proceedings

MDPI

Type of the Paper (Proceedings, Abstract, Extended Abstract, Editorial, etc.)

Antiviral Therapies against Corona Virus – In the new era of COVID-19 pandemic †

Dr. Darshit Ram[1]*

[1] Assistant Professor, Noble Pharmacy College, Junagadh, Gujarat, India, 362310; dramahir@gmail.com
* Correspondence: dramahir@gmail.com; Tel.: +91-898-000-5862
† The 1st International Electronic Conference on Antibiotics—The Equal Power of Antibiotics And Antimicrobial Resistance, 08/05/2021 - 17/05/2021

Abstract: Today the entire world is suffering from coronavirus (COVID-19) disease, with regards to the treatment of this many therapies used, amongst them antiviral therapy is on the top of the list. Many healthcare professionals and pharmaceutical companies focusing their path on the effectiveness of antiviral treatment conducted so many clinical trials of antiviral therapy. The effectiveness of antiviral drugs against coronavirus is still controversial. In the treatment of coronavirus, various antiviral drugs like remdesivir, HCQ, CQ, LPV/r, IFN, camostat mesylate, favipiravir, nitazoxanide, ribavirin, etc used and results of those drugs are analyzed based on their clinical reports. In present review mention various findings and the latest progress in antiviral therapy, to support ongoing numbers of clinical studies for better management against virus. Also, include detailed analysis of antiviral therapy results of various clinical studies with core discussion on the efficacy of antiviral treatments. In the treatment of coronavirus, it is necessary to summarize various clinical studies cover antiviral therapy to ensure the efficacy and safety of drugs or treatment for the betterment of making healthy mankind.

Keywords: coronavirus; COVID-19; antiviral; clinical

1. Introduction

Coronavirus disease 2019 (COVID-19) has spread all over the world and become a global pandemic (Velavan and Meyer, 2020; Zhu et al., 2020a). According to data from the World Health Organization, as of June 16, 2020, 7, 941, 791 cases have been diagnosed with COVID-19 globally, of which 434, 796 died (Organization, 2020). The estimated fatality of COVID-19 is 6.9%. Compared to severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), COVID-19 appears to be relatively mild with lower mortality, but more contagious.

The clinical manifestations of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) range from mild nonspecific symptoms to severe pneumonia and impaired organ function. Most patients present with fever, cough, and shortness of breath (Wang et al., 2020a). Some patients with COVID-19 presented with diarrhea (Zhang et al., 2020). Furthermore, many patients may be asymptomatic (Guan et al., 2020). Elderly COVID-19 patients and patients with comorbidities, such as hypertension, diabetes, and other diseases, are more likely to develop into severe conditions and have higher mortality rates (CDC, 2020; Lippi et al., 2020). Severe SARS-CoV-2 infection can rapidly develop into organ dysfunction, such as acute kidney injury, shock, and acute heart injury, which eventually causes death (Wang et al., 2020a).

Citation: Lastname, F.; Lastname, F.; Lastname, F. Title. *Proceedings* **2021**, *68*, x. https://doi.org/10.3390/xxxxx

Published: date:

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus (Zhu et al., 2020a). Similar to SARS-CoV, SARS-CoV-2 targets the cell via the combination of viral structural spike protein and the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell (Hoffmann et al., 2020a). ACE2 is abundantly distributed in the lung and small intestine epithelial cells, which suggests a possible entry route for SARS-CoV-2 (Hamming et al., 2004). Another protease on the host cell membrane, TMPRSS2, can promote cell entry through the spike protein (Hoffmann et al., 2020a). The SARS-CoV-2 genome encodes nonstructural proteins for viral replication, such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase (RdRp) (Li and De Clercq, 2020). These four nonstructural proteins play key roles in the viral life cycle, and together with the spike protein are considered as potential pharmacological targets of anti-SARS-CoV-2 therapy (Zumla et al., 2016). The life cycle of SARS-CoV-2 from attachment to reproduction and the therapeutic targets of antiviral drugs are shown in Fig. 1 and Table 1. The mechanisms of anti-SARS-CoV-2 therapy include acting on the genetic material of the virus to prevent the synthesis of viral RNA, inhibiting virus replication by acting on key enzymes of SARS-CoV-2, blocking the binding of SARS-CoV-2 to human cell receptors, or inhibiting the self-assembly process of SARS-CoV-2 via acting on some structural proteins (Wu et al., 2020b). With the development of this pandemic, the number of clinical studies on antiviral therapy, including remdesivir, chloroquine (CQ) and hydroxychloroquine (HCQ), lopinavir/ritonavir (LPV/r), ribavirin, arbidol, interferon (IFN), favipiravir, oseltamivir, nitazoxanide, nelfinavir, and camostat mesylate, has been increasing. In this review, the recent progress and findings on antiviral therapy are summarized, aiming to provide clinical support for the management of COVID-19.

