Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Drug treatment of coronavirus disease 2019 (COVID-19) in China.

Zhe Jin, Jing-Yi Liu, Rang Feng, Lu Ji, Zi-Li Jin *, Hai-Bo Li *

National Engineering Research Center of Immunological Products, Department of Microbiology and Biochemical Pharmacy, College of Pharmacy, Third Military Medical University, Chongqing, 400038, PR China

** Corresponding author. College of Pharmacy, Third Military Medical University, Chongqing, 400038, PR China.

E-mail addresses: jinzili@pku.edu.cn (Z.-L. Jin), lihaibo@tmmu.edu.cn (H.-B. Li).

ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Drug treatment
China

ABSTRACT

Since December 2019, the coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has spread throughout China as well as other countries. More than 8,700,000 confirmed COVID-19 cases have been recorded worldwide so far, with much more cases popping up overseas than those inside. As the initial epicenter in the world, China has been combating the epidemic for a relatively longer period and accumulated valuable experience in prevention and control of COVID-19. This article reviewed the clinical use, mechanism and efficacy of the clinically approved drugs recommended in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (DTPNCP) released by National Health Commission of P.R. China, and the novel therapeutic agents now undergoing clinical trials approved by China National Medical Products Administration (NMPA) to evaluate experimental treatment for COVID-19. Reviewing the progress in drug development for the treatment against COVID-19 in China may provide insight into the epidemic control in other countries.

1. Introduction

Although effective prevention and control measures had been taken, a total of 8,708,008 confirmed cases of COVID-19 cases have been reported worldwide, resulting in 461,715 deaths until June 21, 2020. The outbreak of COVID-19 not only severely threatened the health of people around the world, but also had great impact on the global economy. On January 30th, the World Health Organization (WHO) declared the COVID-19 outbreak to be a Public Health Emergency of International Concern.

Drugs are regarded as an essential way for preventing and controlling epidemic diseases. However, drug discovery is a time-consuming, sophisticated, and costly process, which can be always divided into several important stages, including preclinical research, clinical trials and additional review process. An average of 15 years are required for an experimental drug to travel from the lab to the patients (Hughes et al., 2011). Therefore, it is difficult to have an immediate effect on the prevention and control of COVID-19 by developing de novo drugs against SARS-CoV-2. New use of old drugs, that is searching for clinically approved drugs that have antiviral activities against SARS-CoV-2, may be a feasible strategy in the fight against COVID-19 (Alimuddin et al., 2016; Sachs et al., 2017). Since pharmacokinetic properties and toxicity are the main considerations that determirn the successfulness of novel drug development, candidates screened from the existing or licensed drugs in the laboratory could possibly be translated into clinical use in a faster pace (Ferreira and Andricopulo, 2019; Han and Gifford, 2003; Pan et al., 2018).

Since the outbreak of COVID-19, many research institutions have been using the above-mentioned strategy to screen candidate drugs which could inhibit SARS-CoV-2 or excess immune responses. With their continued efforts, drug candidates that display some clinical effects have been included in Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (DTPNCP) released by National Health Commission of China. The current review summarized the clinical use, mechanism and efficacy of the drugs which are recommended in DTPNCP, but also the novel therapeutic agents which are now undergoing clinical trials approved by NMPA to evaluate the treatment for COVID-19 in China. Reviewing these accumulated experience may provide insight into the epidemic control all over the world.

2. Overview of the pathophysiology of COVID-19

The pathogenesis of COVID-19 has been revealed that the spike protein of SARS-CoV-2, including two functional subunits (S1 and S2),

