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ORIGINAL ARTICLE

COVID-19 treatment options

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Abstract

There is no specific treatment for COVID-19 and vaccines are still being developed. This paper presents experimental treatment options proposed by a number of authors. The studies included in this paper have looked into antiviral drugs, chloroquine, hydroxychloroquine, azithromycin, tocilizumab, vitamin D, anticoagulation, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), interferon beta, convalescent plasma, and steroids. Although some of these drugs showed promise in in vitro tests, none was effective or safe to treat patients with novel coronavirus infection.

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INTRODUCTION

The novel coronavirus was identified in late 2019 as the cause of a number of cases of pneumonia in the city of Wuhan in Hubei Province, China[1-4].The virus spread quickly, with growing numbers of cases recorded in other nations. In February 2020, the World Health Organization (WHO) named it COVID-19 (Coronavirus Disease 2019). The virus causing COVID-19 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); it was previously referred to as 2019-nCoV. The WHO elevated COVID-19 to the status of pandemic on March 11, 2020[1-4].

Patients must first be analyzed for severity of disease:[1]

- Mild or moderate disease - no need for supplemental oxygen.
- Severe disease - need for supplemental oxygen or increased initial need for oxygen, without new or growing need for ventilation (non-invasive or invasive).
- Critical disease - need for non-invasive or invasive mechanical ventilation; sepsis; multiple organ failure; or quick deterioration of clinical condition.

Critically or severely ill children with COVID-19 usually require hospitalization[1,5]. Children with mild or moderate COVID-19 may require hospitalization if they are at risk of developing severe disease on account of associated comorbidities[1,2,5].

There is no proven, approved treatment COVID-19. Vaccines are currently being developed. Some are the object of clinical trials on Phase III, such as vaccine ChAdOx1 nCoV-19 developed by Oxford University, in the United Kingdom, which will be tested in volunteers in Brazil. This vaccine is one of 141 registered with the WHO and one of 13 being tested in humans[6].

The following sections contain experimental treatment plans recommended based on information available to date.

ANTIVIRAL THERAPY

The decision to prescribe antiviral therapy must be individualized based on the severity of the disease, clinical progression, and underlying conditions that may increase the risk of poorer outcomes. Studies on the efficacy of antiviral therapy included primarily adult individuals with severe lower respiratory tract disease[5].

Retrospective data from patients with SARS indicate that early treatment, in the case of influenza, may be more effective than waiting to start therapy until severe organ failure sets in.[5]

However, most patients progress well without treatment and do not require antiviral therapy.[5]

Other antiviral drugs:

LOPINAVIR / RITONAVIR

The efficacy of Lopinavir/ Ritonavir has not been proven beyond doubt.[5,7] In vitro studies reported a 50% decrease in the replication of the MERS-CoV virus (the beta coronavirus that causes respiratory diseases in the Middle East)[5] It is a potent CYP3A4 inhibitor.[5] According to the WHO, this agent may be tried in combination with interferon alpha or ribavirin.[5]

Remdesivir

Several randomized trials are currently in progress to assess the efficacy of remdesivir, but none has reached Phase III yet.[5] Related activity has been reported in vitro against SARS-CoV-2 at decreasing the severity of lung disease.[5] It cannot be used in combination with other experimental antivirals.[5] It was also tested as a medication against the Ebola virus.[5] The mode of action includes early termination of viral RNA transcription.[5]

Ribavirin

No results are available for studies looking into the effectiveness of this medication against SARS-CoV-2. Studies on MERS-CoV found that the levels necessary to inhibit the pathogen in vitro exceeded blood levels after the administration of therapeutic doses in humans.[5] Toxicity is an element to consider in this drug, and it is contraindicated for individuals with hemolytic anemia. It inhibits RNA polymerization.[5]

Oseltamivir

The efficacy of oseltamivir at combating SARS-CoV-2 has not been assessed in a clinical trial.[5] The mode of action of this drug revolves around inhibiting enzyme neuraminidase in individuals with influenza.[5] Early COVID-19 may emulate the symptoms seen in individuals with influenza. Treatment with oseltamivir should be started in cases in which influenza cannot be ruled out.[5,7]

Other treatment options:

Chloroquine/Hydroxychloroquine (CQ/HCQ)

Hydroxychloroquine or chloroquine, often used in combination with a second-generation macrolide, have been broadly used in the treatment of COVID-19 despite the lack of conclusive evidence to its effect.[8] Hydroxychloroquine is believed to alter endosomal and lysosomal pH, thereby inhibiting viral replication and propagation, although the exact mechanism still remains undefined.[5]