2. Antiviral therapy

2.1. Preclinical screening of anti-SARS-CoV-2 drugs

In the past fight against the coronavirus, scientists have proposed three strategies for developing new drugs (Zumla et al., 2016). The first strategy is to test the role of existing broad-spectrum antiviral drugs in the treatment of coronavirus pneumonia, such as interferon and ribavirin (Chan et al., 2013). The advantage of these therapies is that their metabolic characteristics, dosages used, potential efficacy and side effects are clear, as they have been approved for the treatment of other viral infections. But the disadvantage is that these therapies are too broad-spectrum to kill the coronavirus in a targeted manner, so their side effects should not be underestimated. The second strategy is to develop new targeted drugs directly based on the different genome information and pathological characteristics of coronavirus. New discovered drugs will show better antivirus effects theoretically, but the development of new drugs may take huge time and economic costs. The third strategy is to use existing molecular databases to screen for molecules that may have therapeutic effects on the coronavirus (Dyall et al., 2014). Virtual screening makes this strategy possible, and through this strategy, new functions of many drugs can be discovered, for example, the anti-HIV drugs lopinavir/ritonavir (Baldelli et al., 2020), various antiviral drugs with targets mentioned in table 1.

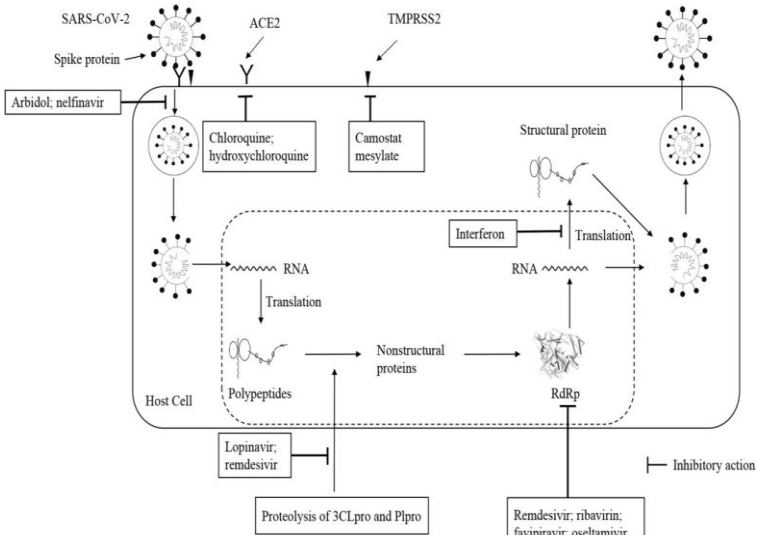

Fig. 1. Schematic diagram represent replication and synthesis of SARS-CoV-2 in the host cell with targets of antiviral drugs.

