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REVIEW ARTICLE

Infectious Disease

COVID-19: A review of therapeutics under investigation

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Abstract

The COVID-19 outbreak has disrupted global health care networks and caused thousands of deaths and an international economic downturn. Multiple drugs are being used on patients with COVID-19 based on theoretical and in vitro therapeutic targets. Several of these therapies have been studied, but many have limited evidence behind their use, and clinical trials to evaluate their efficacy are either ongoing or have not yet begun. This review summarizes the existing evidence for medications currently under investigation for treatment of COVID-19, including remdesivir, chloroquine/hydroxychlorquine, convalescent plasma, lopinavir/ritonavir, IL-6 inhibitors, corticosteroids, and angiotensin-converting enzyme inhibitors.

KEYWORDS

chloroquine, coronavirus, COVID-19, IL-6, lopinavir, medications, remdesivir, SARS-CoV-2, therapeutics

1 | INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the greatest global health crisis since the 1918 Spanish flu pandemic.[1] Countries around the world continue to take increasingly desperate steps to control the spread of the virus. As the scope of the crisis grows, more attention is directed toward treatment options for those who become ill.

The World Health Organization (WHO) has released general guidelines for managing the illness caused by the virus (COVID-19), which includes supportive care similar to other viral pneumonias: airway and respiratory support, empiric antibiotics for secondary bacterial infection, and acute respiratory distress syndrome (ARDS) management.[2] While these treatments are thought to offer the best chance of survival for the approximately 20% of COVID-19 cases that progress to severe disease, limited health care resources and the speed at which the pandemic has developed are pressuring clinicians and scientists to provide therapeutics that specifically target SARS-CoV-2 and improve mortality.[3]

Public misinformation regarding treatment has run rampant, especially through traditional and social media. Gargling warm water and ingesting colloidal silver are some of the false treatment claims disseminated online.[4] The WHO has specifically targeted these questionable assertions, but misinformation can be hard to combat in an era of worldwide connectivity.[5] This review is intended to provide details on the pathogenesis of SARS-CoV-2 and the evidence behind potential therapeutic targets, in order that clinicians can arm themselves with knowledge to dispel false rumors and inform their patients.

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TABLE 1 Therapeutic interventions used in patients with COVID-19

Therapeutic	Mechanism	Evidence	Ongoing trials (clinical trials ID)
Chloroquine	Anti-inflammatory and inhibition of viral fusion	Unpublished data suggesting shortened disease course and faster viral clearance	NCT04303507 NCT04316377 NCT04322123
Remdesivir	Nucleoside analog inhibiting RdRp[a]	Significant clinical improvement in MERS-CoV[c] with animal models.	NCT04280705
Lopinavir/Ritonavir (Kaletra)	Inhibits Mpro[b]	Small RCT[d] suggesting no significant difference in 28-day morality	NCT04307693 NCT04255017
Sarilumab, Tocilizumab	IL-6 Inhibitor	Small non-peer-reviewed trial showing decrease O_2 requirement and improved lung disease	NCT04315298
Convalescent Plasma	Passive immunotherapy	Small case series of 5 patients who improved after administration	NCT04292340

[a]RNA-dependent RNA polymerase.
[b]Main protease.
[c]Middle East respiratory coronavirus.
[d]Randomized controlled trial.

2 | PATHOGENESIS OF SARS-CoV-2

SARS-CoV-2 belongs to the family *Coronaviridae* which are enveloped, single-stranded RNA viruses. Around 30 kilobases in length, two-thirds of its genome encode non-structural proteins, while the remaining third encodes spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins.[6] The non-structural genes encode an RNA-dependent RNA-polymerase (RdRp), and main protease (Mpro) that serve the purpose of cleaving polypeptides responsible for viral replication.[7,8] The viral envelope "S protein" first binds to the angiotensin-converting enzyme 2 (ACE2) receptor located on host cell surfaces and inserts its RNA into the host cell cytoplasm.[9] This ACE2 receptor is thought to be the main target the SARS-CoV-2 virus uses to infect a host.