https://doi.org/10.1016/j.ejphar.2020.173326
Received 23 March 2020; Received in revised form 25 June 2020; Accepted 26 June 2020
Available online 27 June 2020
0014-2999/© 2020 Elsevier B.V. All rights reserved.
promoted the binding to angiotensin converting enzyme 2 (ACE2) and the entry into host cells (Gralinski and Menachery, 2020; Richardson et al., 2020; Walls et al., 2020). The S1 subunit served as the pathway of binding to the host cell receptor and S2 subunit played a role in the fusion of the viral and cellular membranes. The spike protein of SARS-CoV was incorporated without cleavage. In contrast, the S1/S2 site of SARS-CoV-2 with the unique existence of furin cleavage site was entirely subjected to cleavage during biosynthesis, which makes SARS-CoV-2 virus more aggressive in pathogenicity compared with SARS-CoV (Yuki et al., 2020). Autopsy of COVID-19 victims in China has confirmed the existence of coronavirus particles in the cytoplasm of tracheal and bronchial mucosa epithelia and alveolar type II pneumocytes under electron microscopy. The autopsy has also shown injuries in multiple organs and tissues with prominent and extensive pulmonary lesions caused by SARS-CoV-2. This was considered as a pathological basis for the lethal respiratory dysfunction. Apparent lesions in lymphatic and hematopoietic organs were also observed (Bian and Team, 2020). The body injury may also be associated with the induction of excessive immune responses, resulting in self-attack and multiple organ damage (Zamla et al., 2020). In a peripheral blood sample from an early case, both CD4⁺ and CD8⁺ T cells were hyper activated, which was considered to be responsible for the severe immune injury in this patient (Xu et al., 2020b).

3. The old drugs recommended in DTPNCP

3.1. Small molecule drugs

3.1.1. Lopinavir/ritonavir

Lopinavir/ritonavir (Abidol®/Kaletra®), developed by Alberta, is a human immunodeficiency virus (HIV) protease inhibitor, which can enhance the antiretroviral activity against the virus by inhibiting cytochrome P450 (Cvetkovic and Goa, 2003). Lopinavir/ritonavir was approved for the treatment against HIV infection in the United States in 2000 and was available in China in 2008.

During the epidemic of SARS, it was found that patients with SARS treated with the combination of lopinavir/ritonavir and ribavirin had lower risk of the acute respiratory distress syndrome (ARDS) or death, compared with those treated with ribavirin alone (Chu et al., 2004). In the DTPNCP (trial version 2) released on January 22, it was declared that there was no existing drug against COVID-19 at present, and lopinavir/ritonavir could be tried for no more than 14 days. In a study including 47 patients with COVID-19, treatment with the combination of lopinavir/ritonavir and pneumonia-associated adjuvant drugs showed a notable therapeutic effect in lowering the body temperature and restoring normal physiological mechanisms with no evident toxic and side effects, compared with treatment of adjuvant drugs alone (Ye et al., 2020). However, a randomized controlled open-label trial conducted by Bin Cao et al. observed no benefit with lopinavir/ritonavir treatment (Cao et al., 2020), and trials in the mild COVID-19 cases also showed similar results (Cheng et al., 2020). Moreover, lopinavir/ritonavir was found to be related to the emerging abnormal liver functions after admission, causing a prolonged length of stay (Fan et al., 2020).

3.1.2. Chloroquine phosphate

Chloroquine phosphate is mainly used as an antimalarial and anti-inflammatory agent for treatment of malaria and rheumatic diseases (Bijker et al., 2013). Previous studies have also found that it has broad-spectrum antiviral effects (Delvecchio et al., 2016; Mizui et al., 2010). Chloroquine can strongly bind to the nuclear protein and decrease the twist of the double helix of DNA, forming a complex and preventing the replication of DNA or the transcription of RNA. In addition, chloroquine can cause pH changes of endosomes, and it is also an effective autophagy inhibitor, which interferes with viral infection and replication by affecting autophagy (Schultz and Gilman, 1997). Besides the antiviral activity, chloroquinines also have the immunomodulatory ability, which may enhance its antiviral abilities in vivo. Apart from chloroquine phosphate, hydroxychloroquine is also an antimalarial drug used in clinical setting, which has the similar structure and mechanism to those of chloroquine, but is less toxic (Ben-Zvi et al., 2012).

