



COVID-19 Drug Treatment in China

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Abstract

Purpose of Review An unprecedented outbreak of the novel coronavirus in China (COVID-19) occurred in December 2019, and then engulfed the entire world, presenting a significant and urgent threat to global health. Many research institutes have been involved in the development of drugs and vaccines against COVID-19.

Recent Findings At present, the strategy of new use of old drugs is mainly used to screen candidate drugs against the novel coronavirus (later termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) and inhibit excessive immune response. Related research has made great progress.

Summary In this review, we summarize the drugs used for COVID-19 treatment in China based on the emerging basic and clinical data. It is hoped that this review will be useful to provide guidance for the prevention, treatment, and control of COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Medical treatment · New drug research and development

Introduction

An outbreak of a series of pneumonia cases associated with a novel coronavirus has been reported in Wuhan, Hubei Province, China, since December 2019 [1–3]. It is highly contagious and has rapidly spread to the entire China and multiple other countries worldwide since then [4–6]. On January 5,

2020, Professor Zhang of Fudan University completed virus sequencing and submitted the first novel coronavirus genome sequence to the National Bank of the US National Center for Biotechnology Information (Acc. No. MN908947). After that, this global health threat was officially and internationally named SARS-CoV-2 by the World Health Organization (WHO) on February 11, 2020 [7]. On January 30, 2020, the WHO declared the Chinese outbreak of COVID-19 to be a public health emergency of international concern, which means the outbreak of COVID-19 raised intense attention internationally; all countries around the world should be prepared for a potential global outbreak [8–10]. Up to now, there had been 1,524,334 confirmed cases, 340,335 cured, and 88,468 deaths (as of April 9, 2020). Clinically, most patients developed mild symptoms of dry cough, dyspnea, fever, and bilateral lung infiltrates on imaging [11–13]. Besides, numbers of researches have confirmed that while the mortality rate of the elderly and patients with underlying diseases is high, that of the young is relatively low through the deadliest outbreak of COVID-19 [14].

There are six strains of coronaviruses that are confirmed infectious to humans, which are named for their coronary appearance with positive single-stranded RNA genomes [15]. Similar to SARS and MERS, SARS-CoV-2 is a kind of highly pathogenic coronavirus that could cause severe respiratory illness and even death [16]. However, SARS-CoV-2 has higher transmissibility from human to human

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comparatively, which makes humans vulnerable to infection and makes it harder to get this outbreak under control [17–19].

As the epidemic is getting worse, the control of COVID-19 presents multiple challenges in the short term [20]. Nevertheless, no specific antiviral medicine is available either to treat or to prevent the aggravation of COVID-19 [21, 22]. More potent antiviral drugs are urgent to be developed [23]. It usually takes about 12 to 15 years for a new drug transitioning from development to market, which is a fairly long process. Therefore, it is not feasible to study antinovel coronavirus drugs from the beginning to get a direct effect on the prevention and control of this outbreak. Only by adopting the strategy of “old drugs for new use,” that is, finding effective drugs against novel coronavirus from existing drugs on the market, making it be rapidly applied to clinical practice [24, 25]. COVID-19’s therapeutic strategies mainly relied on the experience of clinicians [26, 27]. Up to now, some medicines are confirmed clinically to be effective in eliminating SARS-CoV-2 and improving symptoms [28, 29]. Among them, traditional Chinese medicines have received broad adoption, especially in treating cases of mild symptoms [30, 31]. In this review, we summarized the drugs used for COVID-19 treatment in China based on the emerging basic and clinical data. It is hopeful that this review will be useful to provide guidance for the prevention and control of COVID-19.

