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Mini-Review

Research Progress of Drug Treatment in Novel Coronavirus Pneumonia

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Abstract. As of March 10, 2020, more than 100,000 novel coronavirus pneumonia cases have been confirmed globally. With the continuous spread of the new coronavirus pneumonia epidemic in even the world, prevention and treatment of the disease have become urgent tasks. The drugs currently being developed are not adequate to deal with this critical situation. In addition to being controlled through effective isolation, we need a rapid response from the healthcare and biotechnology industries to accelerate drug treatment research. By reviewing the currently available literature published at home and abroad, we summarize the current research progress of drug treatment during the epidemic period. At present, the drugs that can be used for treatment mainly include antiviral drugs, antimalarials, glucocorticoids, plasma therapy, biological agents, and traditional Chinese medicine. The effectiveness and safety of drug therapy need to be confirmed by more clinical studies.

KEY WORDS: novel coronavirus (2019-nCoV); pneumonia; drug therapy; research progress.

INTRODUCTION

On December 31, 2019, an unknown outbreak spread from Wuhan City, Hubei Province, China, and spread rapidly worldwide (1). The main clinical symptoms of this unexplained pneumonia are similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which can quickly develop from mild fever, fatigue, and dyspnea to severe pneumonia. Starting from the management experience of the SARS epidemic, China has rapidly carried out comprehensive prevention and control. On January 7, 2020, China officials officially announced that it would temporarily name the unexplained pathogen in Wuhan as 2019-novel coronavirus (nCoV) (2,3). The confirmed cases reported from outside China support human-to-human transmission (4,5), which indicates that the outbreak is difficult to control (6,7). After two meetings on January 30, 2020 (January 22 and January 23, respectively), the World Health Organization regarded the outbreak of the 2019-nCoV as a public health emergency (8,9). Although the development of vaccines has long-term prevention and control effects, rapid identification of drug treatment during the epidemic is the key to responding to the outbreak (10), and there is no clear treatment method at present (11). Studies have found that

2019-nCoV is a single-stranded RNA beta coronavirus similar to SARS and MERS (12), so current treatment is mainly based on the treatment experience of these two diseases (13) and further development of new targeted drugs. Currently, the drugs studied for the treatment of 2019-nCoV mainly include antivirals, antimalarials, glucocorticoids, plasma therapy, biological agents, and traditional Chinese medicine, among which lopinavir/ritonavir, ribavirin, remdesivir, chloroquine phosphate, and interferon are the main drugs. Here, we systematically review the current research that can be used in the treatment of 2019-nCoV, providing a theoretical basis for the next step of treatment and prevention.

ANTIVIRAL THERAPY

Protease Inhibitor

Disulfiram, as a protease inhibitor, is mainly represented by lopinavir and ritonavir, which have been proved to have inhibitory effects on SARS and MERS (14). Chinese studies have found that the combined use of lopinavir and ritonavir has a more obvious inhibitory effect on coronavirus during SARS (15). It is considered that the half-life of lopinavir can be increased by inhibiting cytochrome P450, thereby enhancing the antiviral effect. Lopinavir/ritonavir is a known antiretroviral drug targeting the human immunodeficiency virus (HIV), which is being evaluated for anti-2019-nCoV treatment (16). A randomized controlled clinical study of the effect of 2019-nCoV cases (ChiCTR2000029308) is also underway (17,18). At present, the National Health Council has recommended the use of lopinavir and ritonavir as antivirus regimens for 2019-nCoV-related pneumonia. The latest recommended dose is listed in our table (19).

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Nucleoside Analogues

Favipiravir and ribavirin are representatives of nucleoside analogues and have broad-spectrum antiviral effects. Theoretically, favipiravir and ribavirin have certain antivirus effects, while *in vitro* experiments have proved that ribavirin has little antivirus effects (20). However, their combined effect cannot be ignored. For example, favipiravir combined with oseltamivir is better than application of oseltamivir in severe influenza (21). Ribavirin combined with lopinavir/ritonavir seems to improve the clinical efficacy of SARS (22). It has been used for experimental treatment of 2019-nCoV.

Experimental Nucleoside Analogues

Remdesivir (GS-5734), a new nucleoside analogue, has been shown to be a potential broad-spectrum anticoronavirus drug (23,24). However, unlike the approved nucleotide analogues, experimental results confirmed that they had a stronger effect on both human infection coronavirus and various bat-derived coronavirus, significantly inhibiting virus replication in human primary cell culture (25). A recent cell experimental study indicated that remdesivir could inhibit 2019-nCoV *in vitro* infections (26). It is considered that remdesivir can effectively inhibit respiratory virus replication and improve virus-infected lung tissues (23). Here is a report on the cure of an American patient infected with 2019-nCoV after remdesivir (27). Theoretically, remdesivir is currently the most promising drug for the treatment of 2019-nCoV and has relatively complete data on human pharmacokinetics and safety (28). More relevant clinical randomized controlled studies have been registered (mild-to-moderate 2019-nCoV: NCT04252664; severe 2019-nCoV: NCT04257656) and are expected to be completed within the next 2 months.

