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Potential Drugs and Therapies to Treat COVID-19 and Other Related Coronaviruses

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Introduction

The novel coronavirus that has recently emerged in Wuhan, China with probable bat origin is part of the betacoronavirus family which is similar to previously seen zoonotic based out breaks in the early 2000's with SARS as well as in 2012 with MERS[1]. COVID-19 is the disease obtained from being infected by the novel SARS-CoV-2 virus, which enters through ACE2 (angiotensin-converting enzyme 2) cell receptors which is similar to SARS-CoV and MERS-CoV uses the DDP4 (dipeptidyl peptidase 4) cell receptor[1]. SARS-CoV-2 shares approximately 80% of its genomic identity with SARS-CoV[2]. Currently, there is a lot research being conducted to understand how SARS-CoV-2 infects humans to be able to develop drugs and therapy options to treat the virus as well as produce a vaccine to protect the global population from becoming infected. Understanding how SAR-CoV-2 enters cells will be able to provide important information for vaccine designs and drug targets[1]. There are four main categories for therapies to treat viral drugs depending on the activity, which are: preventing the viral RNA synthesis and replication, blocking the virus from binding to human cell receptors, restoring the host's innate immunity, and blocking host's specific receptors or enzymes[2]. This review discusses current nonspecific antiviral drugs that are being explored for potential treatments, potential biotherapeutic and small molecule drug candidates, use of convalescent plasma and monoclonal antibodies as other therapies, and explore possible drug targets and computational studies currently in progress to able to develop specific antiviral drugs and vaccines.

1. Repurposing of Generic Antiviral Drugs to Treat COVID-19

Since there are no drugs or treatments currently available to specifically treat COVID-19, there are clinical trials being conducted using general antiviral drugs until a vaccine or drugs can be developed. Additionally, since all current drug options are currently undergoing clinical trials, there is no proven effective treatment for COVID-19[3].

Lipinavir-Ritonavir

As reported in the New England Journal of Medicine by Cao et al., a trial was conducted of Lopinavir-Ritonavir in adults that are hospitalized with severe COVID-19[3]. A randomized, controlled, open-label trial was conducted with hospitalized adult patients with confirmed SARS-CoV-2 infections[3]. These patients were either given lopinavir-ritonavir twice a day for 14 days along with standard care, or standard care alone with the primary goal of clinical improvement[3]. The authors saw that there was no significant improvement with this drug combination

compared to standard care as the time for clinical improvement was only shortened by 1 day[3]. The observed gastrointestinal adverse events were more common in the lopinavir-ritonavir group, but they found more serious adverse events were more common in the standard-care group[3]. Lopinavir is an aspartate protease inhibitor used to treat HIV type 1 infections and was shown to have inhibitory activity against SARS-CoV[3]. Ritonavir, when combined with Lopinavir can increase its plasma half-life through the inhibition of cytochrome P450[3]. This drug combination was used in a study in 2004 to treat patients with SARS and that along with ribavirin, was able to reduce the risk of adverse clinical outcomes as well as reduce the viral load[3]. This drug combination has also shown similar results in vitro studies and animal models for MERS-CoV and suggest that lopinavir-ritonavir with ribavirin and interferon alpha could result in virologic clearance and survival[3]. This trial only consisted of a total of 199 patients between the two groups[3] and it would be interesting to see a similar trial conducted on a larger scale to see if this drug combination could be successful to treat SARS-CoV-2.