Table 1: Antiviral drugs with targets

Sr. no.	Drugs	Mechanism	Targets
1	Interferon	Decompose viral mRNA, inhibit synthesis of viral polypeptide chains, and stop replication.	Antiviral protein
2	Chloroquine, hydroXychloro-quine.	Viral receptor protein on the host cells which binds to viral S protein	ACE2
3	Camostat mesy-late	Host type 2 transmembrane serine protease, promotes cell entry through the S protein	TMPRSS2
4	Arbidol, nelfina-vir	A viral surface protein for binding host cell receptor ACE2	Spike protein
5	Remdesivir, riba-virin, favipiravir, oseltamivir	RNA-dependent RNA polymerase for replicating co-ronavirus genome	RNA-dependent RNA polyme-rase
6	Remdesivir	Protease cleaves multiple proteins to produce proteins (non- structural)	Papain-like protease
7	Lopinavir	Protease cleaves multiple proteins to produce proteins (non- structural)	3-chymotrypsin- like protease

2.2. Remdesivir

Remdesivir is a phosphoramidate prodrug of 1′ -cyano-substituted adenosine nucleotide analogs, which can be integrated into the nascent viral RNA chain and inhibit viral RNA synthesis via delaying chain termination (Tchesnokov et al., 2019). Remdesivir has broad-spectrum antiviral activity against a variety of viruses, including SRAS-CoV and MERS-CoV (Sheahan et al., 2017). Study in vitro showed that remdesivir can effectively control SARS-CoV-2 infection (Wang et al., 2020b). Moreover, remdesivir significantly improved the lung function of mice infected with SRAS-CoV-2 (Pruijssers et al., 2020). A similar therapeutic effect was observed in the rhesus monkey model infected with SARS-CoV-2 (Williamson et al., 2020). Remdesivir was first applied compassionately to

COVID-19 patients in the United States (Team, 2020). Clinical improvement was observed in patients who were hospitalized for severe COVID-19 and received compassionate. These early reports were only retrospective descriptive studies, which are not sufficient to support the clinical use of remdesivir, but have aroused the interest of researchers. A terminated clinical trial (NCT04257656) suggests that remdesivir usage cannot reduce the time to clinical improvement (Wang et al., 2020c). Patients who received remdesivir within 10 days after onset achieved clinical improvement earlier than patients who received placebo, although the difference was not statistically significant (Wang et al., 2020c). There was no difference in mortality between remdesivir recipients and placebo recipients (Wang et al., 2020c). However, remdesivir treatment reduced the time of ventilator application (Wang et al., 2020c). Previous reports have suggested that the survival rate of patients using a ventilator is notably lower than that of patients who do not use it (Grasselli et al., 2020).

Table 2: Clinical studies of remdesivir for COVID-19

Reference	Study	Finding	Adverse effects	Prognosis	Recovery time
Grein et al.	Drug was administered to 61 confirmed patients; 200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days.	53 cases were available for analysis. During the 18-day median follow-up, 36 patients (68%) had improved oxygen support levels. 25 patients (47%) were discharged and 7 patients (13%) died. Among patients receiving invasive ventilation, the mortality rate was 18% (6/34), and 5% of patients not receiving invasive ventilation (1/19)	32 patients (60%) reported adverse events during follow-up. The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension.	Improved	No report
Wang et al.	A randomized, double-blind, placebo- controlled, multicentre trial; 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo)	Remdesivir use was not associated with a difference in time to clinical improvement (HR 1.23 [95% CI 0.87–1.75]). Although not statistically-significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (HR 1.52[0.95–2.43]).	The most common adverse events in the remdesivir group were constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin	No improvement	Improved

2.3. Chloroquine and hydroxychloroquine

CQ and HCQ have closely related chemical structures and are used in the prevention and treatment of malaria and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus (Ben-Zvi et al., 2012; Zhou et al., 2020). CQ interferes with the virus life cycle, inhibiting the virus at different stages (entry, uncoating, assembly, and release) (Romanelli et al., 2004; Savarino et al., 2003, 2006; Yan et al., 2013). CQ and HCQ can also effectively control the life activities of viruses by interfering with ACE2 glycosylation, increasing endosomal pH, and preventing degradation of lysosomal proteins (Hashem et al., 2020; Zhou et al., 2020). And CQ was reported to inhibit SARS-CoV-2 infection effectively in vitro (Wang et al., 2020b). Owing to the antiviral effects of CQ and HCQ mentioned above, they have garnered considerable attention for their potential to treat COVID- 19 (Zhou et al., 2020). An early clinical study in China reported that clinical improvement was observed in more than 100 COVID-19 cases with CQ treatment, manifested in improving radiological performance, enhancing virus clearance, and shortening the

clinical course (Gao et al., 2020). However, the summary report did not publish data supporting these findings, provide clinical information including the severity an prognosis of the disease, or provide statistical analysis (Gao et al., 2020) study results and finding shows in table 3

