

Protease inhibitor

Kaletra (Lopinavir/Ritonavir)

Kaletra is a compound preparation with two specifications (Lopinavir/Ritonavir). Lopinavir is an HIV protease inhibitor, which can influence the formation of matured virus particles and weaken the infectivity of the virus [39]. Lopinavir has poor bioavailability and short half-life time. Ritonavir is a cytochrome CYP3A4 enzyme inhibitor, which can inhibit the metabolism of Lopinavir. The combined treatment of Lopinavir and Ritonavir can significantly enhance the bioavailability of Lopinavir and improve its antiviral effect in vivo [13].

Safety

A retrospective analysis with Kaletra for 60 weeks showed that diarrhea, nausea and vomiting are the main adverse reactions [40]. A retrospective study with 417 patients with COVID-19 revealed that the use of Lopinavir/Ritonavir lead to increased odds of liver injury (OR from 4.44 to 5.03, both $p < 0.01$) [41]. Another study revealed that Lopinavir/Ritonavir has an uncertain antiviral effect and even some potentially severe side effects in solid organ transplant recipients with COVID-19 [42]. Lopinavir/Ritonavir have a synergistic effect on tacrolimus, resulting in higher trough blood concentrations of tacrolimus and cause severe liver and kidney dysfunction and also greatly damage the function of the immune system [43].

Clinical application

Kaletra was previously approved by FDA for AIDS in 2000. In 2020, Kaletra was chosen as clinical candidate for the treatment of COVID-19. In the "*Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Edition Fifth)*" issued by Chinese government, the medication for adult patients with COVID-19 is Lopinavir 400 mg/Ritonavir 100 mg twice a day for no less than 10 days [27]. The dosage for children is adjusted according to body weight: 12 mg/kg for 7–15 kg, and 10 mg/kg for 15–40 kg, with the maximum dose of 400/100 mg per time.

Antiviral research

As early as 2003, Kaletra was considered as a clinical option for the treatment of SARS, and it indeed showed antiviral effect on SARS both in tissues and patients [44]. One clinical research in Hong Kong showed that Kaletra reduced the mortality rate of SARS-CoV from 15.6% to 2.3%, but it mainly exhibited good effect on patients with mild symptoms [45].

The *in vitro* study revealed that Lopinavir had antiviral effect in Vero E6 cells infected with SARS-CoV-2 with EC50 of 26.63 μM [46]. A recently published research showed that no benefit was observed with Kaletera treatment in patients with severe COVID-19 as compared with standard supportive care alone [47]. A multicenter, prospective, open-label, phase 2 trial with 127 COVID-19 patients revealed that triple combination of interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin was safe and superior to Lopinavir-Ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 [48]. A randomized, controlled, open-label trial with 199 COVID-19 patients revealed that no benefit was observed with Lopinavir–Ritonavir treatment beyond standard care. However, the secondary outcomes of this trial showed that the 28-day mortality was numerically lower in the Lopinavir–Ritonavir group than in the standard care group, and the Lopinavir–Ritonavir group had shorter stay in the intensive care unit (ICU) [49]. It seems that the combination of Lopinavir-Ritonavir with interferon β-1b, and Ribavirin or other drugs could have better effect than Lopinavir-Ritonavir alone.

Endosomal acidification inhibitors

Chloroquine/Hydroxychloroquine

Chloroquine (CQ) is a weak base, which can enter cells and accumulate in lysosome, trans Golgi network and other acidic organelles through protonation, so as to increase the pH value and destroy the structure and function of the organelles [50]. Some viruses can enter the lysosome in cells through endocytosis. The acidity of lysosomes and the function of related enzymes can destroy virus particles and make virus release reproducible nucleic acid, thereby infecting host cells. After entering cells, Chloroquine can block virus infection by increasing lysosomal pH via protonation. Therefore, it has a broad-spectrum antiviral effect. Hydroxychloroquine(HCQ) is a less toxic derivative of CQ which shows better clinical efficacy than CQ.

Safety

The therapeutic and toxic dose of CQ/HCQ is narrow. The main toxicological outcomes initiated by CQ and HCQ reported are related to retinopathy, neuromyopathy, and cardiomyopathy after long term use [51]. The doses used for COVID-19 are often much higher than the treatment of chronic rheumatic diseases [52]. Thus the improper use of CQ or HCQ can easily cause serious side effects. A phase IIb clinical trial with 81 COVID-19 patients showed that Creatine phosphokinase (CK) and Creatine Kinase-MB (CKMB) levels were elevated in 13 of 33 patients (39.4%) and 10 of 26 patients (38.4%), respectively. Hemoglobin decrease was observed in 11 of 42 patients (26.2%) and creatinine increase was observed in 16 of 38 (42.1%). No apparent hematological or renal toxicity were seen among these patients [53].