ACE2 has an important function in human physiology. It is responsible for cleaving several peptides in the renin-angiotensin system and is present mostly on cell membranes of the kidneys, gastrointestinal tract, and type 2 pneumocytes in the lungs.[10] ACE2 in lung tissue converts angiotensin II to angiotensin (1-7). When SARS-CoV-2 binds to these ACE2-expressing cells, it both inhibits ACE2 and downregulates its production. This results in the buildup of unconverted angiotensin II, leading to increased vascular permeability and pulmonary edema. This mechanism is thought to be a major contributor to the severe lung injury seen in COVID-19.[11] ACE2 is also present at high levels in intestinal epithelial cells, which raises suspicion that SARS-CoV-2 was initially transmitted to humans by ingestion of infected food at the Wuhan market.[12]

SARS-CoV-2, like the earlier SARS coronavirus, seems to cause a dysregulated immune response in addition to lung injury. Although the exact mechanism is unclear, several studies analyzed SARS-CoV-2's effect on the host's immune response. Notably, most of these revealed a significant T-cell lymphopenia, particularly decreased regulatory T cells. There was also a significant increase in the pro-inflammatory cytokines TNF-α, IL-1, IL-6, as well as D-dimer, erythrocyte sedimentation rate (ESR), and C-reactive peptide (CRP).[13] When the virus initially targets the lungs, it produces this hyper-inflammatory response that results in a viral pneumonia in those that develop severe disease. If left unchecked, the infection can progress to sepsis and multi-organ dysfunction.[14]

3 | THERAPEUTICS UNDER CONSIDERATION

Worldwide, medical scientists are testing over 50 drugs and their efficacy in treating COVID-19.[15] While this review is not exhaustive, the major therapeutics highlighted are: remdesivir, chloroquine/hydroxychloroquine, convalescent plasma, lopinavir/ritonavir, and IL-6 inhibitors (Table 1).

3.1 | Remdesivir

One of the more promising drugs under consideration is remdesivir. Remdesivir (GS-5734) was developed in 2017 by Gilead Science Inc. for use against the re-emerging Ebola virus. Mechanistically, it acts as an adenosine analogue and prematurely terminates viral replication. It incorporates into newly formed viral RNA chains and inhibits RdRp.[16] Given its broad anti-viral activity, it was tested against other viruses, including the Middle East respiratory coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus of 2003–2004 (SARS-CoV-1). A recent study by de Wit et al demonstrated promising prophylactic and therapeutic results in a live rhesus macaque model against MERS-CoV.[17] When remdesivir was initiated 24 hours before inoculation, viral replication in lung tissue was suppressed and ultimately clinical disease and histologic lung lesions were prevented. When given 12 hours after MERS-CoV inoculation, remdesivir yielded reduced clinical severity of disease, decreased viral replication in lung tissue and fewer and less severe lung lesions. In another study examining human airway

epithelial cells, it was shown to inhibit viral replication of SARS-CoV-1 and MERS-CoV.[18]

Before the COVID-19 pandemic, remdesivir was used therapeutically in compassionate-use scenarios to treat Ebola virus disease (EVD). The drug was given to around 400 patients in the Democratic Republic of Congo, and in 1 study no clinical or biochemical adverse effects were attributable to its administration.[19]

As COVID-19 entered the United States, patient 0 in Washington State was treated with remdesivir starting on day 7 of illness.[20] Although direct causation is difficult to prove, there were notably decreased SARS-CoV-2 viral loads by nasopharyngeal and oropharyngeal swabs following administration. The dosing regimen employed was a loading dose of 200 mg intravenous infusion, followed by 100 mg intravenous infusion daily for a total treatment length of 10 days.[21]

Given the robust response to remdesivir in other coronavirus diseases, there are ongoing trials looking at its effectiveness in treating COVID-19. There is currently a multicenter, adaptive, randomized, double-blinded trial enrolling patients in the United States, Singapore, and South Korea, and 2 trials underway in China.[22]

3.2 | Chloroquine and hydroxychloroquine

In the fight against a pandemic public health emergency, staple medicines may be repurposed. Listed by the WHO as an "essential medicine," chloroquine has been used as an antimalarial since its creation in Germany by Bayer in the 1930s. Hydroxychloroquine belongs to the same molecular family and differs from chloroquine only by a hydroxyl group.[23] These drugs have demonstrated a range of treatment potential against viral infections.[24] Chloroquine's anti-viral activity is thought to work by alkalizing a virus' phagolysosome, which increases the lysosomal pH. Many viruses require a relative acidic environment to promote host cell fusion. Alkalizing the pH thereby impedes fusion and uncoating, and ultimately viral replication.[25]