It was found that chloroquine phosphate could effectively inhibit the infection of SARS-CoV-2 at the cellular level (50% effective concentration (EC₅₀) = 1.13 μM, semi-cytotoxic concentration (CC₅₀) > 100 μM and selection index (SI) > 88.50) in a joint study (Wang et al., 2020a). As of May 23rd, there are 22 ongoing clinical trials using chloroquine for the treatment of COVID-19 in China (Cortegiani et al., 2020). A multi-center, prospective observational study in China including 197 cases showed that the clearance rate of viral RNA in the chloroquine group was significantly higher and faster than that in the non-chloroquine group after 14 days (95.9% and 79.6%), but the rate of adverse reactions showed no significant difference in the two groups (Huang et al., 2020). However, a recent randomized trial in Brazil to evaluate effect of high and low-dose chloroquine diphosphate as adjunctive therapy for patients with SARS-CoV-2 infection suggested that high-dose chloroquine diphosphate was not recommended for the treatment of critically ill patients because of potential safety hazards (Borba et al., 2020).

Azithromycin together with hydroxychloroquine effectively reduced the viral carriage at D6 post-inclusion, and led to a much lower average carrying duration compared with controls. The potential effect of hydroxychloroquine against COVID-19 may be reinforced by azithromycin (Gautret et al., 2020). However, in a recent observational study of hydroxychloroquine in clinic from March 7th to April 8th, no association between hydroxychloroquine and changed risk of the composite end point of intubation or death was found, indicating that COVID-19 may be unsensitive to hydroxychloroquine (Geleris et al., 2020). Generally, existing evidence is not enough to further clarify recommendations for hydroxychloroquine treatment in patients with COVID-19. More randomized controlled clinical trials are needed to provide convincing information.

3.1.3. Arbidol

Abidol is a non-nucleoside antiviral drug developed by the Pharmaceutical Chemistry Research Center of the former Soviet Union, which shows the antiviral activity against many viruses (Kadam and Wilson, 2017; Pécheur et al., 2007), the main indication of abidol is the disease caused by influenza A and B viruses. Abidol specifically inhibits the contact, adhesion and fusion of the viral lipid envelope and the host cell membrane, and blocks viral genes from penetrating into the nucleus, inhibiting the synthesis of viral DNA or RNA by activating 2-oligoadenylate synthetase (antiviral protein) in vivo. Abidol was first approved in Russia in 1993 and is now mainly used in Russia and China, but has not been approved by Western countries.

Abidol showed an efficient inhibitory ability against SARS-CoV-2 infection in vitro with the EC₅₀ at 4.11 (3.55–4.73) μM (Wang et al., 2020b). It was predicted in structural and molecular dynamics studies that arbidol may target the SARS-CoV-2 spike glycoprotein and block the trimerization of spike glycoprotein, which is a key for host cell adhesion and hijacking (Vankadari, 2020). A retrospective cohort study found that arbidol and lopinavir/ritonavir treatment showed more favorable clinical response in treating COVID-19 (Deng et al., 2020). Also another retrospective study including 50 cases indicated that arbidol monotherapy may be superior to lopinavir/ritonavir, in which no viral load was detected in arbidol group, but the viral load was found in 15 (44.1%) patients treated with lopinavir/ritonavir after 14 days (Zhu et al., 2020).

3.1.4. Ribavirin

Ribavirin, a purine nucleoside analog, is a broad-spectrum nucleoside antiviral drug. During the epidemic of SARS and MERS, it has been widely adopted in clinical setting, but its efficacy is still controversial.
Ribavirin is metabolized intracellularly into 5'-phosphate derivatives that directly or indirectly inhibit viral replication, and is rapidly excreted in the human body as a prototype or as a derived glycosylation product (Gilbert and Knight, 1986). It is mainly used for severe hospitalized patients with bronchiolitis and pneumonia caused by respiratory syncytial virus (RSV), the patients with Lassa fever, or epidemic hemorrhagic fever (with manifestations of the renal syndrome), and those with chronic hepatitis C and viral upper respiratory tract infection (Zhang et al., 2020).

Because of the direct antiviral activity of ribavirin against SARS-CoV-2, its usage has been considered as dosage guidelines for testing new therapeutic concepts (Khalili et al., 2020). Molecular docking results showed that the potential target of ribavirin was RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 (Elfiky, 2020). It was recommended that ribavirin should be used in combination with alpha-interferon or lopinavir/ritonavir, 500 mg per adult, 2 to 3 times per day, and be given by intravenous infusion, and the course of treatment should not exceed ten days (Zhang et al., 2020).