Clinical application

CQ is a widely used drug for malaria and autoimmune diseases, and it has been used for over 70 years. In 2020, CQ was recommended for the therapy of COVID-19 in the "*Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Edition Sixth)*" issued by Chinese government [54]. CQ phosphate is applicable to patients aged 18–65. The administration mode for patients weighing over 50 kg is 500 mg per time, twice a day, with 7 days treatment; for those weighing no greater than 50 kg is 500 mg per time, twice a day for the first and second days, and 500 mg per time, once a day for the third to seventh days, with 7 days treatment.

Antiviral research

It was reported in 2004 that Chloroquine can effectively inhibit SARS coronavirus at the cellular level [55]. In 2020, Chinese researchers revealed that Chloroquine had the EC90 of 6.90 μM for Vero E6 cells infected with SARS-CoV-2 [20]. A Chinese clinical trial with more than 100 COVID-19 patients found that Chloroquine had superior to the control group in reducing symptom duration, exacerbation of pneumonia including radiological improvement and promoting virus-negative seroconversion without any severe side effects [56]. Another randomized clinical trial with 81 adult patients suggested that the higher CQ dosage (600 mg CQ twice daily for 10 days) should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards [53]. A retrospective multicenter cohort study of 1438 hospitalized COVID-19 patients revealed that treatment with Hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality [57]. A comparative observational study with 181 COVID-19 patients suggested that Hydroxychloroquine should not be recommended to be used in COVID-19 patients who require oxygen [58]. Multinational registry analysis of CQ and HCQ for 96,032 COVID-19 patients revealed that CQ/HCQ independently associated with an increased risk of in-hospital mortality [59]. Despite many observational studies have been performed to evaluate the efficacy of CQ/HCQ, we cannot exclude the possibility of unmeasured confounding factors, making it difficult to judge the therapeutic effect of CQ/HCQ.

Immunoregulant

Interferon

Interferons (IFNs) are cytokines that activate the innate immune system in response to viral infection. As a broad-spectrum antiviral drug, interferon-α (IFN-α) itself has no direct antiviral activity, but IFN-α can provoke the synthesis of proteins that have antiviral and immunomodulatory effects. In addition, IFN can enhance the specific cytotoxic action of immune cells on target cells through immune regulation, thereby containing the invasion of virus.

Safety

In an systematic review including 8 studies(116 patients) of MERS-CoV treatment by interferon, interferon-α combined with Ribavirin caused adverse reactions: two patients had increase in pancreatic enzyme and one patient had obvious hemolysis after the treatment of interferon-α2a combined with Ribavirin [60].

Clinical application

Interferon-α (IFN-α) is generally used for the treatment of malignant tumors and the prevention and treatment of virus through improving the immune function of human body [61]. The "*Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Edition Seventh)*" issued by Chinese government recommended that IFN-α aerosol inhalation can be used for antiviral treatment of COVID-19 [62]. The administration mode for adults is 5 million U or equivalent dose, with 2 mL sterile water for injection, by aerosol inhalation, twice a day.

Antiviral research

The *in vitro* study showed that both IFN-α and IFN-β exhibited antiviral effect on MERS-CoV and SARS-CoV [63,64]. IFN in combination with Ribavirin showed better antiviral effect than Ribavirin alone in the renal cell line of rhesus monkey infected with MERS-CoV [65]. A clinical study compared the clinical effects of IFN-α combined with glucocorticoid and glucocorticoid alone in the treatment of SARS-CoV patients [66]. The results showed that the symptomatic relief time in pulmonary imaging of interferon-α group was shortened by 50% ($P = 0.001$), and the oxygen saturation was significantly improved. A recent triple therapy study of interferon beta-1b, Lopinavir–Ritonavir and Ribavirin presented that remarkable differences were observed in symptom alleviation, shorten the duration of viral shedding and hospital stay in combination group [48]. However, more clinical benefits and potential anti-cytokine approaches of IFN are still under investigated for COVID-19.

