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REVIEW

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Current pharmacological modalities for management of novel coronavirus disease 2019 (COVID-19) and the rationale for their utilization: A review

Richard A. Giovane[1] | Shadi Rezai[2] | Ellen Cleland[3] | Cassandra E. Henderson[4]

[1]Department of Family Medicine, Regional Medical Center of Central Alabama, Greenville, Alabama, USA

[2]Department of OB/GYN, Valley Community Healthcare, North Hollywood, California, USA

[3]Department of Family Medicine, University of Alabama, Tuscaloosa, Alabama, USA

[4]Garden OB/GYN, Mercy Medical Center, New York, New York, USA

Correspondence
Richard A. Giovane, Regional Medical Center of Central Alabama, 29 L.V. Stabler Drive, Greenville, AL, 36037.
Email: richardgiovane357@gmail.com

Summary

SARS-CoV-2 has caused a pandemic which is putting strain on the health-care system and global economy. There is much pressure to develop both preventative and curative therapies for SARS-CoV-2 as there is no evidence to support therapies to improve outcomes in patients with SARS-CoV-2. Medications that inhibit certain steps of virus life cycle that are currently used to treat other illnesses such as Malaria, Ebola, HIV and Hepatitis C are being studied for use against SARS-CoV-2. To date, data is limited for medications that facilitate clinical improvement of COVID-19 infections.

KEYWORDS

2019-nCoV, acetazolamide, acute respiratory distress syndrome (ARDS), autoimmune, camostat mesylate, chloroquine, COVID-19, high altitude pulmonary edema (HAPE), hydroxychloroquine, Lopinavir/Ritonavir, novel coronavirus 2019, pandemic, Remdesivir, RNA-dependent RNA polymerase inhibitors, SARS coronavirus (SARS-CoV), SARS CoV-2, severe acute respiratory syndrome (SARS), Umifenovir

1 | BACKGROUND

Severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 which causes coronavirus disease 2019 or COVID-19 was initially identified in Wuhan, China during December 2019; has spread worldwide, causing a pandemic.[1] Although the amount of reported cases is uncertain due to the variable sensitivity of testing and reported symptoms, it is estimated that over 1 million cases and 60 000 deaths have occurred.[1] Symptoms of COVID-19 vary and include fever, fatigue, dry cough and myalgia. Severity of the illness ranges from asymptomatic to severe with a fatality rate of at least 2.3%.[1]

As this pandemic causes strain on global health-care, there has been an urgent need to establish standard therapies to improve outcomes. Moreover, there is no known effective prophylactic therapy against COVID-19 and so far, there are no medications that have undergone large clinical trials that demonstrate improved outcomes against SARS-CoV-2.[1] Currently, there are only recommendations against further spread through proper hand hygiene, respiratory hygiene, self-quarantine and person protective equipment [PPE] for health-care workers.[2] Vaccination using BCG against COVID-19 has been proposed, however human trials are still being conducted and limited data is available on their efficacy, safety and when they will be available to the general public.[3] Given the current pandemic of COVID-19, there has been proposed use of available medications to improve outcomes in patients with SARS-CoV-2. We present a review of proposed therapies for COVID-19, their mechanisms of action and their efficacy.

2 | DISCUSSIONS

Selecting a medication to reduce viral load and infection relies on current understanding of SARS-CoV-2 life cycle. SARS-CoV-2 is a non-segmented, enveloped, positive-sense RNA virus, belonging to the *Nidovirales* order.[4] Structurally, SARS-CoV-2 had 4 proteins of interest; the spike [S], membrane [M], envelope [E] and nucleocapsid [N] with the spike protein being used for the viral entry into host cells by attaching onto angiotensin-converting enzyme 2 [ACE2].[5,6] Once

bound, SARS-CoV-2 gains access to the cytosol of the host cell by cleavage of the S protein by TMPRRS2.[4,6] Within the cytosol, SARS-CoV-2 begins the synthesis of replicase and other nonstructural proteins. Once this is complete, it begins the synthesis of its structural proteins through the use of its own RNA-dependent RNA polymerase.[4,6] After assembly of the virus, it exits the cell and begins the process again. Although the exact pathogenesis of SARS-CoV-2 is poorly understood, one proponent of its pathogenesis is that it induces pro-inflammatory cytokines and chemokines such as IL-6, TNF α, IL-1B and GCSF which can lead to a cytokine storm and subsequent endothelial damage.[7]

Understanding the replication cycle of SARS-CoV-2 can help researchers hypothesize potential medications agents that prevent the viral entry, protein synthesis and replication cycle [Table 1].