Table 3: Clinical studies of *Chloroquine and hydroxychloroquine* for COVID-19

Reference	Study	Finding	Adverse effects	Prognosis	Recovery time
Huang et al.	A randomized controlled trial; 22 patients were randomly divided into CQ group (CQ 500 mg for 10 days) and LPV/r group (LPV/r 400 mg for 10 days)	Compared with LPV/r, CQ can more effectively shorten the time of virus clearance, accelerate the improvement of lung function, and recover and di charge earlier	Vomiting, abdominal pain, nausea, diarrhea, rash or itchy, cough, and shortness of breath	Improved	Improved
Rosenberg et al.	Retrospective multicenter cohort study; 1438 confirmed patients were divided into four groups, receipt of both HCQ and azithromycin, HCQ alone, azithromycin alone, or neither.	Compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving HCQ + azithromycin [HR, 1.35 (0.76–2.40)], HCQ alone [HR, 1.08 (0.63–1.85)], or azithromycin alone [HR, 0.56 (0.26–1.21)].	Cardiac arrest; abnormal electrocardiogram findings	No Improvement	No Improvement

2.4. Lopinavir/ritonavir

Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor approved by FDA. Lopinavir is mainly eliminated in the intestine and liver through CYP3A4 (the main enzyme involved in the metabolism of most protease inhibitors) (Kappelhoff et al., 2004). Ritonavir is an effective CYP3A4 inhibitor, which forms the basis for the enhancement of lopinavir administered at the same time (Hsu et al., 1998). Ritonavir can increase the plasma concentration of lopinavir by improving its bioavailability or increasing its elimination half-life in plasma (Hill et al., 2009). Therefore, lopinavir is recommended to be used in combination with ritonavir (Hammer et al., 2008). Early reports had different opinions on LPV/r for COVID-19 treatment. Ye et al. Reported that compared with the control group, LPV/r can effectively reduce body temperature and restore normal physiological function, with no obvious toxicity and side effects (Ye et al., 2020). However, another study showed that LPV/r did not promote the negative conversion or clinical improvement of COVID-19 patients (Wen et al., 2020). A recent randomized, controlled, open-label trial showed that the time to clinical improvement, 28-day mortality rates, and virus negative conversion of patients with LPV/r treatment was not different from that with the standard treatment (Cao et al., 2020). This study suggested that LPV/r treatment cannot improve the clinical condition and prognosis of COVID-19 (Table 4).

Table 4: Clinical Studies of LPV/r, arbidol, IFN, ribavirin and FPV for COVID-19

Reference	Study	Drugs	Results
Ye et al.	A retrospective singlecenter cohort study; 47 confirmed patients were divided into the test group and the control group according	LPV/r	Compared with the treatment of pneumoniaassociated adjuvant drugs alone, the combination treatment with LPV/r and adjuvant drugs has a more evi-

	to whether they had been treated with LPV/r or not during hospitalization.		dent therapeutic effect in lowering the body temperature and restoring normal physiological mechanisms with no evident toxic and side effects.
Yuan et al.	A retrospective singlecenter study; 94 discharged patients with COVID-19 infection	IFN-α, LPV/r, ribavirin	Therapeutic regimens of IFN-α + LPV/r and IFN-α + LPV/r + ribavirin might be beneficial for treatment of COVID-19.

2.5. Ribavirin

Ribavirin is usually used to treat virus infection like hepatitis C virus via inhibition of the replication viruses (Crotty et al., 2002). Ribavirin can also enhance the antiviral response of the immune system to indirectly exert antiviral properties (Hultgren et al., 1998). Its activity against other coronaviruses showed its potential in treating COVID-19 (Ferron et al., 2018). A retrospective study suggested that treatment with IFN-α + LPV/r + ribavirin might be beneficial for COVID-19 patients (Yuan et al., 2020). A recently terminated clinical trial (NCT04276688) reported that the group treated with combined IFN-1b, LPV/r, and ribavirin had a significantly shorter time to negative conversion than the control group treated with LPV/r (Hung et al., 2020).