Traditional Chinese Medicine

Although there is no specific medicine recommended to prevent or treat the novel coronavirus to date, when the outbreak started, Chinese medicine (CM) approaches including oral administration of preventive herbal formulae, wearing CM sachets, and indoor herbal medicine fumigation were recommended for prevention and treatment and have shown pretty good effects [32, 33]. Under the guidance of clinical experience, the treatment for COVID-19 was divided into medical observation period and clinical treatment period (confirmed cases). The clinical treatment period (confirmed cases) is further stratified into four manifestations including mild case (cold-damp constraint in the lung pattern or damp-heat accumulation in the lung pattern), moderate case (damp-toxin constraint in the lung pattern or cold-damp obstructing the lung pattern), severe case (epidemic toxin blocking the lung pattern or blazing of both Qi and Ying patterns), and critical case (internal blockage and external desertion pattern) followed by a rehabilitation stage (lung and spleen qi deficiency patterns or deficiency of both qi and yin patterns). Depending on the patient’s pathological condition, different medications or prescriptions were used at different stages [30, 34]. At present, a total of 23 different Chinese medicines are recommended nationwide for the treatment of mild, severe, and critical symptoms [35]. According to prescriptions and standards,

under the guidance of traditional Chinese medicine theory, Chinese medicines were made into certain dosage forms, which could be directly used for the prevention and treatment of diseases [36–42]. Those Chinese medicine formulation used on COVID-19 are listed in Table 1.

Chemical Medicine

Lopinavir/Ritonavir

Lopinavir/ritonavir tablets (trade name: Clevee) are broad-spectrum antiviral drugs developed by AbbVie Inc., which was first approved by the European Union in 2001 [43, 44]. It is a type of human immunodeficiency virus (HIV) protease inhibitor that can block the cleavage of Gag-Pol precursor protein into mature protein, which eventually leads to the production of immature and non-infectious virus particles [45, 46]. It has been confirmed that ritonavir is an active peptidomimetic inhibitor against HIV-1 and HIV-2 aspartyl proteases. The enzyme cannot cleave the Gag-Pol precursor protein by inhibiting HIV protease which could lead to the formation of immature forms of HIV particles and prevent a new round of infection [47]. Currently, *in vitro* studies have shown that lopinavir/ritonavir can inhibit the replication of Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) to exert antiviral effects [48]. Based on that, lopinavir/ritonavir has been recommended for the clinical treatment of COVID-19 in China. According to the advantages of lopinavir/ritonavir in antiviral therapy, it is suggested that lopinavir/ritonavir should use in the early period of antiviral treatment to improve clinical symptoms and reduce viral load. The oral dosage is recommended once a day (800 mg/200 mg) that may increase treatment compliance, reduce adverse reactions, control the spread through urine and feces, and hinder the spread of the epidemic [32, 49]. However, the latest research has reported that lopinavir/ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with COVID-19 [50]. Besides, it should be noted that lopinavir/ritonavir is an inhibitor of liver P450 isoenzyme CYP3A. When it is combined with drugs that are mainly metabolized by CYP3A, it may lead to increased blood concentration of the combining drugs, which increases the adverse reaction.

Ribavirin

Ribavirin is a synthetic nucleoside antiviral drug with broad-spectrum antiviral activity, which inhibits both DNA and RNA viruses and widely used for the treatment of SARS and MERS [43, 51–53]. It was recommended that the combined use of ribavirin and α -interferon or lopinavir, 500 mg/