3.2.1. Interferon (IFN)

IFN is a cytokine secreted by mammalian hosts during resistance to pathogens, which can interfere with virus replication and enhance the antiviral ability of cells (CE, 2001). It is known that IFN can be divided into three types: type I, type II, and type III (Chen et al., 2020). Type I IFN (IFN-α, IFN-β) is also called “viral IFN”. IFN-α inhibits both RNA and DNA viruses, but does not directly kill them (CE, 2001). IFN-α can inhibit viral gene and protein synthesis by activating signaling pathways, thus activates a variety of immune cells and improves the immunity, while IFN-β takes effect by inhibiting the adsorption of certain viruses, enhancing phagocytosis of natural killer cells and mononuclear macrophages to viruses, thus indirectly conducting the secretion of antiviral proteins in cells (Liu et al., 2011; Montoya et al., 2002).

IFN-α can effectively inhibit the replication of MERS-CoV and SARS-CoV in vitro or in animal models, and it has been used in combination with other antiviral drugs (such as ribavirin) to treat patients with SARS-CoV and MERS-CoV (Omrani et al., 2014). An open-label, randomized, phase II trial concluded that triple antiviral therapy with IFN-β1b, lopinavir/ritonavir and ribavirin was safe and superior to lopinavir/ritonavir alone in shortening virus shedding, and alleviating symptoms of COVID-19 patients (Hung et al., 2020). It was also stated that inhaled IFN-α can be used as a trial treatment against COVID-19 in the DTPNPC.

3.2.2. Tocilizumab

The analysis of the peripheral blood samples of severe COVID-19 patients indicated that severe lung injury caused by SARS-CoV-2 was associated with the elevated pro-inflammatory cytokine responses. Pathogenic T-cells are rapidly activated by viruses and produce cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 6 (IL-6), which are two key inflammatory factors. The progressive increase of IL-6 has been regarded as a clinical warning indicator of disease deterioration (Alzghari and Acuna, 2020; Fu et al., 2020; Zhang et al., 2020a).

Tocilizumab is a recombinant humanized anti-IL-6 receptor (IL-6R) monoclonal antibody, which can specifically bind to soluble and membrane-bound IL-6 receptors and inhibit signal transduction mediated by IL-6, thereby reducing inflammation and blocking cytokine storm caused by COVID-19 (Scheinecker et al., 2009). Tocilizumab was initially used in a study of 21 Chinese patients with severe COVID-19 (Xu et al., 2020a). Based on its encouraging therapeutic effect, a multi-center, large-scale clinical trial (ChiCTR2000029765) was further initiated, and approximately 500 severe or critically ill patients were included. In the DTPNPC (Trial Version 7), tocilizumab was recommended for the treatment of patients with extensive lung lesions or laboratory tests for elevated IL-6 levels (Antinori et al., 2020). In addition, tocilizumab combined with other drugs has been applied in more than 20 countries including Italy (Toniati et al., 2020).

3.2.3. Convalescent plasma product of COVID-19

The convalescent plasma donated by patients recovered from COVID-19 contains a high titer of specific antibody to SARS-CoV-2, which may mediate a strong passive immunity against the virus (Cao and Shi, 2020). The plasma products have already been used in the treatment against influenza, SARS and Ebola infection (Burnouf and Radosevich, 2003; Van Griensven et al., 2016; Zhou et al., 2007).

Convalescent plasma was listed in the DTPNPC since Trial Version 4. China National Biotec Group launched a research on the convalescent plasma for treatment of COVID-19 since January 20. The results indicated that one dose (200 ml) of convalescent plasma was well tolerated, and patients who received plasma transfusion were improved in terms of several parameters, including lymphocyte counts and C-reactive protein. In addition, no severe adverse effects were observed (Duan et al., 2020). Serological findings showed that the plasma from six donors recovered from COVID-19 had high IgG titers (above 1:320), and patients who received plasma transfusion showed no related adverse event and did not require mechanical ventilation 11 days after plasma transfusion (Zhang et al., 2020b). Though several cured cases have been reported, more expanded clinical trials remains to be fulfilled.
4. Novel therapeutic agents undergoing clinical trials in China