Chloroquine and Remdesivir

Multiple clinical trials are currently being conducted so show that Chloroquine can be used as an effective treatment for COVID-19. In the review article by Cortegiani et al, they report that there are 23 ongoing clinical trials in China that shows Chloroquine is effective in limiting the replication of SARS-CoV-2 in vitro[4]. Chloroquine is an immunomodulant drug traditionally used to treat malaria, but in vitro studies show that it is effective in reducing the viral replication in other infections such as SARS-CoV and MERS-CoV[4]. Although the World Health Organization (WHO) list Chloroquine as an essential medicine, the efficacy and safety of Chloroquine for the treatment of SARS-CoV-2 pneumonia remains unclear[4]. They report a narrative letter from a news briefing from the State Council of China that indicates Chloroquine phosphate has demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China[5], but evidence of this data has not been found[4]. They also reported that an expert consensus reported that a Chloroquine phosphate dose of 500 mg twice a day for ten days is recommended for patients with cases of SARS-CoV-2 pneumonia, but with several precautions to prevent possible side effects, but this report was based on in vitro evidence and is still unpublished[4]. Currently there are multiple ongoing trials in China to prove the efficacy of Chloroquine as a potential treatment of SARS-CoV-2, but no published data is available yet[4]. There will be more data released on this topic once more information from the clinical trials is released[4]. Early in vitro studies showed that Chloroquine was found to block COVID-19 infection at a low micromolar concentration with a half-maximal effective concentration of 1.13μm[5]. Multiple clinical trials are being conducted in China to show the efficacy of chloroquine and hydroxychloroquine for treatment of COVID-19 associated pneumonia in more than 100 pateints[5]. The results show that chloroquine phosphate is superior to control the treatment in inhibiting the exacerbation of pneumonia, improving lung imaging, promoting a virus-negative conversion and shortening the disease according to a news briefing form China[5]. Studies has shown that Chloroquine has potential for broad spectrum antiviral

activity by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-COV[5,6]. In a study by M. Wang et al, they show that besides antiviral activity, chloroquine also has immune-modulating activity, which could synergistically enhance its antiviral effect in vivo and is also distributed in the whole body including the lungs after oral adminiatration[6].

In a letter to the editor published in Cell Research by M. Wang et al., they stress the need to urgently identify effective antiviral agents for treating COVID-19 is needed and suggest the most efficient approach is to test existing antiviral drugs that are effective in treating related viral infections[6]. This novel viral infection falls under the β-Coronavirus family, which also includes SARS-CoV and MERS-CoV[6]. To treat these infections in the past, antiviral drugs such as ribavirin, interferon, lopinavir-ritonavir, and corticosteroids were used, but the efficacy of some drugs remains controversial[6]. The authors studied 5 FDA approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, and two broad spectrum antiviral drugs remdesivir and favipiravir in an in vitro study with a clinical isolate of SARS-COV-2[6]. The authors conducted standard assays to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates for the COVID-19 in Vero E6 cells[6]. They found that ribavirin, penciclovir, and favipiravir were required to reduce the viral infection[6]. They also found that Nafamostat, which is a potent inhibitor for MERS-CoV was inhibitive against COVID-19 infection[6]. Nitazoxanide, which is a commercial antiprotozoal agent with antiviral potential was able to inhibit COVID-19 as a low-micromolar concentration[6]. Two possible drug options, remdesivir and chloroquine were able to potently block virus infection at a low-micromolar concentration[6]. The authors suggest that remdesivir and chloroquine are effective to control COVID-19 infection in vitro and since there is previous data on the safety of the drugs in humans, it suggested that they be assessed in humans to treat COVID-19[6].

Remdesivir is a promising antiviral drug against a wide array of RNA virus infections in cultured cells, mice and nonhuman primate models[6] and is currently under clinical development for the treatment of Ebola[6]. This adenosine nucleoside analog acts as an RdRp (RNA-dependant RNA polyermase) inhibitor that targets the viral genome replication process[6,7]. The host will metabolize the drug into NTP which competes with ATP to incorporate into the nascent RNA strand[7]. Once the substitution occurs, the new strand will result in premature termination of RNA synthesis[6,7]. The benefit of remdesivir is that it will outpace the proofreading activity that many coronaviruses possess to be able to detect and remove other nucleoside analogs. This takes away the activity that makes the viruses resistant to many RNA based antiviral drugs[7]. Currently, there are multiple-site clinical trials in progress to treat SARS-CoV-2 in hospitalized adults using remdesivir that are a result of in vitro and in vivo studies on similar coronaviruses[7]. Studies have been done on SARS-CoV and MERS-CoV using human epithelial cell cultures and found that remdesivir had strong antiviral activity against MERS-CoV[7]. The use of remdesivir was first reported to treat COVID-19 in humans on the first infected patient in the US after developing

