JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2021, VOL. 11, NO. 2, 187–193
https://doi.org/10.1080/20009666.2021.1874093

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REVIEW ARTICLE

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Experimental therapies under investigation for COVID-19

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ABSTRACT

Coronavirus Disease 2019, caused by the virus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is a pandemic first discovered in Wuhan, China which has claimed over 1.7 million lives to date across the globe as of 24 December 2020. As the virus spreads across the world affecting millions of patients, there has been a massive movement to discover readily available and effective treatment options including vaccines. One of the limiting factors in treating the disease is its varied presentation and effect in patients, ranging from asymptomatic patients to those left in intensive care units, intubated and fighting for their lives. There are numerous clinical trials and small-scale studies underway to investigate potential treatment options. However, very few studies and drugs demonstrated efficacy while many more are under investigation, leaving care teams dependent on supportive care coupled with experimental treatment options. In this review, we summarize the various treatment options explored to treat COVID-19, discussing possible the mechanisms of fighting the virus.

ARTICLE HISTORY
Received 12 October 2020
Accepted 6 January 2021

KEYWORDS
COVID-19 treatment; therapies for COVID-19; pandemic drugs; remdesivir; hydroxychloroquine

Introduction

Of the seven coronaviruses known to infect humans, majority of them cause a mild upper respiratory disease [1]. Three exceptions to these are severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, middle east respiratory syndrome coronavirus (MERS) in 2012 and the current SARS CoV-2 virus in 2020. Both the SARS-CoV and MERS outbreak were treated with supportive therapy as the main stay treatment since no clear drug or vaccine emerged as a winner [2,(3]. The novel coronavirus, known as SARS-CoV-2 is very closely related to SARS-CoV with a 79.6% sequence similarity [4]. Because of the sequence similarity, many of the drugs which were investigated during the prior pandemics, re-surfaced as potential treatment options. With the gravity of the outbreak, the R_0 being 2.24–3.58 [5,(6], and disease claiming more lives when compared to the prior outbreaks, there has been tremendous push towards developing effective treatment options. It is known that SARS-CoV-2 uses the receptor angiotensin-converting enzyme-2 (ACE2) for entry and employs the serine protease TMPRSS2 for S protein priming [7] (Figure 1). COVID-19 patients, in their early stages of contracting the illness, present with a decrease in both $CD4^+$ and $CD8^+$ T-cells subsets leading to impairment in the host's immunity [8]. Thus, the use of anti-viral agents early in the disease course has shown to be beneficial in controlling the severity of COVID-19 [9].

The current management focuses on supportive care in the mild-moderate setting and fluid/ventilation management in the acute respiratory distress phase (ARDS) and extracorporeal membrane oxygenation (ECMO) phases [10,(11]. The role of steroids in this disease has been debated as well. We chose to review many potential medications that have been studied in this regard (Figure 1).

Treatment options

One of the earlier drugs that were studied during the evolution of this pandemic was Chloroquine/hydroxychloroquine. In this review, we discuss major potential treatments studied until December 2020.

Chloroquine, hydroxychloroquine

The mechanism of action of chloroquine is via inhibition of viral cell entry and cell fusion by increasing endosomal pH. It also impairs the glycosylation of ACE2 receptors which the SARS viruses use for cellular entry [12,(13]. It has shown efficacy in in-vitro studies against SARS-CoV-2, however, failed to demonstrate efficacy as more information was gained during the course of the pandemic [14].