Beginning with viral entry via the S-protein and ACE2 receptor, Umifenovir [Arbidol] targets the S-protein/ACE2 interaction which prevents viral entry into cells. It is currently being studied as both a treatment and prophylactic agent against SARS-CoV-2.[8] In a study done by Wang et al on the use of this medication, it showed to decrease mortality and increase discharge rate[8]; however, there were many limitations with this study such as nonrandomization and there needs to be more data on this therapy to prove efficacy. Camostat mesylate is another agent being investigated to inhibit viral entry, as it inhibits TMPRSS2 which facilitates viral entry into the host cell.[9] Although in vitro, this medication inhibits viral entry into cells, human trials are still pending.[9]

Chloroquine and Hydroxychloroquine are anti-malarial drugs are being studied as potential drugs of choice for SARS-CoV-2. These medications work by inhibiting membrane fusion, glycosylation of host receptors, endocytosis as well as decreasing cytokine production.[10] Despite its mechanism of action, there has been no study that shows clear benefit of using either agent.[11] In a systematic review by Sarma et al hydroxychloroquine showed no difference in cure [OR 2.37, 0.13-44.53], worsening of disease [OR 1.37, 1.37-21.97] or safety concerns [OR 2.19, 0.59-8.18][11] when compared to conventional treatment. Also, chloroquine and hydroxychloroquine have adverse effects such prolonged QT interval, hypoglycemia, cardiomyopathy; although well tolerated in healthy individuals, these side effects can be more prominent in critical ill patients.[12]

Protease inhibitors used in HIV such as Lopinavir/Ritonavir had potential for SARS-CoV-2 therapy as it inhibits 3-chymotrypsin-like protease.[6] in vitro studies did demonstrate some efficacy. However, in a randomized trial done by Cao et al the use of Lopinavir-Ritonavir showed no decrease in time to clinical improvement and no statistical difference in mortality rates.[13] Another study by Chan et al investigated the early use of Lopinavir-Ritonavir within 7-10 days of initial infection finding its use was associated with a decrease in death rate by 2.3%.[14] Early use does pose a challenge to the utility of this medication as this time frame is still within the incubation phase and most patients are asymptomatic.[1] Lopinavir/Ritonavir does cause gastrointestinal upset as well as hepatotoxicity; which is further exacerbated by SARS-CoV-2 infection.[13]

TABLE 1 Potential Therapies for COVID-19

Medication	Mechanism of action	Dose	Efficacy
Umifenovir [Arbidol]	S-protein/ACE2 inhibitor	200 mg TID PO for 7-14 days[6]	Limited studies; decrease mortality and increase discharge rate
Camostat mesylate	Inhibits TMPRSS2	2 × 100 mg TID PO for 5 days[27]	Effective in vitro, human trials pending
Chloroquine hydroxychloroquine	Inhibit membrane fusion, inhibit glycosylation of host receptors, inhibit endocytosis, decrease cytokine production	400 mg BID PO for 1 day then 200 mg BID for 4 days[6]	No clear benefit of use shown
Lopinavir/Ritonavir	Inhibits 3-chymotrypsin-like protease	400 mg/100 mg BID for 14 days[6]	Effective in vitroHuman trials show no decrease in time to clinical improvement and no change in mortality
FavipiravirRibavirin Remdesivir	Inhibit RNA-dependent RNA polymerase	Dose not established for Favipiravir Dose proposed for Ribavirin: 1.2-2.4 g TID PO Remdesivir 200 mg IV X1 then 100 mg q24 hours[6]	Favipiravir; limited studies; no proven benefit Ribavirin; limited studies, most inconclusive or show no proven benefit Remdesivir; effective in vitrohuman studies show clinical benefit however more trials needed
Tocilizumab Sarilumab	Inhibit IL-6	400 mg IV for 1–2 doses, may repeat in 8-12 hours[6]	Limited studies; shown to decrease in patient hospital stay, an increase in respiratory function and a decrease in mortality
Acetazolamide Nifedipine	Carbonic anhydrase inhibitorCalcium channel blocker	No dose established	No human trials; theoretical benefit but not recommended