Table 1 Reported use of Chinese medicine formulations on COVID-19

Proprietary Chinese medicines	Composition	Application stage	Indications
Jinhua Qinggan granules	Jin-yin-hua, shi-gao, ma-huang, xing-ren, huang-qin, lian-qiao, zhe-bei-mu, zhi-mu, niu-bang-zi, qing-hao, bao-he, gan-cao	Medical observation period—clinical manifestation 2	Fever, headache, sore body, sore throat, cough, bad wind or cold, runny nose, red tongue, thin yellow fur
Huoxiangzhengqi capsule (pill, oral liquid)	Cang-zhu, chen-pi, hou-pu, bai-zhi, fu-ling, da-fu-pi, ban-xia, gan-cao, huo-xiang, and zi-su-ye	Medical observation period—clinical manifestation 1	Aversion to cold without sweat, headache body weight, limb pain, chest Diaphragm full, thirst not to drink, loose stools, drowning short, and yellow
Lianhua Qingwen capsules (granules)	Lian-qiao, jin-yin-hua, ma-huang, xing-ren, shi-gao, ban-lan-gen, guan-zhong, yu-xing-cao, huo-xiang, da-huang, hong-jing-tian, bao-he, gan-cao	Medical observation period—clinical manifestation 2	Fever or high fever, chills, muscle soreness, stuffy nose, runny nose, cough, headache, dry throat, sore throat, red tongue, yellow, or greasy fur
Jingyin granules	Jing-jie, yin-hua, niu-bang-zi, da-qing-ye, si-ji-qing	/	Clearing heat and detoxifying, moistening lung, and throat
Shufeng Jiedu capsules (granules)	Hu-zhang, lian-qiao, ban-lan-gen, chai-hu, bai-jiang-cao, ma-bian-cao, lu-gen, gan-cao	Medical observation period—clinical manifestation	Fever, bad wind, sore throat, headache, stuffy nose, runny nose, cough, red tip of tongue, thin white dry or yellow tongue coating, floating pulse
Xiyanping injection	Chuan-xin-lian	Clinical treatment period—severe	Severe fever and polydipsia, dyspnea and anhelation, delirium, blurred vision, rash, or hematemesis and epistaxis, or convulsion of the limbs. Tongue with little or no fur, deep and count pulse, or large and rapid pulse
Xuebijing injection	Hong-hua, chi-shao, chuan-xiong, dan-shen, dang-gui	Clinical treatment period—severe and critical	Severe fever and polydipsia, dyspnea and anhelation, delirium, blurred vision, rash, or hematemesis and epistaxis, or convulsion of the limbs. Tongue with little or no fur, deep and count pulse, or large and rapid pulse
Reduning injection	Qing-hao, jin-yin-hua, zhi-zi	Clinical treatment period—severe and critical	Severe fever and polydipsia, dyspnea and anhelation, delirium, blurred vision, rash, or hematemesis and epistaxis, or convulsion of the limbs. Tongue with little or no fur, deep and count pulse, or large and rapid pulse
Shenfu injection	Hong-shen, fu-zi	Clinical treatment period—critical	Dyspnea, asthma requires assisted ventilation, dizziness, irritability, cold sweaty limbs, purple tongue, thick or dry fur, large floating, and rootless pulse.
Shengmai injection	Hong-shen, mai-dong, wu-wei-zi	Clinical treatment period—critical	Dyspnea, asthma requires assisted ventilation, dizziness, irritability, cold sweaty limbs, purple tongue, thick or dry fur, large floating, and rootless pulse.
Angongniuhaung-wan	Niu-huang, she-xiang, zhen-zhu, zhu-sha, xiong-huang, huang-lian, huang-qin, zhi-zi, yu-jin, bing-pian	Clinical treatment period—clinical period 2	Clearing away heat, detoxifying, calming and resuscitating, fever, pathogen into pericardium, febrile convulsion, delirium, red or crimson tongue, powerful pulse number; apoplexy coma and encephalitis, meningitis, toxic encephalopathy, cerebral hemorrhage, septicemia
Xiangshaliujun-wan	Ban-xia, chen-pi, mu-xiang, sha-ren, dang-shen, bai-zhu, fu-ling, jiu-gan-cao	Clinical treatment period—clinical period 3	Invigorate the spleen and stomach. Used for spleen deficiency and qi stagnation, indigestion, belching Shao, wan abdominal distension and fullness, loose stool, tongue pale moss white greasy
Tanreqing injection	Huang-qin, xiong-dan, shan-yang-jiao, jin-yin-hua, lian-qiao	Clinical treatment period—severe and critical	Severe fever and polydipsia, dyspnea and anhelation, delirium, blurred vision, rash, or hematemesis and epistaxis, or convulsion of the limbs. Tongue with little or no fur, deep and count pulse, or large and rapid pulse
Xingnaojing injection	She-xiang, bing-pian, zhi-zi, yu-jin	Clinical treatment period—severe and critical	Severe fever and polydipsia, dyspnea and anhelation, delirium, blurred vision, rash, or hematemesis and epistaxis, or convulsion of the limbs. Tongue with little or no fur, deep and count pulse, or large and rapid pulse