2.6. Arbidol

Arbidol, also known as umifenovir, is another antiviral agent that exerts antiviral effect by inhibiting spike protein/ACE2 binding and inhibiting viral envelope fusion (Blaising et al., 2014; Kadam and Wilson, 2017). Early studies reported that arbidol treatment showed a tendency to improve the discharge rate and decrease the mortality rate of COVID-19 patients (Wang et al., 2020d; Wang et al., 2020e). But they cannot support the effectiveness of arbidol. Recently, a retrospective study showed that arbidol administration may be superior to LPV/r in COVID-19 treatment (Zhu et al., 2020b). Another retrospective study suggested that combination therapy with LPV/r and arbidol may be more helpful (Deng et al., 2020). In addition, arbidol/IFN-2b therapy was suggested to be an effective method to improve COVID-19 pneumonia in mild patients, although it does not accelerate virus clearance (Xu et al., 2020).

2.7. Interferon

Interferons are cytokines with spectral antiviral properties (de Weerd et al., 2007). Early retrospective studies found that IFN-α + LPV/r + ribavirin might be beneficial for the treatment of COVID-19 (Yuan et al., 2020). A recent clinical trial reported that COVID-19 patients receiving treatment of combined IFN-1b, LPV/r, and ribavirin had a shorter time to clinical improvement and negative conversion than patients with LPV/r treatment alone (Hung et al., 2020).

2.8. Favipiravir

Favipiravir (FPV), is an antiviral compound that selectively and potently inhibits the RdRP of influenza and many other RNA viruses (Furuta et al., 2013). Clinical data to support the use of FPV for COVID-19 are limited. In an open-label controlled study, enrolled patients were divided into the FPV arm and LPV/r arm. A short time to viral clearance and more clinical improvement were achieved in FPV arm versus the LPV/r arm (Cai et al., 2020).

3. Discussion

COVID-19 has become a huge global health threat, and hundreds of related clinical studies and drug experiments have been reported. Reviewing the investigation processes of anti-SARS-CoV-2 drugs, we found that most of the drugs currently in use are drugs that have proven to be effective or have potential therapeutic value in other viral infections such as SARS and MERS. On the one hand, SARS-CoV and SARSCoV- 2 have homology and have similar structures and life

activities. Antiviral drugs that are effective against SARS-CoV may be the most potential drugs for the treatment of COVID-19, such as arbidol and nelfinavir that inhibit the combination of spike protein and the ACE2 receptor. On the other hand, some broad-spectrum antiviral drugs are also worthy of attention, such as remdesivir and IFN. And some drugs which have been approved to treat other viral infections have inhibitory effects on the non-structural proteins of SARS-CoV-2, such as 3-chymotrypsin- like protease, papain-like protease, helicase, and RdRp. Reseachers reconsidered them for the treatment of COVID-19, such as LPV and Ribavirin. Although no effective drugs and vaccines have been found for COVID-19, some clinical studies have provided a reference for the clinical treatment of patients, which helps patients recover quickly, such as remdesivir (Beigel et al., 2020). A small number of antiviral treatments have been proven effective in rigorous clinical trials, such as the triple combination of IFN-1b, LPV/r, and ribavirin (Hung et al., 2020). There are also some controversies about the efficacy of some drugs, such as CQ and HCQ, as treatment for COVID-19 (Huang et al., 2020a; Rosenberg et al., 2020). More clinical researches are needed to further explore the effectiveness and safety of antiviral treatments for COVID-19. Recalling the current reports related to antiviral treatments forCOVID-19, several drug studies have reported controversial conclusions, such as remdesivir, CQ, and arbidol. The research on CQ and HCQ suffers from the same problems (Huang et al., 2020a; Tang et al., 2020). At the same time, we noticed problems in the design of some studies. For example, in a retrospective study on arbidol (Zhu et al., 2020b), patients were divided into the arbidol and control groups based only on drug history, and there was no good exclusion. It is suggested that the overall methodological quality of COVID-19 research is very low (Alexander et al., 2020). For example, we examined the results of the HCQ clinical trial, and results showed that the quality of the test was very low (Alexander et al., 2020). In another article, Dr. West reported that low-quality papers related to COVID-19 have become a reference for government decision-makers (London and Kimmelman, 2020). Dr. West urged researchers around the world not to use the urgency of the current COVID-19 outbreak as a reason to lower their research standards in virus research and vaccine development (London and Kimmelman, 2020). Clinical decision-makers must obtain evidence that is reliable and of the highest quality. Defective methods and sub-optimal reports of research results may lead to biased estimates of effectiveness. This may result in treatment decisions with biased estimates that are not optimal and may even harm the patient.