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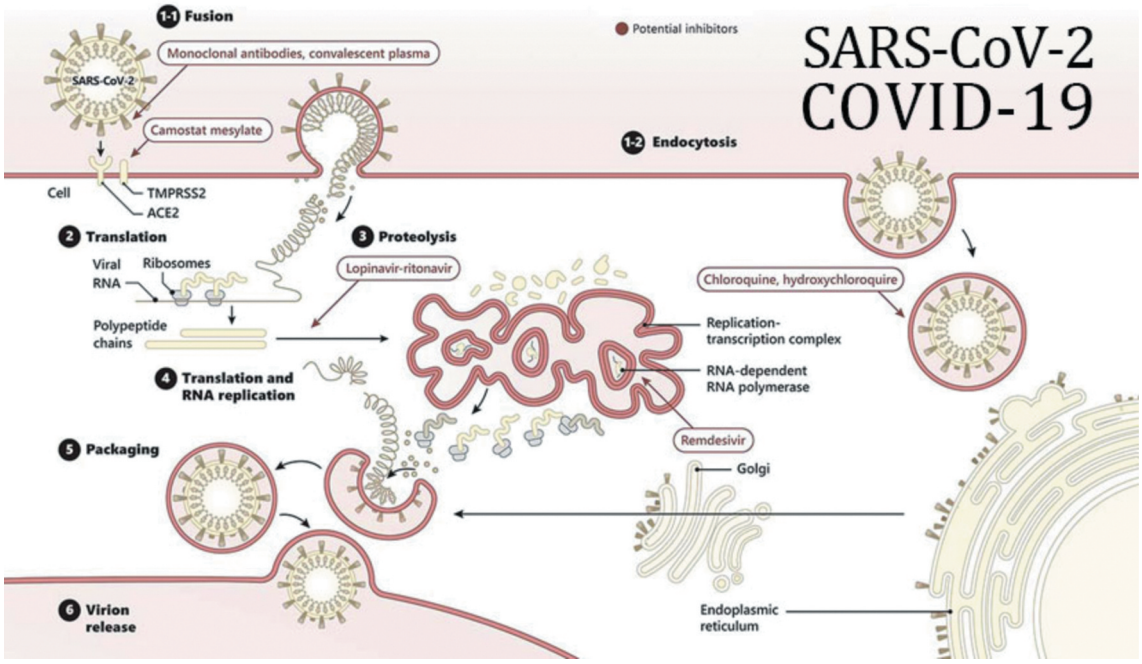

Figure 1. Diaphragm representing various experimental drugs used in the treatment of COVID-19 and their mechanisms of action.

According to *Gautret et al.* azithromycin was added to hydroxychloroquine for treating 20 patients with severe COVID-19 [15]. The combination therapy showed significant viral load reduction/disappearance [15]. This was followed by *Chen et al.* where a dose of 400 mg hydroxychloroquine did not lead to nasal clearance in 30 patients [16]. Both of these studies were randomized control trials. However, another study by *Molina et al.* showed that the combination therapy did not result in viral clearance at 5 or 6 days of treatment [17]. A recent observational study showed that hydroxychloroquine administration was not associated with either a lower or an increased risk for intubation or death [18]. Hydroxychloroquine was also studied for post-exposure prophylaxis and it did not prevent illness after being exposed to confirmed COVID-19 infection when given after 4 days of exposure [19].

Based on a myriad of data proving that these medications did not fasten viral clearance or symptom improval, there has been a change of practice to not include them for routine COVID-19 treatment.

Remdesivir (RDV)

Remdesivir has shown some promise in the treatment of COVID-19. This drug targets viral RNA-dependent RNA polymerase leading to premature termination of viral RNA transcription [20,(21]. Remdesivir has been shown to inhibit the activity of *Orthocoronavirinae* (such as pathogenic SARS-CoV and MERS) and has shown some efficacy in treating SARS-CoV-2 in vitro [13,22,23]. Since there is sequence of similarities between SARS-CoV and SARS-CoV-2, this was trialled in patients with COVID-19.

This drug was first utilized in the USA in January 2020 in the state of Washington, where the very first COVID-19 patient was treated with it on day 7 for pneumonia [24]. The patient cleared the virus from the respiratory tract by day 12. In a study containing 237 patients by *Wang et al.* in April 2020, patients admitted to hospital for severe COVID-19 who were treated with remdesivir did not have statistically significant clinical benefits when compared to placebo [25]. The primary endpoint in this study was time to recovery within 28 days. However, it was important to note that the patients who received remdesivir showed faster time to clinical improvement. Remdesivir did not show any statistically significant improvement whether treated for 5 or 10 days duration in patients with severe COVID-19 who were not mechanically ventilated [26].

Compassionate use of remdesivir in severe COVID-19 patients led to clinical improvement in 68% patients which led to the utilization in multiple health care facilities all across the world [27]. For the first time, a randomized-controlled trial in 1063 patients revealed positive results in terms of shortening time to recovery in adult patients hospitalized with COVID-19 [28]. Based on this data, the Food and Drug Administration has approved remdesivir for use in hospitalized patients with COVID-19 and the most benefit may be observed in time to recovery, with remdesivir shortening the disease course.

More recently, remdesivir was one of the medications studied among three other to look at in-hospital mortality in a multi-country randomized controlled trial (Solidarity trial). In that study, remdesivir did not show any in-hospital mortality benefit [29]. This study led to changing recommendations from World Health Organization (WHO) recommending against the use of remdesivir in hospitalized patients.

Favipiravir

Favipiravir inhibits the RNA polymerase activity of the viral genome of RNA viruses leading to chain termination and chain elongation [30]. Favipiravir has shown in-vitro viral inhibition activity against SARS-CoV-2 which resulted in it being a potential treatment option [13].