Neuraminidase Inhibitor Oseltamivir

Neuraminidase inhibitors (NAI), such as oral oseltamivir, inhaled zanamivir, and intravenous peramivir, are recommended as antiviral therapy for influenza (29). Studies have shown that neuraminidase inhibitors have been used to control MERS-CoV infection (30). According to empirical treatment, clinical used oseltamivir is widely to treat confirmed or suspected cases of 2019-nCoV in hospitals in China. And the research mentioned above shows that oseltamivir combined with fapilavir is more effective in treating severe influenza (21).

Membrane Fusion Inhibitor

Abidol, as a non-nucleoside drug, is a membrane fusion inhibitor with the activity of broad-spectrum antiviral drugs (31). It is more commonly called arbidol, as a membrane inhibitor, that blocks viral replication by inhibiting the fusion of influenza virus lipid membranes with host cells (32). Research considerations are mainly to prevent hemagglutinin (HA), a protein on the surface of influenza virus, which mediates membrane fusion, thereby inhibiting virus attachment to host cells (32,33). Recent studies have shown that abidol can be used for the treatment of 2019-nCoV (19). Currently, a randomized multicenter controlled clinical study of abidol for 2019-nCoV (ChiCTR2000029573) has been initiated in China.

ANTIMALARIAL DRUGS

A multicenter clinical trial of chloroquine phosphate for treating the 2019-nCoV-associated pneumonia is underway in China, according to a press conference held by the State Council of China on February 17, 2020. Soon, chloroquine or hydroxychloroquine was tested in hospitals of Beijing, Shanghai, Wuhan, and other places for the treatment of 2019-nCoV-associated pneumonia (34). Chloroquine, as a known antimalarial drug, can inhibit the production and release of inflammatory factors in viral diseases and has antiviral effects on many diseases including HIV-1, hepatitis B, and HCoV-229E (35). Recent studies have shown that chloroquine can inhibit 2019-nCoV by increasing the endosome pH required for viral cell fusion (26), and its antiviral and antiinflammatory activity considerations are also involved (36). A related open trial (ChiCTR2000029609) is ongoing.

GLUCOCORTICOID

A recent article published did not recommend glucocorticoids for 2019-nCoV patients (37). And study also opposes the widespread use of corticosteroids according to the latest expert consensus (38). However, there is also research evidence that low-dose corticosteroids can be used appropriately in subgroups such as severe patients to improve the survival advantage of patients (39,40). Study suggested that low-to-moderate short-term corticosteroids can be used in severe patients with 2019-nCoV (41). Therefore, the current glucocorticoid treatment of 2019-nCoV-related pneumonia is still controversial. At present, it is only recommended to try intravenous methylprednisolone for 3–5 days, and it is not suitable for long-term use (42,43).

PLASMA THERAPY

Previous research has shown that convalescent plasma can produce polyclonal antibodies to neutralize the virus (44), which can reduce the mortality of patients with viral infection (45). Therefore, cured patients can donate plasma for treatment (46) and research (47). And the Chinese Academy of Sciences research found that the 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of severe patients could be neutralized by the serum of several patients. However, due to the timing of the recovery period, plasma may have lower antibody titers (48) and even other disease infections may occur. Therefore, the collection of plasma is very important; it needs to be at the right time and to ensure its safety. Due to the rapid outbreak and virus variability, plasma treatment has become relatively unsatisfactory (49).

BIOLOGICAL AGENTS

Monoclonal Antibody

Regarding monoclonal antibodies, some studies have suggested that monoclonal antibody CR3022 for SARS treatment may be used to treat 2019-nCoV (50). Monoclonal