4. Conclusion

Remdesivir is currently the most potential antiviral drug for the treatment of COVID-19. Triple combination of IFN-1b, LPV/r, and ribavirin was confirmed to be more effective. CQ and HCQ are not recommended for the treatment of COVID-19. The efficacy and safety of other antiviral treatments still have controversy and require more highquality clinical trials.

Acknowledgments

We are grateful for the contributions of health care workers and researchers worldwide in the fight against COVID-19.

References

Alexander et al 2020. COVID-19 coronavirus research has overall low methodological quality thus far: case in point for CQ/HCQ. J. Clin. Epidemiol. S0895-4356(0820) 30371-30371.

Baldelli, S. et al, 2020. Lopinavir/ ritonavir in COVID-19 patients: maybe yes, but at what dose? J. Antimicrob. Chemother. 75, 2704–2706.

Ben-Zviet al 2012. HCQ: from malaria to autoimmunity. Clin. Rev. Allergy Immunol. 42, 145–153.

Blaising, J., et al., 2014. Arbidol as a broad-spectrum antiviral: an update. Antivir. Res. 107, 84–94.

Cai, Q., et al 2020. EXperimental Treatment with Favipiravir for COVID-19: an Open-Label Control Study. Engineering (Beijing. https://doi.org/10.1016/j.eng.2020.1003.1007.

Cao, B., et al., 2020. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N. Engl. J. Med. 382, 1787–1799.

CDC, 2020. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua liu Xing bing xue za zhi Zhonghua liuXingbingxue zazhi 41, 145–151.

Chan, J.F., et al, 2013. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J. Infect. 67, 606–616. Crotty, S., Cameron, C., Andino, R., 2002. Ribavirin's antiviral mechanism of action: lethal mutagenesis? J. Mol. Med. (Berl.) 80, 86–95.

De Weerd, N.A., et al., 2007. Type I interferon receptors: biochemistry and biological functions. J. Biol. Chem. 282, 20053–20057.

Ferron, F., et al L., molecular basis of mismatch correction and ribavirin excision from coronavirus RNA. Proc. Natl. Acad. Sci. U. S. A. 115, E162–e171.

Furuta, Y., et al, 2013. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antivir. Res. 100, 446–454.

Gao, J., Tian, Z., Yang, X., 2020. Breakthrough: CQ phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. BioScience Trends 14, 72–73.

Grein j., et al, ., 2020. Compassionate use of remdesivir for patients with severe covid-19. N. Engl. J. Med.

Hammer, S.M., et al 2008. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. Jama 300, 555–570.

Hill, A., van der Lugt, J., Sawyer, W., Boffito, M., 2009. How much ritonavir is needed to boost protease inhibitors? Systematic review of 17 dose-ranging pharmacokinetic trials. AIDS 23, 2237–2245.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., Müller, M.A., Drosten, C., Po¨hlmann, S., 2020a. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280 e278.

Hsu, A., Granneman, G.R., Bertz, R.J., 1998. Ritonavir. Clin. Pharmacokinet. 35, 275–291.

Huang, M., et al, 2020b. Treating COVID-19 with CQ. J. Mol. Cell Biol. 12, 322–325.

Hung et al. Triple combination of interferon beta-1b, lopinavir- ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID- 19: an open-label, randomised, phase 2 trial. Lancet 31042–31044. London, England), S0140-6736(0120.

