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Review Article

Possible treatments of COVID-19 present and future

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ABSTRACT

Since the outbreak of COVID-19 infection in December 2019, millions of people are infected, and thousands of people have died. Genetic shift and high infectivity rate made SARS-Cov-2 a pandemic. Doctors, researchers, and world leaders are scratching their heads, how to contained or treat the virus. Several treatment options are tried, but so far, there is no effective treatment available. Thousands of articles are published about COVID-19, and so much information is available that it is challenging for a practicing physician to review these articles in the limited time they have. This article summarized the treatment options for COVID-19 that have tried or are in clinical trials. The article also reviews other possibilities that are either briefly or not discussed in the literature but could play a role in the fight against COVID-19.

Keywords: COVID-19, SARS-Cov-2, Genetic shift

INTRODUCTION

SARS-CoV-2 is a positive sense, single-stranded, enveloped RNA virus. It belongs to a family of coronaviruses, which mostly cause respiratory illness in humans. The virus has a lipid bilayer in which four proteins, S=Spike, M=membrane, E=envelope, and N=nucleocapsid, are anchored. The spike (S) glycoprotein on the viral envelope binds to ACE2 receptors in human cells.¹ Once bind to the ACE2 receptor, cellular protease (TMPRSS2 and CatB/L) on the human cell's surface prime the spike protein and allow the virus membrane to fuse with the human cell membrane. Once viral membrane fuses with the human cell membrane, viral RNA enters into the host cell. Research showed that the virus also enters the human cell by endocytosis. ACE2 receptors are found in lung epithelial cells, especially in pneumocytes II, heart, blood vessel, and kidney. Once inside the cell, translation of viral proteins, replication, and transcription of genome RNA, packing, and assembly takes place in the cytoplasm, and virions bud out to infect new cells. Infected cells present antigen to antigen-presenting cells,

which in turn activate pro-inflammatory markers, such as cytokines, macrophages, leukocytes, TNF- alfa, and result in a cytokine storm. The overstimulated immune system causes severe damage to the lung epithelial cells, endothelial cells, heart, and kidney.

So far, there is no effective treatment of COVID-19. Early preventions like social distancing, washing hands, wearing masks seem the only effective option. Following is a brief description of the drugs used or are in the clinical trials for the treatment of COVID-19.

REMEDSIVIR

It is an investigational nucleotide analog with broad antiviral activity. In vitro, it showed activity against COVID-19. Remdesivir inhibits viral replication by incorporating into RNA by RNA dependent RNA polymerase, which results in delayed chain termination. In clinical trials, remdesivir did not significantly improve the mortality rate, but it did reduce the recovery time compared to placebo.² There are several ongoing clinical trials all over the world. At this time, the NIH COVID-19

guidelines panel does not say about its use as there is not enough data available. FDA permits the use of the drug only in a hospital setting with severe disease.

HYDROXYCHLOROQUINE AND CHLOROQUINE

These immuno-modulating and anti-malarial drugs have antiviral activity in vitro against SARS-CoV-2. Hydroxychloroquine is a more potent inhibitor than chloroquine in vitro.³ Glycosylation of ACE-2 receptors, binding to sialic acid of the host cell, and alkalization of endosomes are proposed mechanisms of action of these drugs against the virus. Earlier studies showed some benefit of decreasing viral load, especially in combination with azithromycin.³ However, later studies suggested no benefit in COVID-19.^{4,5} According to NIH COVID-19 panel, there is insufficient data to recommend the drugs for the treatment of COVID-19.⁶

AZITHROMYCIN

has some in vitro antiviral activity against Zika, and Ebola virus, but did not show any against SARS-Cov-2. Azithromycin has anti-inflammatory and immunomodulatory effects and has been used as adjunctive therapy to provide antibacterial coverage in the treatment of viral infection, including COVID-19.^{3,7,8} An uncontrolled observational study in France showed possible clinical benefits when used with hydroxychloroquine.⁹ NIH COVID-19 guidelines recommend against the use of combination with hydroxychloroquine except in a clinical trial setting due to prolonged QT-interval, which may lead to life-threatening arrhythmias.⁶

CORTICOSTEROIDS

The use of corticosteroids in COVID-19 appeared to be ineffective and possibly harmful.¹⁰ According to WHO guidelines, corticosteroids should only be used in patients with specific conditions such as asthma, COPD, or sepsis after considering benefit vs risk.