Table I. The Drugs of 2019-nCoV-Related Pneumonia

Drug type	Representative drug	Reference dose	Reference
Antiviral therapy			
Protease inhibitor	Lopinavir	400 mg q12h, po, 14 days	[15,19]
	Ritonavir	100 mg q12h, po, 14 days	[15,19]
Nucleoside analogues	Favipiravir	1800 mg/800 mg	[20,21]
	Ribavirin	500 mg tid, i.v. gtt, 14 day	[58]
Experimental nucleoside analogues	Remdesivir	10 mg/kg	[26,27]
Neuraminidase inhibitor oseltamivir	Oseltamivir	75 mg bid, 10 days	[21,29]
Membrane fusion inhibitor	Arbidol	0.2 g, tid, po, 2 weeks	[19,32]
Antimalarial drugs			
Chloroquine	Chloroquine phosphate	500 mg bid	[34,35]
Glucocorticoid			
Corticosteroids	Methylprednisolone	1–2 mg/kg/day, 3–5 days,	[57]
Plasma therapy			
Cured patients plasma	Convalescent plasma	no symptoms in 14 days, COVID-19 negative	[46]
Biological agents			
Monoclonal antibody	CR3022	\	[50]
Interferon	Interferon-α	2–4 μg/kg bid, 5–7 days	[57]
ACE2-Fc	ACE2-Fc	\	[60,61]
Chinese traditional medicine			
Heat-clearing and detoxicating drugs	SFJDC	2.08 g, tid, po, 2 weeks	[19]

antibodies based on passive immunotherapy overcome many shortcomings of serum and intravenous immunoglobulin preparations and have been the focus of antiviral therapy. Previous studies have shown that monoclonal antibodies can remarkably improve the MERS-CoV infection [51]. Research by Mark *et al.* shows that monoclonal antibodies REGN-EB3 and mAb114 can significantly reduce the mortality of patients with Ebola [28]. Reviewing the recently research progress, it is suggested that monoclonal antibodies can be used for the treatment of 2019-nCoV [52]. However, no relevant monoclonal antibodies have been successfully marketed yet [53]. It is mainly based on the latest experiments that the CR3022 can effectively bind to the 2019-nCoV receptor–binding domain [50] that mainly targets the spike protein and inhibits the virus from attaching to the host cell, thereby preventing the virus from invading. Through this passive immunotherapy, it makes the treatment more targeted, and it is conducive to the development of vaccines [53].

Interferon

Studies have shown that the treatment of 2019-nCoV infection can improve survival by interferon [1]. Interferon and ribavirin, these two antiviral drugs, are always used in combination for hepatitis C treatment. Studies show that ribavirin can enhance the antiviral effect of interferon through the mTOR [54] and EKR1/2 pathways [55]. And trials involving it, such as the approved interferon plus ribavirin trial (ChiCTR2000029387), have begun. Using marmoset animal models, Chinese scholars found that interferon-β combined with lopinavir/ritonavir had better efficacy to treat the MERS-CoV [56]. New research shows that interferon-α nebulization, injection of interferon-α2b [57], and α-interferon combined with lopinavir/ritonavir drugs [58] may be applicable to the current treatment of 2019-nCoV infection.

ACE2-Fc

Studies have shown that the entry receptor for 2019-nCoV-infected lung cells may be angiotensin-converting enzyme II (ACE2) [2], so cells expressing ACE2 can serve as target cells [59]. Moreover, studies have shown that the receptor mechanism about 2019-nCoV is mainly based on the coronavirus spike (S) glycoprotein [60,61]. Current treatments can fuse the ACE2 into the immunoglobulin Fc domain to block virus entry and establish lasting immunity [62]. This provides a new direction for the treatment of the 2019-nCoV**.**

CHINESE TRADITIONAL MEDICINE

Relevant research has used computer and biological processing to extract natural compounds with antiviral effect that have been verified by PubMed. These compounds were searched in the unique research database, found out 13 compounds, and identified more than 100 kinds of herbs. At last, 26 kinds of herbal plants, such as Bupleurum, Coptischinensis, Forsythia, and Glycyrrhizae, were selected out, which are highly likely to directly inhibit the 2019-nCoV [63]. This method of promoting drug research through science and technology promotes the choice of clinical treatment. An example of combining traditional Chinese and western medicine shows that SFJDC can be used for the treatment of new coronary pneumonia [19]. This drug is also recommended in the treatment on the disease (5th edition). Of course, the treatment principle is constantly being updated.

CONCLUSION

Current studies have shown that the drug treatment of 2019-nCoV-related pneumonia mainly includes antivirals,

antimalarials, and interferon. The main representative drugs are lopinavir/ritonavir, ribavirin, remdesivir, interferon, and so on (Table I). More choices are being put into the research process, such as barretinib (64), imatinib (31), sunitinib, erlotinib (65), nitazoxanide (26), and other potential drugs, as well as fusion peptide (EK1) (66), HR2P (67), and other new peptides. And the development of vaccines is also a long-term goal. We need more clinical practice to test out more old drugs that can be used for treatment and, at the same time, search for new drugs with targeted and effective results.

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COMPLIANCE WITH ETHICAL STANDARDS

Competing Interests The authors declare that they have no competing interests.

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