4.1. Small molecule agents

4.1.1. Favipiravir

Favipiravir (Avigan®) is a RdRp inhibitor with broad-spectrum anti-influenza activity (Furuta et al., 2013), developed by Toyama Chemical Industry, and was conditionally licensed in Japan in 2014. Favipiravir can selectively inhibit RNA polymerase related to the replication of the influenza virus and can be phosphorylated by host cell enzyme to produce bioactive favipiravir furlurlybo-5-triphosphate-inositol (favipiravir RTP). Virus RNA polymerase misrecognizes favipiravir RTP, resulting in insertion of favipiravir RTP into the viral RNA chain or its binding to the viral RNA polymerase domain, which hinders the transcription and transcription of the RNA chain of the virus (Furuta et al., 2009). Because of the specific mechanism, favipiravir has an inhibitory effect on the Ebola virus, yellow fever virus, norovirus and so on (Furuta et al., 2009; Oestereich et al., 2014; Rocha-Pereira et al., 2012).

Nowadays, favipiravir has been used in the antiviral treatment of influenza A and B. Besides, the drug-drug interactions and mechanisms of favipiravir against SARS-CoV-2 were also analyzed (Du and Chen, 2020).

Favipiravir showed a significant inhibitory effect on SARS-CoV-2 in vitro (EC50 = 61.88 μM) (Wang et al., 2020a). On February 16th, favipiravir was approved by the NMFA for the treatment of new or recurrent influenza in adults. Up to now, there are 4 trials of favipiravir for COVID-19 ongoing in China (Khammadja and Asudani, 2020). The preliminary result of a clinical study (ChiCTR2000029600) showed that favipiravir might relieve the progression of COVID-19 by accelerating the virus clearance. Another open-label study declared that favipiravir showed significantly better therapeutic effects on the disease progression and viral clearance, with an improvement rate of 91.43% versus 62.22% (P = 0.004) in the chest imaging, compared with lopinavir/ritonavir (Cai et al., 2020).

4.1.2. Remdesivir

As a nucleotide analogue prodrug developed by Gilead, remdesivir can also inhibit RdRp with the same mechanism of action similar to that of favipiravir (Tchesnokov et al., 2019). The structure of RdRp-Remdesivir complex indicates that the partial double-stranded RNA template is inserted into the central channel of RdRp where remdesivir is covalently incorporated into the primer strand at the first replicated base pair, thus terminating the chain elongation (Yin et al., 2020). Once incorporated at position i, the inhibitor causes RNA synthesis arrest at position i-3 (Gordon et al., 2020). In addition, the importance of the balance between incorporation and excision properties of nucleoside analogues between the RdRp and exonuclease also received increasing attention (Shannon et al., 2020). In general, remdesivir is a broad-spectrum antiviral candidate drug with the potential against many viruses (Agostini et al., 2018; de Wit et al., 2020).

On January 31st, the clinical symptoms of a patient infected with SARS-CoV-2 in the United States were significantly improved after treatment with remdesivir, and the oxygen saturation recovered to 94%-96% (Holshue et al., 2020). Four days later, it was reported that remdesivir had the strongest in vitro inhibitory effect on SARS-CoV-2 among the six tested antiviral drugs (EC50 = 0.77 μM) (Wang et al., 2020b). A phase III, randomized, double-blind, placebo-controlled multicenter clinical study lasting for 8-11 days and including 237 cases (158 to remdesivir) with mild to moderate SARS-CoV-2 infection (NCT04257656) was conducted in China. The results showed that the use of remdesivir was not associated with a difference in time to clinical improvement, yet patients receiving remdesivir had a significantly faster clinical improvement with symptom duration of 10 days or less, and the adverse events were reported in 66%, compared to 64% of the placebo group (Wang et al., 2020c). Moreover, the results of a phase II trial revealed by Gilead suggested that remdesivir had a better effect in the 10-day group. Remdesivir was also found to have a synergy effect with emetine, and remdesivir at 6.25 μM in combination with emetine at 0.195 μM may achieve 64.9% inhibition in viral yield (Choy et al., 2020). Based on these clinical findings, USFDA has made remdesivir available under an emergency-use authorization for the treatment of adults and children with severe COVID-19 disease (Hendaus, 2020). Though remdesivir was considered as a promising option for COVID-19, its safety and effect in humans still requires more evidence from additional clinical trials (Li et al., 2020).