time for adults with 2 to 3 intravenous injections per day, could control and improve patient's condition, but the therapeutic process should be limited to 10 days [32]. Notably, patients with contraindications should be excluded before clinical application for the reason that the incidence of adverse reactions of ribavirin is high and the individualized differences are obvious [54]. Studies on the effect of ribavirin in vitro showed that ribavirin could reduce viral infection [55]. However, the effectiveness and safety of ribavirin for COVID-19 still need further clinical trials to confirm. Medical workers should carefully and comprehensively evaluate the patient's various indicators to ensure the safety of patients' medication.

Arbidol

Arbidol is a non-nucleoside antiviral drug developed by the research center for pharmaceutical chemistry of the Soviet Union. Arbidol exerts an antiviral effect by inhibiting the fusion of the viral lipid membrane with the host cell to block the replication of the virus [56, 57]. It is active against many enveloped and non-enveloped viruses and has an interferon-inducing effect [58]. It has been found that 10–30 μmol of arbidol could effectively inhibit SARS-CoV-2 proliferation by 60 times compared with a drug-untreated control group and significantly inhibit the pathological effects of viruses in vitro [54, 59].

Remdesivir

Remdesivir is a nucleoside drug and an RNA polymerase (RdRp) inhibitor which was developed by Gilead Sciences in the USA [60, 61]. Accumulating evidence indicates that remdesivir could inhibit virus replication and play an antiviral role through blocking the synthesis of negative-strand RNA by inhibiting SARS-CoV-2 RdRp, subgenomic mRNA, and subviral genomic RNA [62, 63]. Remdesivir has shown good anti-MERS-CoV and anti-SARS-CoV activities in vitro and in animal models [64] and has anti-SARS-CoV-2 activity in vitro, indicating it could be used as a potential anti-SARS-CoV-2 drug [65]. On January 31, 2020, the prestige medical journal "New England Medical Journal" (NEJM) reported the diagnosis and treatment process of the first SARS-CoV-2 infected patient in the USA, showing that remdesivir has a certain role in the treatment [25, 54, 66]. Cell research published an article stating that among the six antiviral drugs tested, remdesivir had the strongest inhibitory effect of COVID-19 in vitro ($\text{EC}_{50} = 0.77 \mu\text{mol/L}$) [32]. Currently, remdesivir's clinical trials have been officially launched in China that a total of 761 patients are planned to be included in this study.

Favipiravir

Favipiravir is a wide-spectrum nucleoside antiviral drug developed by FUJIFILM Toyama Chemical Co., Ltd. [67]. It is a precursor drug that could be metabolized into the active metabolite favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-rtp) in vivo, which has an inhibitory effect on the RNA virus RdRp. The drug's initial indication was against influenza [68]. But subsequent studies have shown that the drug has inhibitory activity against almost all RNA viruses, such as West Nile virus, yellow fever virus, enterovirus, and Ebola virus [69–72]. On February 15, 2020, favipiravir tablets were marketed in China, and the indication was approved for the treatment of new or recurrent epidemics in adults. Thus, favipiravir became a potential drug for treatment of COVID-19 patients [73]. In a small-scale clinical trial of COVID-19, favipiravir has shown promising efficacy and low adverse reactions. It has been shown that favipiravir is effective against SARS-CoV-2 ($\text{EC}_{50} = 61.88 \mu\text{mol/L}$) [32].