pneumonia and being hospitalized for more than 12 days[7]. Intravenous remdesivir was used on the seventh day and by the eighth day, his condition was improving, and no adverse effects related to remdesivir were reported[7]. There have been other reports of remdesivir being used on humans outside the clinical trials. As reported in the review by E. Amirian and J. Levy, a newspaper article reported that 17 passengers on the Diamond Princess cruise ship were treated with remdesivir for 10 days and the doctors felt the patients were less dependent on ventilators[7]. There are multiple clinical trials currently in progress in the US, Republic of Korea, and China, as well as a sponsored study by Gilead Sciences in which patients with different severities of COVID-19 receive the drug or placebos and to see how they improve overtime based a scale from death to no longer hospitalized[7].

Drug Combinations and Antibiotics for Treating COVID-19

Additionally, there are other reports of potential drug combination to treat SARS-CoV-2, but more information and testing will be needed to show the efficacy of these drug combinations. In an article by Gautret et al., they report the findings of a non-randomized clinical trial of hydroxychloroquine and azithromycin to treat COVID-19[8]. In this French study, patients with confirmed cases were treated with 600 mg of hydroxychloroquine daily and their viral loads tested daily by nasopharyngeal swabs and the addition of azithromycin was added to the treatment depending on the clinical presentation[8]. Day 6 was considered the end point of the study and looking at the presence or absence of the virus[8]. The negative control group consisted of untreated patients from another center or patients who refused the protocol[8]. The authors found that there was a significant reduction in viral carriage compared to the controls and the addition of azithromycin was significantly more efficient for virus elimination[8]. They found that 100% of the patients who received the drug combination were cleared after 6 days compared to 57.1% of patients treated with only hydroxychloroquine and 12.5% in the control group[8]. The authors report that there has been previous data to show that azithromycin is active against ZIKA and Ebola viruses as well as to prevent severe respiratory tract infections in patients suffering viral infections[8]. There were only 20 cases treated in this study with an additional 16 patients in the control group[8] and it would be interesting to see the results of this trial with a larger population. If these results are repeatable, this drug combination could be useful in the fight against COVID-19 as the added use of an antibiotic will also be able to fight possible superinfections[8].

In an article by Stebbing et al., they discuss the use of artificial intelligence to look at potential combinations of anti-inflammatory drugs with anti-viral drugs could be used to treat COVID-19[9]. The authors are suggesting that anti-inflammatory drugs that inhibit clathrin-mediated endocytosis could inhibit viral infections in cells[9]. They suggest that the potential drug targets are members of the numb-associated kinase (NAK) family, which includes AAK1 and GAK have been shown to inhibit viral infections in vitro[9]. They further suggest that this drug family along with potential anti-viral drugs such as lopinavir-ritonavir and remdesivir could be effective

to treat COVID-19 by reducing viral infectivity, viral replication, and aberrant host inflammatory response[9]. Since this study was based on data collected from artificial intelligence, it would be interesting to see results of cell studies and potential animal studies on these drug combinations to see if they work. Additionally, if this combination shows successful results from in vitro and animal studies, it would be interesting to see results in clinical studies in humans. Like most drug candidates and combinations of drugs currently being explored to treat COVID-19, the drugs being proposed are safe and approved for treatment of other diseases. Teicoplanin is a glycopeptide antibiotic that is typically used to treat gram-positive bacterial infections such as staphylococcal infections but has also shown to inhibit the first stage of MERS-CoV viral life cycle in human cells as well as being active against SARS-CoV in vitro[10]. It has already shown to be effective against Ebola, influenza, flavivirus, hepatitis C, HIV, and MERS-CoV and SARS-CoV viruses[10]. Teicoplanin is effective in coronaviruses by acting on the early stage of the viral life cycle by inhibiting the low-pH cleavage of the viral spike protein by cathepsin L in late endosomes and preventing the release of genomic viral RNA and the continuation of the replication cycle[10]. As this is shown to have promising results in related coronaviruses, there is a potential that it can have a similar effect on SARS-CoV-2.