4.1.3. Sivelestat sodium

Sivelestat sodium is the first drug to treat acute lung injury caused by systemic inflammatory response syndrome (SIRS), developed by Ono Company in Japan. It was licensed in Japan in April 2002. The low molecular weight enables sivelestat sodium to reach the gap between neutrophils and tissues, and its enzyme inhibitory activity is not affected by reactive oxygen species, which can effectively inhibit neutrophil elastase in the local site of inflammation (Aikawa and Kawasaki, 2014).

Sivelestat sodium can improve respiratory function, shortens the time of using respirator, reduces the complication rate of stress injury and respiratory infection caused by respirator installation, and improves acute lung injury caused by SIRS and idiopathic pulmonary fibrosis (Iwata et al., 2010).

As early as mid-May 2003, NMFA approved the clinical study of sivelestat sodium for the treatment of acute lung injury caused by SARS. Although the phase III clinical trial of sivelestat sodium was completed in 2013, it has not been licensed in China. Aikawa’s research on the safety of sivelestat sodium in treating the acute lung injury showed no negative effect in the long-term treatment. On March 12th, sivelestat sodium was approved by NMFA (CYHS2000102) for the acute lung injury with SIRS and ARDS caused by COVID-19.

4.2. Biological products

4.2.1. Human C5 monoclonal antibody

Abundant studies on acute lung injury caused by highly pathogenic viruses, such as influenza A virus and coronavirus, have found that overactivation of complement (especially C5a) may be the central event in that process (Wang et al., 2015). Therefore, C5a is highly valued as a rational target for the treatment of highly pathogenic virus-mediated acute lung injury.

BDB-001 is a monoclonal antibody targeting human C5a developed in China, it can control the further development of inflammation without inhibiting immune function (Barratt-Due et al., 2013). It is expected to prevent the exacerbation of pneumonia in coronavirus infection and further reduce the incidence of severe pneumonia and acute respiratory distress syndrome. BDB-001 injection has been approved by NMFA and is about to enter a phase 1-b clinical trial for the treatment of COVID-19.

4.2.2. Stem cell therapy

Based on several preclinical studies, mesenchymal stem cell (MSC), which has the characteristics of low immunogenicity and secretion of soluble factors to regulate immune response, plays an important role in attenuating underlying acute lung injury (Monsel et al., 2016). Some induced pluripotent stem cells may serve as suitable infection models for drug screening in vivo (Zhou et al., 2020). In addition, based on the similar pathogenesis and symptoms of H7N9 and COVID-19, MSC transplantation may be a way to improve the symptoms of severe patients with COVID-19 (J. Chen et al., 2020).

Several clinical trials have been conducted to evaluate the safety and efficacy of MSC therapy for COVID-19. Studies showed that ACE2 MSCs could be beneficial for the patients with COVID-19 pneumonia (Leng et al., 2020; Zhao, 2020). Due to the fact that CASTem (Human embryonic stem cell-derived M cells) significantly improved the survival rate in ARDS mice model, CASTem has been approved by NMFA to evaluate
European Journal of Pharmacology 883 (2020) 173326

5

In addition, the strategy of new use of old drugs is not supposed to be a permanent solution for drug discovery to fight COVID-19. Rational drug design, based on the pathomechanism of COVID-19 and target protein structure of SARS-CoV-2, is suggested for discovering novel drugs against COVID-19.

Declaration of competing interest

The authors declare no competing interests.

CRediT authorship contribution statement

Zhe Jin: Data curation, Writing - original draft. Jing-Yi Liu: Data curation, Writing - original draft. Rang Feng: Data curation, Writing - original draft. Liu Ji: Data curation, Writing - original draft. Zi-Li Jin: Investigation, Writing - original draft, Writing - review & editing. Hai-Bo Li: Supervision, Methodology, Validation, Funding acquisition.