Membrane fusion inhibitor

Arbidol

Arbidol hydrochloride is a non-nucleoside antiviral drug. Arbidol can specifically inhibit the contact, adhesion and fusion of virus lipid envelope with host cell membrane by activating the antiviral protein in the host, thereby inhibiting the replication of virus in host cells. Arbidol has dual pharmacological activity: on the one hand, as a broad-spectrum antiviral drug, it can inhibit a variety of viruses, including influenza virus, respiratory syncytial virus (RSV), adenovirus (ADV), hepatitis C virus (HCV) and hepatitis B virus (HBV); on the other hand, it can activate the immune

system, induce the body to produce IFN (interferon), and regulate the immunologic function of the body [40–42].

Safety

The overall adverse effect of Arbidol is mild. The commonly adverse drug reactions was nausea, abdominal discomfort, nausea with headache and leucopenia, increased AKP and increased total bilirubin. The retrospective study to evaluate the efficacy and safety of Arbidol treatment for COVID-19 patients revealed that no apparent side effect was observed during the therapy [67].

Clinical application

Arbidol was first approved in Russia in 1993 for the treatment of influenza. Now, the drug is marketed in China and Russia for the treatment of upper respiratory infection caused by influenza A and B viruses. Arbidol is recommended for the treatment of COVID-19 in the "*Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Edition Sixth)*" [54]. The administration mode for adults is 0.2 g per time, 3 times a day, with the treatment lasting up to 10 days.

Antiviral research

In 2019, Arbidol received extensive attention due to the outbreak of COVID-19. Early studies have shown that Arbidol has an effect of inhibiting the early replication of SARS virus in vitro [68]. Recent study reported that Arbidol efficiently inhibited SARS-CoV-2 infection in vitro with EC50 of 4.11 μM which suggested Arbidol might have potential for the treatment of COVID-19 patients [69]. A retrospective study was performed to evaluate the antiviral effects and safety of Lopinavir/Ritonavir and Arbidol in 50 COVID-19 patients, which indicated that Arbidol group had a shorter viral load compared to those in the Lopinavir/Ritonavir group ($P < 0.01$) and may have better antiviral effect than Lopinavir/Ritonavir [67]. Another retrospective study with 81 COVID-19 patients revealed that Arbidol group had longer hospital stay than the control group, and the median time for turning negative was similar with the control, which suggested that Arbidol might not improve the prognosis or accelerate SARS-CoV-2 clearance [70]. However, one research with 69 enrolled COVID-19 patients revealed that Arbidol had tendency to improve the discharging rate and decrease the mortality rate [71].

Lianhuaqingwen capsule

Clinical application

Lianhuaqingwen (LH) is mainly used to treat influenza which showed antiviral activity and clinical improvement on series of influenza viruses. The relieved symptoms include fever or hyperpyrexia, aversion to cold, muscular soreness, nasal obstruction, running nose, cough, headache and so on. The recommended dosage for adults is 4 capsules per time (0.35 g power/capsule), three times a day.

Antiviral research

Since the outbreak of COVID-19 pandemic, Chinese doctors have used LH to treat patients with common and severe COVID-19. As a potential treatment agent against SARS-CoV-2, LH showed excellent antiviral and anti-inflammatory activity on novel coronavirus in vitro [72]. Another human RCT presented that standard antiviral therapy combined with LH can significantly improve the symptoms of COVID-19, such as fever, cough and fatigue in most of common COVID-19 patients, relieve the pneumonia symptoms, and significantly shorten the duration of pneumonia symptoms without observed serious adverse events [73]. This provides a preliminary evidence of the antiviral activity of LH for COVID-19. LH and other traditional Chinese medicines have also played a positive role in antiviral efficacy against SARS-CoV-2 during pandemic.

Biologics

Biologics have attracted much attention during the epidemic outbreak worldwide, including mesenchymal stem cells, SARS-CoV-2-specific neutralizing antibodies and vaccines.

Convalescent plasma therapy (SARS-CoV-2-specific neutralizing antibodies)

Convalescent plasma may contain the human antibody specific for SARS-CoV-2 produced by whom recovered from SARS-CoV-2 infection. The concept of convalescent serum therapy is based on the human immunity, which is obtained from a patient who has survived a previous infection and developed humoral immunity against the pathogen responsible for the disease [74]. Convalescent plasma could be a valid option for several infections when a specific treatment is not available.