2. Potential Biotherapeutics and Small Molecule Drug Candidates

Research into the spike proteins suggests that there is 89.8% sequence homology between SARS-CoV and SARS-CoV-2 in the S2 subunit of their spike proteins while their S1 subunits use hACE2 to infect human cells[11]. Additionally, the ACE2 binding affinity in the receptor binding domain in the S1 subunit of SARS-CoV-2 is much higher than SARS-CoV, which may contribute to the higher affinity and transmissibility of SARS-CoV-2[11]. Research by Xia et al. suggests that by conjugating a cholesterol molecule to an EK1 peptide, they were able to show that this lipopeptide, EK1C4 was able to exhibit a highly potent inhibitory activity against SARS-CoV-2 S-mediated membrane fusion and PsV infection[11]. The EK1 peptide was previously developed by the authors and is a pan-coronavirus inhibitor that targets the HR1 domain[11]. They also found that the EK1C4 peptide was effective against in vitro and in vivo infections for other live coronaviruses such as SARS-CoV-2, HCoV-OC43, and MERS-CoV which could suggest the development of a further inhibitor based therapeutic and prophylactics for other coronavirus based infections[11].

In a paper by Sheahan et al., they report that the ribonucleoside analog, β-D-N^4-hydroxycytidine had broad spectrum antiviral activity against SARS-CoV-2, MERS-CoV, and SARS-CoV[12]. β-D-N^4-hydroxycytidine is an orally bioavailable ribonucleoside analog that has broad spectrum antiviral activity against various RNA viruses such as influenza, ebola, CoV, and Venezuelan equine encephalitis[12]. The authors preformed antiviral assays in cells lines with MERS-CoV and SARS-CoV-2 to see if β-D-N^4-hydroxycytidine will block replication of the virus[12]. First, they tested the antiviral activity for β-D-N^4-hydroxycytidine against MERS-CoV in the human

epithelial cell line Calu-3 2B4, by testing the virus replication after the cell cultures were exposed to the virus and then exposed to a dose range of drugs for 48 hours[12]. They found β-D-N^4-hydroxycytidine had highly potent antiviral activity with an average half-maximum effective concentration of 0.15μM and did not observe any cytotoxicity in similarly treated uninfected cultures[12]. Then they performed antiviral assays of SARS-CoV-2 with African green monkey kidney cells and found that β-D-N^4-hydroxycytidine was highly potent as well with an average half-maximum effective concentration of 0.3μM[12]. Then they determined the antiviral activity of β-D-N^4-hydroxycytidine on SARS-CoV-2 in human epithelial cell line Calu-3 2B4 cells through the measurement of infectious virus production and viral genomes[12]. They observed a dose-dependent reduction in virus titers and an average half-maximum effective concentration of 0.08μM[12]. They tested the antiviral activity of β-D-N^4-hydroxycytidine against both viruses in primary airway epithelial cell cultures and observed a does dependent reduction of in SARS-CoV-2 infectious virus production and a substantially reduced virus production in MERS-CoV[12]. The authors mention that their study lacks in vivo efficacy testing with SARS-CoV-2 due to robust mouse models that recapitulate SARS-CoV-2 pathogenesis observed in humans does not exist since a noted spike glycoprotein and mouse ACE2 receptor are incompatible and suggest β-D-N^4-hydroxycytidine should be evaluated in primate models[12].

3. Computational and Binding Studies to Develop Drug Targets and Potential Drug Candidates

In addition to repurposing antiviral drugs, there on-going research into characterizing SARS-CoV-2, with the goal to develop specific antiviral drugs and possible vaccine candidates. There is not a lot data published for potential antiviral drugs or vaccines candidate at this time since this is still a relatively novel virus and we are still learning new information about the virus every day. There have been some articles published using docking studies and other computational techniques to probe potential therapeutic targets. Understanding the main binding targets of SARS-Cov-2 can help develop the next generation of targeted drugs and effective vaccines.