Darunavir

Darunavir is an inhibitor of protease dimerization and catalytic activity of HIV-1 [74, 75]. It can selectively inhibit the cleavage of HIV encoded gag-pol precursor protein in virus infected cells, thus blocking the formation of mature infectious virus particles [76, 77]. Clinically, darunavir is mainly used as a drug for AIDS. On February 4, 2020, it was announced that darunavir could significantly inhibit the replication of the virus at concentration of 300 $\mu\text{mol/L}$ [32, 54].

Emtricitabine and Denofovir Alafenamide

Emtricitabine is a nucleoside reverse transcriptase inhibitor which is used in AIDS treatment [78, 79]. It blocks the reverse transcription process of HIV by inhibiting reverse transcriptase and can also effectively inhibit hepatitis B virus (HBV) reverse transcription process [77, 80]. It has been reported that the combination of emtricitabine and denofovir alafenamide in clinical trial for the treatment of COVID-19 was applied with great therapeutic effects [32].

Chloroquine Phosphate

Chloroquine phosphate is mainly used in the treatment of malaria and rheumatism in clinical [81–83]. Numerous studies have presented that it has broad-spectrum antiviral effect [84]. Recently, it has been found that chloroquine phosphate could effectively inhibit the infection of coronavirus at the cellular level [85–87]. It has been recommended for antiviral treatment of the COVID-19 as well [88].

Hydroxychloroquine

Hydroxychloroquine was developed as an antimalarial drug and has been used for the treatment of rheumatoid arthritis and lupus erythematosus [89–91]. Due to its antiviral activity, hydroxychloroquine has also been used as an adjuvant therapy for AIDS [92–94]. It has been confirmed that hydroxychloroquine also has therapeutic effect against Ebola virus and dengue virus in *in vitro* studies [95]. Recently, it has been reported that some COVID-19 patients benefited from the treatment with hydroxychloroquine [96–99]. Moreover, its effect for virus elimination could be reinforced by azithromycin [97].

Biological Medicine

Interferon α

Interferon (IFN) is a kind of multifunctional cytokine family with broad-spectrum antiviral, antiproliferative, and immunomodulatory activities. According to different binding receptors, it can be divided into type I, type II, and type III. Among them, type II IFN (mainly α/β IFN) plays an important role in the control of virus infection. Naturally, IFN- α is a very important immune protective cytokine in human response to virus infection [100, 101]. It could induce the same cell to produce antiviral protein and limit the further replication and spread of the virus [102, 103]. Moreover, IFN- α has been recommended to be applied in the treatment of COVID-19 recently [32].

Tocilizumab Injection

Tocilizumab injection is a recombinant humanized monoclonal antibody against human IL-6 receptor, which specifically binds to soluble and membranous IL-6 receptor to block signal transduction, thus inhibiting the activity of IL-6 receptor and achieving the goal of treating rheumatoid arthritis [104–106]. IL-6R plays an important role in the occurrence and development of some inflammatory and autoimmune diseases. As an activator of IL-6, sIL-6R can enhance the sensitivity of cells to IL-6 [107]. It has been found that as an antagonist of cytokine interleukin-6 (IL-6), tocilizumab injection is likely to block cytokine storm and thus prevent COVID-19 patients from turning to severe and critical diseases [108]. Tocilizumab injection has been recommended as a treatment for COVID-19 by researchers at University of Science and Technology of China.

Glucocorticoids

Glucocorticoid is an extremely important regulatory molecule in the human body [109]. It plays an important role in regulating the body's development, growth, metabolism, and

immune function. It is the most important regulatory hormone in the body's stress response, and it is also the most widely used and effective antiinflammatory and immunosuppressive agent in clinical practice [110, 111]. During the treatment of COVID-19, it is recommended to be used for severe cases with high inflammatory response or children with acute respiratory distress syndrome [32, 112]. However, the side effects of glucocorticoids are severe; WHO recommends that glucocorticoids are not suitable for the routine treatment of COVID-19 except in clinical trials [11, 113, 114].