Acknowledgements

This work was supported by Chinese National Natural Science Foundation Project (No. 31670936/31400788). We thank Prof. Shan Guan and Miss Xiaoqing Zhan (Third Military Medical University) for their linguistic assistance during the revision of this manuscript.

References

Agostini, M.L., Andres, F.L., Sims, A.C., Graham, R.L., Shehata, T.P., Lu, X., Smith, E.C., Case, J.B., Feng, J.Y., Jordon, R., 2018. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio 9 e00221-e00218.

Aikawa, N., Kawasuki, Y., 2014. Clinical utility of the neutrophil elastase inhibitor sivelestat for the treatment of acute respiratory distress syndrome. Therapeut. Clin. Risk Manag. 10, 621–629.

Aminuddin, Z., Zuma, J., Jaber, J., Ee, A., Azhak, D., 2016. Coronavirus - drug discovery and therapeutic options. Nat. Rev. Drug Discov. 15, 327–347.

Allan, M., Guery, P.M., Holbrook, N.J., 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions*. Endocrin. Rev. 5, 25–44.

Algharib, S.B., Acuna, V.S., 2020. Supportive treatment with tocilizumab for COVID-19: a systematic review. J. Clin. Virol. : the official publication of the Pan American Society for Clinical Virology 127, 104380.

Antinori, S., Bonazzetti, C., Garibetti, G., Capetti, A., Pagani, C., Fornara, V., Rimoldi, S., Galimberti, L., Sarzi-Puttini, P., Ridolfi, A.L., 2020. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmun. Rev. 19, 102564.

Barratt-Due, A., Thorgersen, E.B., Egge, K., Fiskhøi, S., Sokolov, A., Hellerud, B.C., Lindstad, J.K., Pharo, A., Borgot, A.K., Rieben, R., Mann, N., Scott, H., Molnes, T. E., 2013. Combined inhibition of complement (CS) and CD14 markedly attenuates inflammation, thrombogenicity, and hemodynamic changes in porcine sepsis. J. Immunol. 191, 819–827.

Ben-Zvi, I., Kivity, S., Langewitz, W., Shenfeld, Y., 2012. Hydroxychloroquine: from malaria to autoimmunity. Clin. Rev. Allergy Immunol. 42, 145–162.

Bian, X.-W., Team, t.C.-P., 2020. Autopsy of COVID-19 victims in China. National Science Review. https://doi.org/10.1093/nsr/nwaa123 nwaa123.

Bijker, E.M., Banzaert, G.J.H., Teirlinck, A.C., van Gemer, G.J., Graumans, W., van de Veeger-Bolmer, M., Siebelink-Stoter, R., Arens, T., Teelen, K., Nahrendorf, W., Remarque, E.J., Roefle, W., Jansen, A., Zimmermann, D., Vos, M., van Schaik, B.C. L., Wierenga, J., van der Ven, A.J.A.M., de Mast, Q., van Lieshout, L., Verweij, J.J., Hermens, C.C., Scholten, A., Sauerwein, R.W., 2013. Protection against malaria after immunization by chloroquine prophylaxis and sporozoites is mediated by preerythrocytic immunity. P Natl Acad Sci USA 110, 7862–7867.

Borba, M.G.S., Val, F.F.A., Carneiro, V.S., Sampaio, V.S., Alexandre, M.A.A., Mello, G.C., Iriti, M., Mourao, M.P.G., Brito-Sousa, J.D., Baia-da-Silva, D., Guerra, M.V.G., Hargreaves, L.A., Pinto, R.C., Palheiro, A.A.S., Caetano, A.G.P., Santos, J.R., J.D.O., Naveira, F.G., Xavier, M.S., Siqueira, M.A., Schwarzbold, A., Croda, J., Neugueira, M.L., Romero, G. A.S., Bastos, Q., Fonseca, C.J., Albuquerque, B.C., Daniel-Ribeiro, C.T., Monteiro, W. M., Lacerda, M.V.G., CloroCovid, T., 2020. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA network open 3, e200887.
Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Liao, G., Wang, X., Lu, Y., Li, H., Wang, S., Ruon, S., Yang, C., Mei, C., Wang, Y., Ding, D., Wu, F., Yang, X., Ye, X., Ye, Y., Liu, B., Yang, J., Yin, W., Wang, A., Fan, G., Zhou, F., Liu, Z., Guo, X., Xu, J., Shang, L., Zhang, Y., Cao, L., Guo, T., Wan, Y., Qin, H., Jiang, Y., Jaki, T., Hayden, F.G., Horby, P.W., Cao, B., Wang, C., 2020c. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 395, 1569–1578.