A research article by C. Wu et al. , used computational methods to analyze therapeutic targets for SARS-CoV-2 and potential drugs[13]. The goal of their study was to provide new lead compounds and targets for further in vitro and in vivo studies, as well as new insights into the drugs currently being used in clinical trials and discover potential new strategies for drug repurposing for SARS-CoV-2 infections[13]. The authors analyzed all the proteins encoded by SARS-CoV-2 genes and compared them with proteins from other coronaviruses and predicted their structures to build 19 structures by homology modeling[13]. They performed a target-based virtual ligand screening, where a total of 21 targets were screened against ZINC drug database and the author's own database of natural products[13]. The results of the screen showed that the important targets were 3-chymotrypsin-like protease (3CLpro), Spike, RNA-dependent RNA polymerase (RdRp), and papain like protease (PLpro) for the development of coronavirus drugs [13]. The

authors also screened a database of 78 commonly used anti-viral drugs including those on the market as well as undergoing clinical trials for SARS-CoV-2[13]. They were able to predict possible targets of these compounds and potential for drugs to act on certain targets[13]. Based on their targets, they were able to find multiple small molecules and natural products for each target that are approved for use in treating many other diseases[13]. Targeting spike proteins or other specific receptors on the host cell surface is valuable for developing therapeutic strategies to block coronaviruses from entering host cells[13]. The authors also looked at the binding interface of Spike-ACE2 complex and found that hesperidin was the only compound that was able to target the binding interface[13]. Additionally, the authors looked at 78 commonly used antiviral drugs and found that remdesivir seemed to be the best at binding to RdRp of SARS-CoV-2 as a possible treatment for COVID-19[13] as described earlier in this review. Another potential drug candidate is lopinavir and ritonavir and was found to have a poor effect on the treatment of SARS-CoV-2 pneumonia with toxic side effects, but the authors did not observe any potential binding sites to the major targets suggesting that this it may not be a suitable treatment for COVID-19[13]. Chloroquine phosphate has been showing positive outcomes in clinical trials to treat COVD-19, but there seems to be no clear target of action[13]. The docking studies predict that chloroquine may combine with Nsp3b and E-channel, but further experiments are needed to verify[13]. Other drugs such as arbidol which treats upper respiratory tract infections caused by influenza A and B, darunavir which is an HIV-1 protease inhibitor, favipiravir which is used to treat the flu, and many other possible drugs were explored and interacted with some of the important targets, but were not discussed further in this paper[13].

The S protein plays the most important roles in viral attachment, fusion, entry and serves as a target for the development of antibodies, entry inhibitors, and vacines[14]. The S protein mediates viral entry into host cells by binding to a host receptor and the receptor-binding domain (RBD) in the S1 subunit and fusing the viral and host membranes through the S2 subunit[14]. It is reported that the SARS-CoV-2 S protein binds the ACE2 receptors in the host cell, making it critical to define the RBD in SARS-CoV-2 S protein as the most possible target to develop virus attachment inhibitors, neutralizing antibodies, and vaccines[14]. In a study by W. Tai et al., they identified the RBD fragment in SARS-CoV-2 S protein to be able to use the region to develop a viral attachment inhibitor and vaccine[14]. They found that using a recombinant RBD protein will bind strongly to ACE2 receptors and blocked the entry of SARS-CoV-2 in hACE2- expressing cells[14]. This suggest that a SARS-CoV-2 RBD protein could be used as a viral attachment or entry inhibitor against SARS-CoV-2[14]. Further studies could be conducted to carry out the development of this protein for in vitro, and animal studies in the lab.

As reported in ACS NANO by Y. Han and P. Kral, they performed computation studies to develop ACE2 based peptide inhibitors of SARS-CoV-2[2]. The inhibitors were formed by two sequential self-supporting α-helices that were extracted from the protease domain of ACE2[2]. Molecular dynamics simulations show that the α-helical peptides maintain their secondary

structure and provide a highly specific and stable binding to SARS-CoV-2[2]. The $\alpha_{1,2}$-helices extracted from ACE2 are shown to support each other and maintain their bent shape which is important as it provides a conformational matching to the RBD of SARS-CoV-2 and fully covers the RBD surface was observed in theses computational studies[2]. The authors suggest that the binding affinity could be further enhanced by binding multiple peptides to surfaces of nanoparticles, dendrimers, and clusters, which could be turned into inhaled therapeutics preventing the virus activation in lungs[2]. Further studies could be conducted to carry out the development of these peptides for in vitro, and animal studies in the lab.