Convalescent Plasma Therapy

Currently, the convalescent plasma therapy has been in the process of promotion; some patients' clinical indicators and symptoms have been improved [32]. There have been a large number of people who have recovered from coronavirus infection, donating valuable serum containing immunoglobulin which seems better than trying to produce large amounts of monoclonal antibodies in the laboratory. However, using antibodies to treat COVID-19 has some obvious problems such as limited sources of therapeutic plasma, different concentrations and activities of antibodies in human plasma of various sources, and non-neutralizing antibodies in plasma that may contribute to cytokine storms and other safety risks. Therefore, the convalescent plasma therapy is only used on a small scale, while large-scale use still needs to wait until we understand the clinical application effect and adverse reactions. The safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients should be studied within the context of a well-designed clinical trial. In the absence of vaccines and specific therapeutic drugs, the recovery plasma therapy is still an exploratory treatment. The current diagnosis and treatment scheme is recommended to try in severe patients and closely monitor the possible risks [115].

Other Biological Medicine

There are also other biological medicines on COVID-19 such as human immunoglobulin and intestinal microecological regulator. Some researchers in China have suggested that human immunoglobulins can be selectively used to treat critically patients. Intravenous immunoglobulin in large doses could be used for severe systemic inflammatory response syndrome [11]. It has been suggested that intestinal microecological regulator could maintain intestinal microecological balance and prevent secondary bacterial infection [32].

Perspective

As for a new emerging acute infectious disease caused by SARS-CoV-2, there are still no specific antiviral drugs. All

options for its prevention and treatment are based on previous experience in the treatment of SARS, MERS, or other new influenza viruses. Active treatment based on the patient's symptoms is still the main direction of treatment. Up to now, China has made a great breakthrough in fighting against COVID-19, but the situation outside China is not optimistic. The Chinese Health Commission has established several versions of diagnosis and treatment plans on COVID-19, which was formulated in a short time by professionals in various fields. But it is just a temporary solution at present. Since these drugs were not developed for the treatment of COVID-19, the clinical therapeutic effect is surely limited. Besides, the efficacy and safety of involved medicines still need to be confirmed in further clinical treatment and research. Even though those medicines we used have certain therapeutic effect, it is still urgent for medical researchers to carry on the research and development of specific medicine and vaccine according to the infection mechanism and characteristic structure of new crown virus. What is more, an effective mechanism for drug development of coronavirus should be established.

Currently, the enthusiasm for COVID-19 drug research runs high, but whether long-term scientific research can persist after the epidemic is a bit more in doubt. The isolation and structure analysis of various coronaviruses have been completed in early period, but there is still no specific drug for each coronavirus in the world. The reasons are as follows: firstly, the replication mutation rate of the virus is very high, and it is easy to produce drug-resistant strains. Secondly, after the acute infectious period of a novel coronavirus, the patient is likely to have developed a corresponding durable immunity. However, compared with the transient infection of virus epidemic, the new drug development cycle is fairly a long time, which is not suitable for the development of coronavirus drugs economically. Therefore, the joint efforts of government departments and drug research and development departments are needed to achieve a breakthrough in a short period of time, for accumulating experience of the possible future coronavirus epidemic.

Conclusions

The drugs used for COVID-19 treatment in China based on the emerging basic and clinical data were summarized above. Among them, Chinese medicines have received broad adoption, especially in treating cases of mild symptoms. There is still a lot for us to do in the face of COVID-19. It is hoped that this review will be useful to provide guidance for the prevention and control of COVID-19.

Funding Information This work was supported by the Scientific Research Project of National Natural Science Foundation of China (Nos. 81872979 and 81973439).

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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