In vitro studies have demonstrated that chloroquine has activity against SARS-CoV-2. In vivo, it has been shown to distribute widely throughout the body and penetrate the lung tissue well.[16] With a low side effect profile and cost, chloroquine was a clear choice for trialing during the early months of the COVID-19 outbreak. Gao et al announced in February 2020 that China had already performed at least 15 clinical trials evaluating the safety and efficacy of chloroquine and/or hydroxychloroquine in the treatment of COVID-19 pneumonia.[26] Over 100 patients were enrolled at 10 participating clinical sites. The results touted chloroquine as "superior to control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course." The results from 1 trial of hydoxychloroquine versus placebo were released to *medRxiv*, an online server for scientific articles.[27] The authors concluded that the hydoxychloroquine group had faster improvement in cough and fever, and higher rates of improvement in pneumonia on imaging. Unfortunately this study, along with the studies mentioned by Gao et al, have not been published or peer-reviewed, and any results should be viewed with caution.

Momentum to investigate the role chloroquine and hydroxychloroquine might play in preventing COVID-19 has led to several additional trials. The University of Minnesota recently announced a study examining the role chloroquine may play in post-exposure prophylaxis.[28] The University of Oxford is also investigating the efficacy of hydroxychloroquine prophylaxis against COVID-19 for health care workers.[29]

3.3 | Convalescent plasma

Another potential therapy for COVID-19 is passive immunotherapy, which has been in use in various iterations since the late 1800s. Passive immunotherapy is defined as administration of preformed antibodies to a non-immune individual. This therapy is thought to be more effective when used as prophylaxis rather than active disease and in earlier stages of infection rather than later.[30] Proposed mechanisms of action in viral infections focus on suppression of viremia and viral clearance after administration. Pathogen-specific antibodies may be harvested from the plasma of a recovered patient, yielding "convalescent plasma."

In recent years, convalescent plasma has been shown to have some degree of efficacy in various viral infections.[31] The evidence for its effectiveness in treating Ebola virus has been mixed.[32,33] There are a number of promising studies that have demonstrated shorter hospital stays, lower mortality rates, and reduced viral loads in SARS-CoV-1 and H1N1 influenza infected patients treated with convalescent plasma.[34]

A recently published case series by Shen et al shared the results of 5 patients with severe COVID-19 who were administered convalescent plasma.[35] All 5 patients had improvement in respiratory status, viral loads, and pulmonary lesions seen on imaging after treatment. All 5 patients made a meaningful recovery from their disease. The authors correctly make no definitive statements on the efficacy of the therapy. This was not a controlled trial, the patients were late into their illness, and they were given multiple other anti-virals and therapeutics. There are also potential complications with the use of passive immunotherapy. Adverse events include serum sickness, transfusion-related acute lung injury (especially in patients with preexisting ARDS), and the theoretical risks of antibody dependent enhancement of infection.[30] While these adverse events are worrisome and a full safety profile has not been well delineated, analysis of the existing data has not revealed a high rate of adverse effects from convalescent plasma treatment.[32]

The predominate limitation in treating COVID-19 is the logistical difficulty of finding appropriate donors with adequate titers of neutralizing antibodies, especially in the setting of a pandemic where health care interactions and blood donations are significantly curbed.[30] Despite these limitations, investigations into convalescent plasma continue at the time of this publication. There is another single ongoing observational trial examining the efficacy of anti-SARS-CoV-2 inactivated convalescent plasma in COVID-19 patients, the results of which remain to be seen.[36]

3.4 | Lopinavir/ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 protease inhibitor with in vitro inhibition of SARS-CoV-1.[37] Ritonavir is often combined with lopinavir to increase its plasma half-life. Combination lopinavir/ritonavir (LPV/r) was suggested to lead to decreased adverse outcomes in the 2004 SARS outbreak.[37,38] The sequences and structures of the LPV/r binding site to SARS-CoV-1 and SARS-CoV-2 proteases are 96% conserved, and it was initially thought that LPV/r could be an effective treatment for COVID-19 by inhibiting the virus' main protease (Mpro).[39,40] Case reports document LPV/r use in Korea, while a small case series revealed mixed results.[41-43]

One study out of China looked at the use of umifenovir combined with LPV/r. Umifenovir (trade name Arbidol) is a "broad-spectrum anti-viral" previously used to treat influenza in Russia and China.[44] The study found faster clearance of SARS-CoV-2 by PCR and faster improvement of chest computed tomography.[45] This was only a small retrospective study with a small sample size, but it suggested that LPV/r may have a role in COVID-19 treatment.