4. Treating COVID-19 by Antibodies and Immunotherapeutic Approaches

In addition to looking at potential drug options, there is an ongoing discussion about using monoclonal antibodies to treat COVID-19. Monoclonal antibodies represent a major class of biotherapeutics for passive immunotherapy to fight against viral infections[15]. Using passive immunotherapy can be used to reduce virus replication and decrease the severity of the illness[15]. These antibodies can be isolated from the blood of infected patients or manufactured in the lab[15]. In recent years, monoclonal antibodies have been developed for use against viruses and many are currently in clinical development[15]. Some potential specific therapeutic molecules could include peptidic fusion inhibitors, anti-SARS-CoV-2 neutralizing monoclonal antibodies, anti-ACE2 monoclonal antibodies, and protease inhibitors[15]. It is being suggested that targeting the RBD of the S1 subunit of the spike protein that interacts with the ACE2 receptor is a potentially effective therapeutic against SARS-COV-2 infection[15]. It has been reported that monoclonal antibodies targeting spike proteins in SARS-CoV and MERS-CoV showed promising results in vitro and in vivo that may be effective for SARS-CoV-2[15]. Using monoclonal antibody cocktails may provide more potent anti-virus activity and could be a more effective treatment since the combination of antibodies would neutralize a wide range of isolates including escaped mutants[15]. Although this is promising, one of the challenges is the time and cost for large scale production of monoclonal antibodies which outweighs the clinical application especially with emerging pathogens[15].

Another Immunotherapeutic approach being explored is the use of convalescent sera or plasma transfer to infected patients to help neutralize viruses and prevent further infection[15]. There is existing evidence that suggests treating viral infections such as influenza, SARS, MERS, and Ebola with convalescent plasma or hyper-immune immunoglobulin from patients that contain significant antibody titers can reduce the viral load and disease mortality[15]. A small study was conducted by K. Duan et al. on 10 patients that were hospitalized with COVID-19 and were treated with convalescent plasma (CP) from recently recovered donors that had neutralizing antibody titers above 1:640 in addition to receiving supportive care and antiviral agents[16]. They were able to find that the viral load was undetectable after transfusion in 7 patients who previously had viremia with no adverse effects observed[16]. Based on their preliminary results, CP

therapy was found to be easily accessible, promising, and a safe rescue options for patients with severe COVID-19[16]. The authors were able to show that one dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and improve clinical outcomes[16]. Besides the study have a small sample size, all the patients in the study received antiviral treatments as well as supportive care so it is not clear how these treatments worked together or if CP therapy alone is enough to treat COVID-19[16]. A similar study by B. Zhang et al. was also conducted with 4 patients with severe cases of COVID-19 and received CP therapy along with supportive care with similar results[17]. A clinical study should be conducted of CP alone to test the efficacy of this therapeutic approach as suggested by the authors from both paper[16,17]. Some key clinical challenges with this approach are the availability of sufficient donors, clinical conditions, viral kinetics, and hoist interactions of SARS-CoV-2 need to be explored before use as a possible therapeutic[15].

Drug Category	Therapy/Drug
preventing viral RNA synthesis and replication	β-D-N^4-hydroxycytidine Lipinavir-Ritonavir Chloroquine Remdesivir hydroxychloroquine and azithromycin anti-inflammatory drugs with anti-viral drugs Teicoplanin
blocking the virus from binding to human cell receptor	SARS-CoV-2 recombinatn RBD protein ACE2 based peptide inhibitor Hesperidin lipopeptide EK1C4
restoring the host's innate immunity	Vaccines Convalescent Plasma Monoclonal Antibodies
blocking the host's specific receptor or enzymes	Vaccines Monoclonal Antibodies

Table 1. Summary of Potential Drug Candidates to Treat COVID-19.