Kadam, R.U., Wilson, I.A., 2017. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc. Natl. Acad. Sci. Unit. States Am. 114, 206–214.

Kappelhoff, B.S., et al 2004. Practical guidelines to interpret plasma concentrations of antiretroviral drugs. Clin. Pharmacokinet. 43, 845–853.

Li, G., De Clercq, E., 2020. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat. Rev. Drug Discov. 19, 149–150.

Lippi, G., et al., 2020. Hypertension in patients with coronavirus disease 2019 (COVID-19): a pooled analysis. Pol. Arch. Intern. Med. 130, 304–309.

London, A.J., Kimmelman, J., 2020. Against pandemic research exceptionalism. Science 368, 476.

Organization, W.H., 2020. Coronavirus Disease (COVID-19) Situation Report – 148.

Pruijssers, A.J., et al, 2020. Remdesivir inhibits SARS- CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. Cell Rep. 32, 107940.

Romanelli, F., Smith, K.M., Hoven, A.D., 2004. CQ and HCQ as inhibitors of human immunodeficiency virus (HIV-1) activity. Curr. Pharmaceut. Des. 10, 2643–2648.

Rosenberg, E.S., et al 2020. Association of treatment with HCQ or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. J. Am. Med. Assoc.

Savarino, A., Boelaert, J.R., Cassone, A., Majori, G., Cauda, R., 2003. Effects of CQ on viral infections: an old drug against today's diseases? Lancet Infect. Dis. 3, 722–727.

Savarino, A., Di Trani, L., Donatelli, I., Cauda, R., Cassone, A., 2006. New insights into the antiviral effects of CQ. Lancet Infect. Dis. 6, 67–69.

Tang, W., et al, 2020. HCQ in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ (Clinical research ed.) 369 m1849-m1849.

Tchesnokov, E.P., et al., 2019. Mechanism of inhibition of ebola virus RNA-dependent RNA polymerase by remdesivir. Viruses 11, 326. Team, C.-I., 2020. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nat. Med.

Velavan, T.P., Meyer, C.G., 2020. The COVID-19 epidemic. Trop. Med. Int. Health 25, 278–280.

Wang, D., et al, 2020a. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. Jama 323, 1061–1069.

Wang, M., et al 2020b. Remdesivir and CQ effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 30, 269–271.

Wang, Y., et al 2020c. Remdesivir in adults with severe COVID-19: a randomised, double- blind, placebo-controlled, multicentre trial. Lancet 395, 1569–1578.

Wang, Z., et al 2020d. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends 14,64–68.

Wang, Z., et al, 2020e. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America ciaa272.

Wen, C.Y., et al, 2020. [Real-world efficacy and safety of lopinavir/ritonavir and arbidol in treating with COVID-19 : an observational cohort study]. Zhonghua Nei Ke Za Zhi 59, E012.

Williamson, B.N., et al, 2020. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 585, 273–276.

Wu, C., et al, 2020b. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm. Sin. B 10, 766–788.

Yan, Y., et al, 2013. Anti-malaria drug CQ is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res. 23, 300–302.

Ye, X.T., et al, 2020. Clinical efficacy of lopinavir/ ritonavir in the treatment of Coronavirus disease 2019. Eur. Rev. Med. Pharmacol. Sci. 24, 3390–3396.

Yuan, J., et al, 2020. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflamm. Res.69, 599–606.

Zhang, J.J., et al, 2020. Clinical Characteristics of 140 Patients Infected with SARS-CoV-2 in Wuhan, China. Allergy.

Zhou, D., Dai, S.M., Tong, Q., 2020. COVID-19: a recommendation to examine the effect of HCQ in preventing infection and progression. J. Antimicrob. Chemother.

Zhu, N., et al 2020a. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733.

Zhu, Z., et al , 2020b. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J. Infect. 30188. S0163-4453(0120), 30182.

Zumla, A., et al 2016. Coronaviruses - drug discovery and therapeutic options. Nat. Rev. Drug Discov. 15, 327–347.