Favipiravir was compared with lopinavir/ritonavir (LPV/RTV) for treatment and in comparison to LPV/RTV, favipiravir led to faster viral clearance times and significant improvement rate in chest imaging [31]. A prospective, multicenter, open-label, randomized trial in China comparing favipiravir for COVID-19 with umifenovir (Arbidol) which is used against influenza viruses in 240 patients, was recently reported. Preliminary results have shown that although favipivar improved time to relief for fever and cough, it did not improve overall clinical recovery rate when compared to Arbidiol [32]. The overall consensus is that there are no definite results to use this drug in routine care of COVID-19 patients.

Additionally, favipiravir is being studied in clinical trials in combination with interferon-α (ChiCTR2000029600) [33] or with baloxavir marboxil (ChiCTR2000029544) [34] in China. Phase 3 clinical trial is currently underway in India.

Interferons

Interferon β (IFNb)-1b was a treatment option during the MERS and SARS-CoV outbreaks [35,(36]. This drug displayed in-vitro susceptibility and SARS-CoV-2 was found to be more sensitive to IFN-I treatment when compared to the SARS-CoV, making this potential option [37]. ACTT-3 is a phase 3 randomized-controlled clinical trial looking at outcomes with combination of interferon beta-1a and remdesivir compared to remdesivir alone in 1038 patients which is ongoing [38]. Although not peer-reviewed yet, IFNb was studied to increase discharge rate at 14 days and decreased mortality rate at 28 days in a study from Iran (IRCT20100228003449N28) [39]. Interferon was also studied as a part of Solidarity trial, it did not show any mortality benefit or decrease the duration of hospital stay [29]

Lopinavir/ritonavir

Protease inhibitors (PIs) are drugs which are widely used in chronic human immunodeficiency virus (HIV) infection. In-vitro, SARS-CoV was susceptible to lopinavir/ritonavir (LPV/RTV) combination [40]. Therefore, it was tested and was deemed susceptible to SARS-CoV-2 in vitro.

LPV/RTV treatment alone failed to improve the primary outcome of clinical improvement in severe COVID-19 neither did it provide a mortality benefit [40]. Per *Baden et al.* reported that the benefit of this drug may not have been observed since the patients were treated with these drugs late in the infection and the concentration of drug necessary to inhibit the virus in the pulmonary circulation may be higher than the serum level [41]. When tested as a part of the solidarity trial, it too did not show any in-hospital mortality benefit [29].

Tocilizumab and other interleukin inhibitors

Tocilizumab is a monoclonal antibody which is an interleukin-6 receptor inhibitor which reduces the severity of illness by dampening the cytokine release syndrome [42]. COVID-19 patients who are severely ill present with a cytokine storm which led to investigators looking at agents that neutralize the inflammatory factors. Tocilizumab given either intravenously or subcutaneously reduced the risk of invasive mechanical ventilation and death in a retrospective observational study done in 1351 patients [43]. Another observational study in 764 patients showed reduced mortality in patients who received Tocilizumab [44]. However, these are retrospective or observational studies. More recently, in a randomized double-blinded controlled trial, Tocilizumab did not prevent intubation or death in moderately hospitalized patients warning clinicians against its use in moderately-ill COVID-19 patients [45]

Interleukin-10 was also hypothesized in reducing COVID-19 mortality by blocking the pro-inflammatory function, however, studies are warranted to prove this finding [46].

Convalescent plasma

Another investigational method is the administration of convalescent plasma made from recovered patients in China. It was studied in prior pandemics – SARS, H1N1, and severe Ebola virus infections [47]. For the first time for COVID-19, *Shen et al.* reported this experimental treatment where neutralizing IgG antibodies were transfused to 5 patients who were in severe ARDS. They theorized that adding antibodies from the convalescent plasma helped clear the virus leading to improvement in symptoms, however, very

small proportion of patients were tested in this study [48]. However, a recently published randomized controlled trial in 103 patients who were severely infected with COVID-19, plasma therapy did not result in a significant clinical improvement within 28 days [49]. Literature such as this, has discouraged clinicians from using plasma as a potential treatment of COVID-19

Corticosteroids

The use of steroids in COVID-19 have been controversial as well. A study by *Wu et al.* reported that methylprednisolone may be beneficial, leading to decreased risk of death in patients with ARDS [50]. Some studies have shown a beneficial effect with low dose prednisone in cancer patients with COVID-19 [51,(52]. A metanalysis of one randomized-controlled trial and 22 cohort studies showed that glucocorticoid therapy reduced the duration of fever but did not affect the mortality, duration of hospitalization or lung inflammation absorption [53]. A recently published open-labelled trial which studied dexamethasone vs usual care showed 28-day mortality benefit in those patients receiving invasive mechanical ventilation or oxygen with dexamethasone (Recovery trial). However, the positive results only applied to patients receiving respiratory oxygen support [54].