Use is generally safe for approved indications, which include autoimmune disease and malaria.[7,8] It should not be prescribed to children with underlying QT anomalies and individuals on medications known to produce adverse interactions.[7] Prolonged use of these drugs may cause retinopathy.[7]

A study published on Lancet described the outcomes of a multinational analysis on the use of chloroquine and hydroxychloroquine with and without macrolides by patients with COVID-19 hospitalized in six different continents from December 2019 to April 2020.[8] All groups treated with the drugs in question had increased risk of death compared to controls.[8] Risk of ventricular arrhythmia was also greater in these patients.[8] On May 25, the WHO announced the suspension of studies using chloroquine and hydroxychloroquine to treat COVID-19. The studies resumed and were suspended again on June 17 based on evidence described in the Recovery trial from the UK and the Solidarity international trial, since neither reported benefits from prescribing hydroxychloroquine to individuals with COVID-19.[9]

Azithromycin/Hydroxychloroquine

A study indicated that azithromycin used in combination with hydroxychloroquine might lead to faster resolution of the disease from detection of the virus than hydroxychloroquine alone. Its outcomes, however, must be interpreted with caution on account of the small size of the study population, substantial methodological concerns, and unclear biological plausibility.[7] The combined therapy was described in observational studies, most of which failed to suggest associated clinical benefit.[7] As in the case of hydroxychloroquine alone, the drug combination also presents increased risk of prolonged corrected QT interval.[7]

Tocilizumab

Tocilizumab is an IL-6 receptor inhibitor used to treat rheumatic diseases and cytokine release syndrome. The use of the drug in individuals with COVID-19 has been tested in randomized clinical trials.[5] Sarilumab and siltuximab are other IL-6 inhibitors currently being tested in clinical trials.[5]

Vitamin D

Proper intake of vitamin D is required for good bone health. Vitamin D deficiency has not been described as a risk factor for severe SARS-CoV-2 infection in children.[10] The role of vitamin D in the treatment and prevention of COVID-19 is uncertain and doses above the upper limit of daily recommended intake levels should not be encouraged.[10]

Anticoagulation

Individuals with COVID-19 may present with a number of coagulation anomalies resulting in an underlying state of hypercoagulability.[4,11] Hypercoagulability appears to adversely affect patient outcomes, although good quality studies that support interventions extending beyond standard indications are lacking, and antithrombotic medication increases the risk of bleeding.[6,11] Therefore, the current indication is to offer prophylactic intravenous therapy for thromboembolism to all patients with COVID-19, particularly the ones with severe disease, unless there is contraindication to anticoagulants as described in medical guidelines.[6,11]

Angiotensin-converting-enzyme (ACE) inhibitors or ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

There has been significant interest in the role of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in the pathophysiology of COVID-19, since SARS-CoV-2 binds to the ACE2 receptor to enter human cells.[5] The mode of action of these drugs includes decreasing the cytokine storm by preventing virus-cell adsorption.[5] In theory, ARBs may block the virus. Therefore, it has been postulated that ARBs might produce protective effects based on their mode of action, although there is no trial-based evidence to support this hypothesis.[5] Thus, ACE inhibitors or ARBs are not used in the treatment of individuals with COVID-19.[5]

Interferon beta

The interest in interferon beta to treat SARS-CoV-2 infection grew from evidence suggesting in vitro activity of the compound against the Middle East respiratory syndrome-related coronavirus (MERS-CoV) and good outcomes in an animal model of infection by MERS-CoV.[12] More studies are required to clarify the role of interferon beta in COVID-19 therapy. Routine use has not been recommended.[5]

Convalescent plasma

The use of convalescent plasma has been studied recently. Convalescent plasma may benefit patients when administered in the early stages of disease to improve clinical signs, the SOFA score, the PaO2/FIO2 ratio, and decrease viral load.[5] The role of convalescent plasma remains unclear. Clinical trials with large populations are needed to assess its potential efficacy.[5]

Steroids

The Centers for Disease Control and Prevention (CDC) and the WHO advise that glucocorticoids should not be routinely administered to individuals with COVID-19, unless there is specific evidence-based indication (e.g.: subjects with asthma or exacerbated chronic obstructive pulmonary disease, refractory septic shock, or adrenal insufficiency).[5,7] In June 2020, preliminary findings from Recovery, a British randomized clinical trial designed to test potential therapies for COVID-19 that included low-dose dexamethasone, were published.[13] The trial found that dexamethasone decreased the number of deaths of adult patients on ventilators by a third and the deaths of other patients on oxygen therapy alone by a fifth.[13] No benefit was described for individuals not requiring respiratory support.[13]. There is no data on pediatric populations.[13]

CONCLUSION

Although some drugs have shown promise in in vitro settings, none has been deemed effective against the novel coronavirus and safe for human beings.

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