The most recently published study, a randomized, open-label trial comparing LPV/r versus placebo in patients with severe COVID-19 found no statistically significant difference in time to clinical improvement or 28-day mortality.[46] The LPV/r arm had a 6% lower 28-day mortality, median ICU stay 5 days shorter, and median hospital stay 2 days shorter but all results were statistically non-significant. In a modified intention-to-treat analysis, there was a modest difference in median time to clinical improvement (15 days in LPV/r and 16 with placebo). Interestingly, serious adverse events from COVID-19 (acute kidney injury, ARDS) were numerically more common in the placebo group.[46] While an overall negative study, it had a small sample size, participants were enrolled late into their disease course, and enrollment was suspended early. It is possible that underpowering, early suspension, and focus on severe disease overshadowed benefit, though more definitive evidence is required before LPV/r therapy can be recommended. At the time of this writing, there are twelve other clinical trials of protease inhibitors in COVID-19 registered with the United States National Library of Medicine database.[47]

3.5 | IL-6 inhibitors

As mentioned above, COVID-19 infections seem to result in a cascade of pro-inflammatory molecules such as interleukins and other cytokines. The resulting "cytokine storm" occurs in a subset of patients and is postulated to result in more severe illness. The immune response itself may cause more damage to the lungs than direct viral toxicity. Previous research during the original SARS CoV outbreak involving these pro-inflammatory cytokines revealed IL-6 as a molecule of interest that contributes to this inflammatory state and cytokine storm.[48] In the current pandemic, two recent small retrospective articles in press suggest elevated levels of IL-6 and D-dimer may predict disease severity in patients with COVID 19.[49,50] Given the potential role cytokine storm plays in COVID-19, therapy blunting this inflammatory response and targeting IL-6 in particular may be effective.

Over the past few years, IL-6 has been targeted in other disease processes that have robust inflammatory responses such as rheumatoid arthritis and cancer. Some anecdotal evidence is emerging regarding its use in COVID-19 patients. In a small retrospective study from China during the initial outbreak, 20 patients with critical COVID-19 were treated with tocilizumab, an anti-IL-6 monoclonal antibody.[51] The authors noted a reduction in pro-inflammatory markers, decreased fever, decreased oxygen requirements and decreased lung disease burden on CT imaging. While showing promise this study, similar to the multiple studies released on chloroquine, has not been peer reviewed.

A randomized controlled trial was announced with Sarilumab (another IL-6 monoclonal antibody) in COVID-19 patients in the United States and abroad.[52] This would be an opportunity to provide more insight regarding the role IL-6 inhibitors might play in treating the disease.

4 | CONTROVERSIAL MEDICATIONS

4.1 | NSAIDs

While a dysregulated host response has been implicated in the development of refractory respiratory failure, the adaptive immune response is still crucial for clearing and ultimately recovering from a coronavirus infection.[53] This has led some to question the safety and utility of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in the treatment of COVID-19.

NSAIDs like ibuprofen work by reducing the production of fever-causing prostaglandins (PGs) via the inhibition of cyclooxygenase enzymes (COX-1 and COX-2). While beneficial in reducing body temperature, they can also inhibit the release of anti-inflammatory prostaglandins. The concern is that this anti-inflammatory inhibition will worsen the COVID-19 "cytokine storm." This, coupled with anecdotal reports of severe illness among young patients taking NSAIDs, has led to public health figures recommending against NSAID use (specifically ibuprofen) in all COVID-19 infections, and to consider acetaminophen (paracetamol) as an alternative.[54]