Clinical application

At present, convalescent blood products are mainly used for acute and severe virus infections without available vaccine or specific therapy, such as SARS-CoV, MERS-CoV, Ebola etc. The "*Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Edition Seventh)*" recommended convalescent plasma therapy for serious and extreme cases of COVID-19 [62].

Antiviral research

In 2015, a systematic analysis of the treatment of SARS-CoV with convalescent plasma and hepatitis B immune globulin was reported [75]. Evidences continuously proved that convalescent blood products can reduce the total mortality of SARS-CoV, especially in the early stage of symptoms. The clinical trials of convalescent plasma are undergoing for the treatment of patients with severe COVID-19. A case series study of convalescent plasma showed that the clinical symptoms were significantly relieved within 3 days of treatment, suggesting that the plasma was effective in treating severe COVID-19 patients [76]. The convalescent plasma is considered to have possible source of specific antibodies for pathogen. However, it can also be challenging due to the limited serum with sufficiently high antibody and small sample size. Convalescent plasma therapy could be a valid option for severe COVID-19 patients when a specific treatment is not available.

Other biologics

Mesenchymal stem cells (MSCs) are multipotent cells isolated from diverse mesenchymal tissues such as bone marrow, umbilical cord, adipose tissue [77]. MSCs can enlarge the proportion of regulatory T cells and decrease pro-inflammatory factors such as IL-6 and TNF-α, which have a great potential to improve the outcome of COVID-19 patients [78]. The immunomodulating effects of MSCs have been proven on avian influenza viruses [79]. More than 10 clinical trials had been registered to estimate the efficacy of mesenchymal stem cells for COVID-19 patients in the world. A clinical study significantly improved functional outcomes without obvious adverse effects in 7 COVID-19 patients [80].

The vaccine could be urgently needed to protect against COVID-19 worldwide. Recently, scientists played great efforts for the development of COVID-19 vaccine with safety and efficacy. As of June 24, 2020, there are 16 candidate vaccines in clinical evaluation which are composed of DNA, RNA, non-replicating viral vector, inactivated virus and recombinant proteins [81]. The first SARS-CoV-2 mRNA vaccine (mRNA-1273, encoding S protein) launched Phase I (NCT04283461) clinical trial which 15 participants seroconverted by day 15 and 8 participants all developed

neutralizing antibodies [82]. Ad5-CoV vaccine was viral vector vaccines (ChiCTR2000030906/NCT04313127) developed by Chen Wei group, which the neutralizing antibodies increased significantly at day 14, and peaked 28 days post-vaccination [83]. Protein vaccines such as NVX-CoV2373 (NCT04368988) usually had high cost, low immunogenicity but high safety and scalability. Despite great efforts have been made for vaccine development, completion dates for early clinical trials have not been estimated and it may still take longer before a vaccine is licensed for use globally.

Other options for the treatment of COVID-19

Besides the drugs introduced above, there are many promising drugs registered with the intention of discovering effective treatments. Triazavirin(TZV) is a broad spectrum antiviral drug. The clinical trial to test the efficacy and safety of Triazavirin for COVID-19 was performed in China(ChiCTR2000030001), but the outcomes of this trial have not been reported. Danoprevir is a potent HCV protease (NS3/4A) inhibitor approved by CFDA(China Food and Drug Administration) to treat chronic hepatitis C patients. A clinical study showed that Danoprevir/Ritonavir could significantly improve respiratory symptoms and obvious lung absorption of COVID-19 patients [84]. Oral LL-37 antiviral peptide (CAS001) was another promising candidate and had been used for clinical trial with 11 COVID-19 patients. The preliminary result showed that CAS001 had definite effect in the improvement of gastrointestinal symptoms and is possible to have effects in improving the systemic symptoms and respiratory symptoms of COVID-19 [85]. Baloxavir Marboxil is a recently developed antiviral prodrug whose metabolite selectively inhibits the cap-dependent endonuclease of the influenza virus polymerase acidic protein. A randomized controlled trial showed that Baloxavir Marboxil had antiviral activity *in vitro* with EC50 of 5.48 μM but lacked of virological effect and clinical benefits partly due to insufficient concentrations or the poor antiviral effect in vivo [86]. Danorevir/Ritonavir was the first protease inhibitor-based single-tablet regimen (STR) available for the treatment of adults and adolescents (aged $\geq$ 12 years) with HIV-1 infection. This drug was also used for clinical trial to assess the efficacy for the treatment of COVID-19, but the results have not been reported [87]. Many other promising drugs were also under clinical trials for COVID-19 patients, such as Emtritabine (FTC)/Tenofovir alafenamide Fumarate tablets (TAF)(ChiCTR2000029468), azvudine, Ganovo/ritonavir(ChiCTR2000030000), ASC09/Ritonavir(ChiCTR2000029603), Tranilast(ChiCTR2000030002) et al. Further studies of their efficacy and safety for inhibiting SARS-CoV-2 in humans needs to be investigated.