Conclusions

There are multiple articles that stress that there are no drugs or treatments specifically available to treat SARS-CoV-2 and there is no proven effective treatment since the virus has recently emerged in late 2019. Currently, there are multiple clinical trials in progress for repurposing potential generic antiviral drugs such as chloroquine, remdesivir, lopinavir-ritonavir, and other drugs to treat the symptoms for individuals who are currently infected. At this time, there is very little data to show that these antiviral drugs can effectively treat COVID-19, but this

is due to the fact that clinical trials are currently in progress and premature publication of results could lead to serious outcomes for future patients. From the data that was found, the clinical trials seemed to have small sample sizes and were specific to select regions. It would be important to see larger sample populations from different regions to be able to understand the outcome of the drugs on treating the virus. There are multiple factors that can affect the outcome of the disease and how these antiviral drugs might work including individual's location, severity of the infection, underlying conditions and other medications which means more than one drug will be important to fight this infection.

In addition to using these generic antiviral drugs, the use of convalescent plasma from recovered patients seems like this would help to improve the ability for infected individuals to generate an immune response to fight the disease which seems like best approach that has been reported to date. Since there are over a million cases globally to date, there should be more access to convalescent plasma from recovered patients to treat the virus. More research can be done to investigate this immunotherapeutic treatment to see if this is this is the best approach to fight the disease.

The research into the characterization of the structure and function of SARS-CoV-2 is still on going and there are computational studies in progress to determine potential targets for the development on specific antiviral drugs and vaccines. As COVID-19 has become a global pandemic with millions infected and thousands dying, there is a need to produce a vaccine to stop the spread of infection. This will take some time as development, testing, and trials are needed to make sure that potential vaccines are safe and will work effectively in humans as well as manufacturing on a large scale will be needed to protect the global population from this disease. Since SARS-CoV-2 has emerged within the past 5-6 months, it is still very early and there is still more research and knowledge to be acquired about the virus. Continuing to work to develop specific drugs and vaccines as well as the effectiveness of the general antiviral drugs on the virus is important, but it will still take a long time to accomplish these tasks.

References

(1) Ou, X.; Liu, Y.; Lei, X.; Li, P.; Mi, D.; Ren, L.; Guo, L.; Guo, R.; Chen, T.; Hu, J.; Xiang, Z.; Mu, Z.; Chen, X.; Chen, J.; Hu, K.; Jin, Q.; Wang, J.; Qian, Z. Characterization of Spike Glycoprotein of SARS-CoV-2 on Virus Entry and Its Immune Cross-Reactivity with SARS-CoV. Nature Communications 2020, 11 (1).

(2) Han, Y.; Kral, P. Computational Design of ACE2-Based Short Peptide Inhibitors of SARS-CoV-2. ACS Nano 2020.

(3) Cao, B.; Wang, Y.; Wen, D.; Liu, W.; Wang, J.; Fan, G.; Ruan, L.; Song, B.; Cai, Y.; Wei, M.; Li, X.; Xia, J.; et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. The New England Journal of Medicine 2020.

(4) Cortegiani, A.; Ingoglia, G.; Ippolito, M.; Giarratano, A.; Einav, S. A Systematic Review on the Efficacy and Safety of Chloroquine for the Treatment of COVID-19. Journal of Critical Care 2020.

(5) Gao, J.; Tian, Z.; Yang, X. Breakthrough: Chloroquine Phosphate Has Shown Apparent Efficacy in Treatment of COVID-19 Associated Pneumonia in Clinical Studies. BioScience Trends 2020, 14 (1), 72–73.

(6) Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G. Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus (2019-NCoV) in Vitro. Cell Research 2020, 30 (3), 269–271.

(7) Amirian, E. S.; Levy, J. K. Current Knowledge about the Antivirals Remdesivir (GS-5734) and GS-441524 as Therapeutic Options for Coronaviruses. One Health 2020, 9, 100128.