While well-intentioned, the recommendations preferring acetaminophen are probably misguided; acetaminophen is also a potent COX-2 inhibitor and exhibits some COX-1 inhibition.[55] Overall, there are no RCTs evaluating the use of NSAIDs in COVID-19, and the WHO currently has no recommendations against NSAID use for those with the disease.[56] Given the absence of data specific to mild COVID-19 infections, the need for non-opiate analgesics, and the many health conditions that respond well to NSAIDs, it is likely best for patients taking NSAIDs for chronic conditions to continue to do so, and for discontinuation decisions to be made on a case-by-case basis.[57]

4.2 | Corticosteroids

Corticosteroids are a class of anti-inflammatory agents used extensively in the early phases of the COVID 19 outbreak.[58] Corticosteroids act via downregulation of key pro-inflammatory molecules and are thought to be helpful in blunting the cytokine storm seen with the virus.

Corticosteroid administration in prior coronavirus outbreaks failed to provide a survival benefit and was likely harmful in cases of SARS-CoV-1 and MERS-CoV due to delayed viral clearance.[59,60] These studies largely informed the WHO interim recommendation against corticosteroid use early in the outbreak of COVID-19, citing potential for multiple harms, especially out of concern for overwhelming Strongyloidiasis infections in endemic areas.[2] The WHO recommendations make allowance for cases of refractory septic shock, commensurate with the Surviving Sepsis Campaign guidelines in 2016.[61]

Controversy with this recommendation comes when COVID-19 patients develop ARDS. The DEXA-ARDS trial, a recent multi-center Spanish study evaluating dexamethasone use in ARDS, showed a significant benefit in reduction of both mechanical ventilation and mortality.[62] The data specific to COVID-19 are limited. One non-peer-reviewed, single-center retrospective review of 46 matched patients with severe COVID-19 disease reported those who received 1—2 mg/kg/day of methylprednisolone had faster improvement in SpO^2, faster resolution of fever, and improvement in chest CT findings.[63]

These limited data informed the forthcoming COVID-19 Surviving Sepsis Campaign guidelines.[64] The authors in these guidelines recommend corticosteroids for refractory shock and for ARDS due to COVID-19. They recommend against corticosteroids in COVID-19 patients without ARDS or refractory shock, even those who are mechanically ventilated.

4.3 | ACE inhibitors

Controversy also surrounds ACE inhibitors and COVID-19. The use of ACE inhibitors and angiotensin II receptor blockers (ARBs) leads to an upregulation of the ACE2 receptors in SARS-CoV-1.[65] While some hypothesize that this might facilitate infection with COVID-19 via the S protein binding, others argue that ACE inhibitors and ARBs could be protective by preventing angiotensin II buildup and ARDS.[66,67] There is no clinical evidence to support a definite benefit or harm, and most experts recommend continuing ACE inhibitors and ARBs if patients are already on the medication to lower the risk of stroke and other consequences of hypertension, but to not add the medications otherwise in treatment of COVID-19.[57]

5 | DISCUSSION

Although a number of these treatments seem promising, many of them are unpublished and have not been vetted through the peer-review process. A healthy sense of skepticism is needed until more definitive data are available. Medications like chloroquine and lopinavir/ritonavir are known to cause QT prolongation and Torsades de Pointes.[68] Haphazardly recommending unproven therapies have the potential to cause significant harm.[69] Experimental therapies used by the public can also promote a false sense of security and an under-reliance on interventions with proven effectiveness like hand hygiene and social distancing.

The authors hold to the WHO stance that COVID-19 therapeutics should be utilized under ethically approved, randomized, controlled trials if possible.[2] A number of ongoing clinical trials will provide a wealth of data for analysis and scrutiny. The WHO is launching a multi-arm "mega-trial" called SOLIDARITY to coordinate the collection of robust scientific data on many of the above medications.[70]

As emergency clinicians, it is our responsibility to advocate for measures that are known to make a difference: social distancing, strict quarantining, increased production of personal protective equipment, and seasonal influenza vaccination. In regard to the rapidly changing therapeutic options for COVID-19, we should consider the evidence and approach them with scientific scrutiny, while having faith in the combined scientific knowledge and ingenuity of our clinical and research colleagues. Our mandate is to "first, do no harm" and that applies in the frantic days of a growing pandemic as much as it ever has before.

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