Discussion

The pandemic of COVID-19 has made an unprecedented crisis for public health and economy both in China and other countries. Scientists worldwide struggle to seek efficacious COVID-19 treatments to control the morbidity and mortality of COVID-19. Numerous drugs have been used in clinical practice to estimate their efficacy and safety for COVID-19 patients. The various clinical trials in patients with these drugs may help to confirm or exclude the possibility of a treatment benefit.

As diagnosis and treatment program of COVID-19 developed rapidly, the therapeutic strategies are quite different in many counties. As the most attractive and promising antiviral agents, Lopinavir/Ritonavir, Remdesivir, and CQ/HCQ have presented potential antiviral activities against COVID-19. For patients with severe or mild COVID-19, no benefit was observed with Lopinavir/Ritonavir treatment beyond standard care [47,88]. However, the triple combination of interferon β-1b, Lopinavir/Ritonavir, and Ribavirin was safe and superior to Lopinavir/Ritonavir alone for patients with mild to moderate COVID-19 patients, indicating the combination therapy may increase the efficacy and safety of Lopinavir/Ritonavir [48]. A result of RCT indicated that Remdesivir alone had clinical improvement in severe COVID-19 patients with shorten duration of hospital stay, but no statistically clinical benefits and difference in mortality were observed. However, some scientists gave hope to the combination of Remdesivir with other drugs such as tocilizumab. Thus, further studies of combination treatment with stronger evidences are needed. The therapeutic and toxic dose of CQ/HCQ is so narrow that the improper use of CQ or HCQ can easily cause serious side effects. Many European countries approved CQ/HCQ only for clinical trials but not for the treatment for COVID-19 patients because of the unsatisfied efficacy and the potential toxicity of CQ/HCQ. However, a cause-and-effect relationship between drug therapy and survival should not be inferred too early according to the observational studies. According to anti-coronaviruses activity and better coronaviruses clearance of Favipiravir, double- and triple-therapy include Favipiravir is recommended for mild or moderated COVID-19 patients. As it is associated with cardiovascular reaction and hepatotoxicity that Ribavirin is not recommended for mild COVID-19. Traditional Chinese Medicine such as LH played an important role during this epidemic for patients both in Fangcang shelter hospital and COVID-19 designated infectious disease hospitals. The combination treatment of LH and standard antiviral agents could somehow relieve symptoms and reduce the time of recovery with mild patients.

Other “old drugs” are under pre-clinical and clinical study for the treatment of COVID-19, such as Triazavirin, Danorevir, Baloxavir Marboxil, darunavir/cobicistat, emtritabine (FTC)/Tenofovir alafenamide Fumarate tablets (TAF) etc, but few of them had solid evidence to support their efficacy and safety for COVID-19 patients. Meanwhile, the development of new drugs for COVID-19 are still ongoing, for instance the small peptides targeting ACE2, small molecule interrupting the interaction of SARS-CoV-2 Mpro (3CLpro) protease with other drugs [14]. These new drugs displayed obvious antiviral activity both *in vitro* and *in vivo*, but their efficacy for COVID-19 patients need to be further investigated. Biologics are considered to be the most promising drugs in the future due to their high specificity and efficacy. Biologics such as mesenchymal stem cells, SARS-CoV-2-specific neutralizing antibodies, vaccines have been used for clinical practice of COVID-19 patients. With the further clinical trials, the safety and efficacy will be revealed for the rational options for the treatment of COVID-19.

Despite many clinical trials have been conducted for the treatment of COVID-19, no drug has been verified to be really effective for COVID-19. To find the “specific drugs” for COVID-19, multicenter clinical trials should be performed with enough enrolled patients to carefully analysis the clinical outcomes. On the other hand, new drugs such as small inhibitors, ACE2 peptide inhibitors or vaccines specific for SARS-CoV-2 are new hope for the treatment of COVID-19. We believe that the numerous experiences reviewed in this paper will promote the development of effective drugs for COVID-19 patients.

Conflict of interest

No potential conflict of interest was reported by the author(s).

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