(8) Gautret, P.; Lagier, J. C.; Parola, P.; Hoang, V. T.; Medded, L.; Mailhe, M.; Doudier, B.; Courjon, J.; Giordanengo, V.; Vieira, V. E.; Dupont, H. T.; Honore, S.; Colson, P.; Chabriere, E.; Scola, B. L.; Rolain, J. M.; Brouqui, P.; Raoult, D. Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Preliminary Results of an Open-Label Non-Randomized Clinical Trial. 2020.

(9) Stebbing, J.; Phelan, A.; Griffin, I.; Tucker, C.; Oechsle, O.; Smith, D.; Richardson, P. COVID-19: Combining Antiviral and Anti-Inflammatory Treatments. The Lancet Infectious Diseases 2020, 20 (4), 400–402.

(10) Baron, S. A.; Devaux, C.; Colson, P.; Raoult, D.; Rolain, J.-M. Teicoplanin: an Alternative Drug for the Treatment of COVID-19? International Journal of Antimicrobial Agents 2020, 105944.

(11) Xia, S.; Liu, M.; Wang, C.; Xu, W.; Lan, Q.; Feng, S.; Qi, F.; Bao, L.; Du, L.; Liu, S.; Qin, C.; Sun, F.; Shi, Z.; Zhu, Y.; Jiang, S.; Lu, L. Inhibition of SARS-CoV-2 (Previously 2019-NCoV) Infection by a Highly Potent Pan-Coronavirus Fusion Inhibitor Targeting Its Spike Protein That Harbors a High Capacity to Mediate Membrane Fusion. Cell Research 2020, 30 (4), 343–355.

(12) Sheahan, T. P.; Sims, A. C.; Zhou, S.; Graham, R. L.; Pruijssers, A. J.; Agostini, M. L.; Leist, S. R.; Schäfer, A.; Dinnon, K. H.; Stevens, L. J.; Chappell, J. D.; Lu, X.; Hughes, T. M.; George, A. S.; Hill, C. S.; Montgomery, S. A.; Brown, A. J.; Bluemling, G. R.; Natchus, M. G.; Saindane, M.; Kolykhalov, A. A.; Painter, G.; Harcourt, J.; Tamin, A.; Thornburg, N. J.; Swanstrom, R.; Denison, M. R.; Baric, R. S. An Orally Bioavailable Broad-Spectrum Antiviral Inhibits SARS-CoV-2 in Human Airway Epithelial Cell Cultures and Multiple Coronaviruses in Mice. Science Translational Medicine 2020.

(13) Wu, C.; Liu, Y.; Yang, Y.; Zhang, P.; Zhong, W.; Wang, Y.; Wang, Q.; Xu, Y.; Li, M.; Li, X.; Zheng, M.; Chen, L.; Li, H. Analysis of Therapeutic Targets for SARS-CoV-2 and Discovery of Potential Drugs by Computational Methods. Acta Pharmaceutica Sinica B 2020.

(14) Tai, W.; He, L.; Zhang, X.; Pu, J.; Voronin, D.; Jiang, S.; Zhou, Y.; Du, L. Characterization of the Receptor-Binding Domain (RBD) of 2019 Novel Coronavirus: Implication for Development of RBD Protein as a Viral Attachment Inhibitor and Vaccine. Cellular & Molecular Immunology 2020.

(15) Shanmugaraj, B.; Siriwattananon, K.; Wangkanont, K.; Phoolcharoen, W. Perspectives on Monoclonal Antibody Therapy as Potential Therapeutic Intervention for Coronavirus Disease-19 (COVID-19). Asian Pacific Journal of Allergy and Immunology 2020.

(16) Duan, K.; liu, B.; Li, C.; Zhang, H.; Yu, T.; Qu, J.; Zhou, M.; Chen, L.; Meng, S.; Hu, Y.; et al. Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients. Proceedings of the National Academy of Sciences 2020.

(17) Zhang, B.; Liu, S.; Tan, T.; Huang, W.; Dong, Y.; Chen, L.; Chen, Q.; Zhang, L.; Zhong, Q.; Zhang, X.; Zou, Y.; Zhang, S. Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection. Chest 2020.