Other Experimental Modalities

Monoclonal or polyclonal antibodies were used to treat infections such as SARS-CoV, MERS [55]. LY-CoV555 (bamlanivimab) was studied in patients with mild to moderate COVID-19 studies as a phase 2 clinical trial, it led to fewer hospitalization and lower symptom burden leading to FDA approval among outpatients [56]. REGN-COV2 is a cocktail containing two neutralizing antibodies studied among 275 outpatients in a 1–3 phase trial, it showed that it reduced viral load with greater efficacy among those with a high baseline viral loads or those who have not yet developed immunity [57]. It is also now FDA approved for non-hospitalized COVID-19 patients.

Baricitinib, a janus kinase inhibitor, has been studied as a potential treatment for COVID-19 by preventing virus infectivity via inhibition of clathrin-mediated endocytosis [58]. A randomized-controlled trial was done comparing remdesivir plus baricitinib vs usual care and the combination with baricitinib reduced time to recovery in patients with high-flow oxygen and non-invasive ventilation [59].

Type II transmembrane serine protease (TMPRSS2) is a host protease that activates the SARS-CoV protein in cell cultures which makes it an exciting treatment option [7]. The protease inhibitor camostat plus EST [[23,25]*trans*-epoxysuccinyl-L-leucylamindo-3-methylbutane ethyl ester], a cathepsin inhibitor effectively stopped the SARS-CoV entry into host cells [60]. A randomized-controlled trial is underway to test the efficacy of camostat for COVID-19 (NCT04321096) [61].

Mesenchymal stem cells have improved the pulmonary functions in a case report described in China [62]. On a large scale, stem cell therapy for COVID-19 is being investigated in China currently (NCT04288102) [63].

Medications for concomitant conditions

The most common comorbidities of COVID-19 are hypertension and diabetes [64]. Many of these patients are on ACE inhibitors or angiotensin receptor blockers (ARB) and SARS-CoV-2 uses the ACE2 receptors to enter a host cell [64]. The theory is that these medications cause upregulation of ACE2 receptor which facilitates the viral entry. This is a double-edged sword since the use of these medications may prevent cardiovascular morbidity with could potentially be caused by the virus. A randomized-controlled trial evaluating the safety of continuing vs discontinuing ACE/ARBs is underway [65].

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, were hypothesized to increase ACE2 receptors thereby facilitating the viral entry [64]. However, FDA released a statement that there is no scientific data suggesting that NSAIDs would worsen COVID-19 symptoms [51,(66].

Vaccines

Currently, as of 22nd December, per WHO's draft evaluation, there are 61 vaccines under clinical investigation and 172 under pre-clinical investigation [67]. Two vaccines have been approved for emergency use authorization by FDA.

Conclusions

Till date, very few vaccines or specific anti-SARS-CoV-2 drug regimens have been identified to treat or prevent COVID-19. None of the drugs that have been studied has emerged as a clear winner. Remdesivir appears to be the most promising agent, however, results have been conflicting and it's use has shown to have no effect on mortality. The most benefit from remdesivir is that it hastens time to recovery. Dexamethasone may be beneficial in severe COVID-19 cases, including patients on high-flow oxygen and invasive ventilation. The treatment atleast for now mainly focuses on supportive care and preventive measures including social distancing, wearing masks and avoiding large group gatherings.

Abbreviations

SARS-CoV2- severe acute respiratory syndrome coronavirus-2
SARS- CoV- severe acute respiratory syndrome coronavirus
MERS- Middle East Respiratory Syndrome Coronavirus
ACE2- angiotensin converting enzyme 2
ARDS- acute respiratory distress phase
ECMO- extracorporeal membrane oxygenation
RSV- respiratory syncytial virus
WHO- world health organization
IFN- interferon
HIV- human immunodeficiency virus
LPV/RTV- lopinavir/ritonavir
RA- rheumatoid arthritis
SOFA- sequential organ failure assessment
ARB- angiotensin II receptor blockers
NSAIDs- non-steroidal anti-inflammatory drugs
SIC- sepsis-induced coagulopathy
FDA- food and drug administration

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure statement

The authors do not have financial relationships with any commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Author Contributions

RG, NK, NS assisted in acquisition of data, drafting of the manuscript. TD, CK, RJ assisted in article concept and design, interpretation of data, revision of the manuscript and final approval. RJ, NS, RJ further assisted in revisions of the final manuscript.

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