Wilcken, T., Rijik, R.D., 1997. Glucocorticoids and immune function: unknown dimensions and new frontiers. Immunol. Today 18, 418–424.

Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Zhou, Y., Zheng, X., Yang, Y., Li, X., Zhang, X., Pan, A., Wei, H., 2020a. Effective treatment of severe COVID-19 patients with tocilizumab. Proc. Natl. Acad. Sci. U. S. A. 117, 10970–10975.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., Wang, F.-S., 2020b. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine 8, 420–422.

Yang, Chunxiao, Li, Shijun, Shi, Shaojun, Liu, Yani, Zhou, Jiali, Zhang, Yu, Shi, Chen, 2020. Rational drug use and pharmaceutical care strategies under COVID-19 epidemic. Chin. J. Hosp. Pharm. 1–7 (in Chinese). http://kns.cnki.net/kcms/detail/1/2.1204.R.20200317.0934.002.html.

Ye, X.T., Luo, Y.L., Xia, S.C., Sun, Q.F., Ding, J.G., Zhou, X., Chen, W., Wang, X.F., Zhang, W.W., Du, W.J., Ruan, Z.W., Hong, L., 2020. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. Eur. Rev. Med. Pharmacol. Sci. 24, 3390–3396.

Yin, W., Mao, C., Luan, X., Shen, D.D., Shen, Q., Su, H., Wang, X., Zhou, F., Zhao, W., Gao, M., Chang, S., Xie, Y.C., Tian, G., Jiang, H.W., Tao, S.C., Shen, J., Jiang, Y., Li, H., Xu, Y., Zhang, Y., Xu, H.E., 2020. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. Science. https://doi.org/10.1126/science.abc1560.

Yuki, K., Pujol, E., Koutsogiannaki, S., 2020. COVID-19 pathophysiology: a review. Clin. Immunol. 215, 108427–108427.

Yun, Ling, Xu, Shuibao, Lin, Yi, Xiao, T., Zhu, Zhaoqin, Dai, FaHui, Fan, Wu, Song, Zhigang, Huang, Wei, Chen, Jun, Hu, Bijie, Wang, Sheng, Mao, Enqiang, Zhu, Lei, Zhang, Wenhong, Hongzhou, L., 2020. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin. Med. J. 133, 1039–1043.

Zhang, Zehua, Wang, Qiao, Zhao, Z., 2020. Application, evaluation and pharmaceutical care of ribavirin in the treatment of viral diseases. Chin. J. Hosp. Pharm. 40, 721–725 (in Chinese).

Zhang, C., Wu, Z., Li, J.W., Zhao, H., Wang, G.Q., 2020a. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int. J. Antimicrob. Agents 55, 105954. https://doi.org/10.1016/j.ijantimicag.2020.105954.

Zhang, L., Fang, R., Xue, X., Bao, Y., Xie, S., Dai, Y., Zheng, Y., Fu, Q., Hu, Z., Yi, Y., 2020b. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. Euro. J. Med. Pharmacol. 2020. https://doi.org/10.1016/j.ejmed.2020.105954.

Zhou, H., Liu, L.P., Fang, M., Li, Y.M., Zheng, Y.W., 2020. A potential ex vivo infection model of human induced pluripotent stem cell-3D organoids beyond coronavirus disease 2019. Histol. Histopathol. 10975.

Zhu, Z., Lu, X., Xu, T., Chen, C., Yang, G., Zha, T., Lu, J., Xue, Y., 2020. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J. Infect. 81, e21–e22. https://doi.org/10.1016/j.jinf.2020.03.060.

Zumla, A., Hui, D.S., Azar, E., Memish, Z.A., Maereur, M., 2020. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. Lancet 395, e35–e36.