Drugs that inhibit RNA- dependent RNA polymerase have also been tested for SARS-CoV-2 in to prevent viral structural proteins to be formed. Such drugs include Favipiravir, Ribavirin and Remdesivir. Favipiravir is a medication used in the treatment of Ebola and Influenza and it works as a prodrug to form Favipiravir-ribofuranosyl-5′triphosphate which then inhibits RNA-dependent RNA polymerase.[15] The efficacy of Favipiravir is still unknown as there are limited studies. In a prospective randomized, open-label trial done by Chen et al, which compared the use of Umifenovir vs Favipiravir in treating SARS-CoV-2, there was no difference in clinical recovery.[16] Of the patients that did receive Favipiravir, patients were found to have elevated uric acid and elevated transaminases; this again poses an issue due to SARS-CoV-2 as a potential cause of hepatic damage.[16] The study had many limitations; the most important being is that it was not peer reviewed.

Ribavirin, is another prodrug used to treat hepatitis C and hantavirus. It works by inhibiting RNA-dependent RNA polymerase via acting as a guanosine or adenosine analog that alters RNA-dependent replication and synthesis.[17] Efficacy is unknown for the use of Ribavirin against SARS-CoV-2 as many of the studies done have been inconclusive as researchers could not distinguish benefit of Ribavirin from that of standard therapy.[18] More importantly, patients that received Ribavirin were more likely to develop hemolytic anemia and elevated transaminase.[18]

Remdesivir, another prodrug that forms into an adenosine nucleotide analog that inhibits RNA- dependent RNA polymerase.[19] Data for the efficacy of Remdesivir in vitro studies is promising as Remdesivir has shown inhibitory effects for viral replication in human liver cells.[20] More importantly, in a study done by Grein et al, that looked at compassionate use of Remdesivir in 53 patients, 36 of them had clinical improvement within 10 days.[21] Due to the promise of Remdesivir and having a mild side effect profile of reversible elevation of transaminases, there are several clinical trials being done currently to evaluate the efficacy of this medication.

Immunomodulatory agents such as Tocilizumab and Sarilumab which inhibit IL-6 are also promising therapies. One of the proposed mechanisms of SARS-CoV-2 pathogenesis is the development of a cytokine storm, mainly through IL-6, IFN and TNFα.[6] Inhibiting one or several of these cytokines would help in reducing the pathogenesis of SARS-CoV-2 and could potentially decrease mortality of the patient. Current studies are encouraging with limited trials showing a decrease in patient hospital stay, an increase in respiratory function and a decrease in mortality.[22,23] So far, studies on Tocilizumab and Remdesivir have been most promising in therapies for SARS-CoV-2.

Drugs such as acetazolamide and nifedipine; which are used to treat high altitude pulmonary edema [HAPE], have been proposed as treatments for SARS-CoV-2 as they both develop into acute respiratory distress syndrome [ARDS].[24] The rationale behind using these medications is that there are similarities between HAPE and SARS-CoV-2; both have hypoxia, tachypnea, low PaCO2 levels, elevated fibrinogen levels and develop into ARDS.[24] Although similar, we must remember that the pathophysiology in which ARDS develops in each of these illnesses is different; with HAPE occurs due to elevated pulmonary artery pressure while SARS-CoV-2 is hypothesized to cause endothelial damage through pro-inflammatory cytokines.[7,24] Moreover, the mechanism in which acetazolamide and nifedipine treat HAPE would have different consequences in a patient with SARS-CoV-2. Acetazolamide is a carbonic anhydrase inhibitor, this enzyme is used to acidify the urine and transport bicarbonate back to the body under normal conditions.[25] Inhibiting this enzyme leads to diuresis which will increase urinary bicarbonate and decreases blood pH, this will cause hyperventilation to increase oxygen levels and decrease carbon dioxide in order to compensate the decrease in blood pH.[26] Although this will help a patient with HAPE; decreasing blood volume through diuresis and decreasing blood pH would not be ideal for a patient with SARS-CoV-2.[26] Moreover, acetazolamide is contraindicated in patients with poor renal function, which is seen in patients with SARS-CoV-2.[26,27] Nifedipine, a calcium channel blocker, works in a similar manner as it lowers blood pressure; although effective in HAPE,[24] this would not be ideal for someone with SARS-CoV-2 as it would alter their ventilation/perfusion ratio and lower their oxygenation.[28]

3 | CONCLUSION

SARS-CoV-2 has caused a pandemic that is creating a health-care crisis and economic strain worldwide. As more cases are reported each day, finding a standard therapy to SARS-CoV-2 that shows efficacy in large clinical trials during a pandemic poses an ongoing challenge to clinicians and researchers.

CONFLICT OF INTEREST

The authors have no competing interest.

ORCID

Richard A. Giovane https://orcid.org/0000-0002-8547-2693
Shadi Rezai https://orcid.org/0000-0001-8498-565X

REFERENCES

1. Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. *Lancet Glob Health*. 2020;8:e639-e640.
2. World Health Organization. Advice on the use of masks in the context of the novel coronavirus (2019-nCoV) outbreak. April 6, 2020. https://www.who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak. Accessed April 7, 2020.
3. https://clinicaltrials.gov/ct2/results?cond=COVID&term=BCG&cntry=&state=&city=&dist=
4. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol*. 2015;1282:1-23.
5. Neuman BW, Adair BD, Yoshioka C, et al. Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. *J Virol*. 2006;80(16):7918-7928.
6. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* Published online March 16. 2020;323(18).

7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
8. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020; 70(8):https://doi.org/10.1093/cid/ciaa272.
9. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* Published online March 4. 2020;181 (2):271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052.
10. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Published online March 4, 2020.
11. Sarma P, Kaur H, Kumar H, et al. Virological and clinical cure in covid-19 patients treated with hydroxychloroquine: a systematic review and meta-analysis. *J Med Virol*. 2020;72(7).
12. Kalil AC. Treating COVID-19—off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA*. s. 2020;323(19).
13. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-Ritonavir in adults hospitalized with severe covid-19. *N Engl J Med*. 2020;382:1787-1799.
14. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J*. 2003;9(6):399-406.
15. Guedj J, Piorkowski G, Jacquot F, et al. Antiviral efficacy of Favipiravir against Ebola virus: a translational study in cynomolgus macaques. *PLoS Med*. 2018;15(3):e1002535.
16. Chen C, Huang J, Cheng Z, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. *medRxiv*. Preprint posted March 27. 2020.
17. Ortega-prieto AM, Sheldon J, Grande-pérez A, et al. Extinction of hepatitis C virus by ribavirin in hepatoma cells involves lethal mutagenesis. *PLoS One*. 2013;8(8):e71039.
18. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343.
19. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral Remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio*. 2018;9(2):1-15.
20. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271.
21. Grein J, Ohmagari N, Shin D, et al. Compassionate use of Remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382(24):2327-2336. https://doi.org/10.1056/NEJMoa2007016.
22. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol*. 2020;92(7): 814-818.
23. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *ChinaXiv* Preprint posted March 5. 2020; 117(20):10970-10975.
24. Solaimanzadeh I. Acetazolamide, Nifedipine and phosphodiesterase inhibitors: rationale for their utilization as adjunctive countermeasures in the treatment of coronavirus disease 2019 (COVID-19). *Cureus*. 2020;12(3):e7343.
25. Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis andtreatment of acute mountain sickness. *J Appl Physiol*. 2007;102(4):1313-1322.
26. Koeppen BM. The kidney and acid-base regulation. *Adv Physiol Educ*. 2009;33(4):275-281.
27. https://clinicaltrials.gov/ct2/show/NCT04321096.
28. Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis*. 2020;20(4).

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