IL-6 ANTAGONIST

Includes tocilizumab, sarilumab, siltuximab, which are IL-6 monoclonal antibodies. IL-6 plays an important role in cytokinin storm. Data received from case reports and observational studies from China showed the benefits of decreasing parameters associated with cytokinin storm and IL-6 level.^{11,12} Worldwide various clinical trials are in progress. NIH COVID-19 guideline panel does not say in favor of or against the use due to insufficient data.

COVID-19 CONVALESCENT PLASMA

Contains antibodies against SARS-Cov-2 and provides passive immunity for the short term. Uncontrolled studies done in China shorten the duration of hospital stay and

mortality rate.^{13,14} However, most of the studies done were not controlled, and many were case studies. Several clinical trials are underway in the US, Europe, and other countries. Convalescent plasma is regulated as an investigational product, and there are certain requirements for administering it. Providers can access the site at <https://www.fda.gov/media/136798/download> or <http://www.uscovidplasma.org/> for further detail.

IMMUNE GLOBULIN

Derived from pooled plasma and contain antibodies. Usually, use in patients with humoral immunodeficiency. May also have some antibodies against the previous infection by a coronavirus. The benefits of using Immune globulin in COVID-19 is not clear.^{15,16} Instead, it may cause some complications like anaphylaxis, thrombosis, transfusion-related lung injuries, renal failure. COVID-19 subcommittee recommendation is not to used routinely.

ASCORBIC ACID

Use as an antioxidant, immune system support, and cofactor. Various dosages of IV form of ascorbic acid with and without hydroxychloroquine were used. Clinical trials are ongoing, and we do not have any clear picture. However, current data do not support ascorbic acid in COVID-19, as it may interfere with various lab results. Need further study.¹⁷

ZINC

Zinc does have in vitro antiviral activity against coronavirus. Itself does not enter into the host cell and requires carrier ionophore molecule, such as hydroxychloroquine, to enter into the cell.¹⁸ Clinical trials are ongoing.

CAMOSTAT MESYLATE

Camostat mesylate is a serine protease inhibitor approved in Japan for pancreatitis. Camostat target TMPRSS2 receptor on lung cell and theoretically block the entrance of SARS-Cov-2 into the human cell. Several clinical trials are ongoing, and there is not enough data yet.

Following is the list of drugs that are either not effective or lacking enough data. NIH-COVID-19 treatment guidelines Panel recommends against the use for the treatment of COVID-19 except in clinical trials. Baloxavir, favipiravir, kaletra - HIV protease inhibitor, oseltamivir - neuraminidase inhibitor, ACE inhibitors or ARBS, colchicine, famotidine, ivermectin, and niclosamide.

VACCINE

More than 100 projects around the world are in progress. There are a lot of unanswered questions about the vaccine

and how effective it would be? The urgency and rapid development of vaccines may increase the risk of failure and unknown health issues. Several products are in phase 1 or II clinical trials. There is a race against time and are hoping to have the vaccine before the second wave of pandemic COVID-19 may hit.

OTHER POSSIBILITIES

These are the options that are not tried before in the treatment of COVID-19 but could be a possibility and need further study and clinical trials.

Use of alcohol vapours by inhalation

Ethyl alcohol vapours by inhalation driven by oxygen is used before for the treatment of ARDS and alcohol withdrawal in postoperative patients with gastroesophageal carcinoma without any serious complications.¹⁹⁻²¹

Alcohol has a strong antiviral (envelope virus) activity at a concentration above 30% and immunomodulating effects.^{22,23} However, there is no study available and need further study and clinical research.

THEOPHYLLINE

Theophylline is a xanthine derivative and has broncho dilating, immunomodulating, and anti-inflammatory properties, it may be used as an adjunctive treatment for ARDS in COVID-19.^{24,25}

OTHER ANTIBIOTICS

It has been noted that use of antibiotics in viral infection has some advantages. Using these antibiotics either decrease the severity of the disease or prevent secondary bacterial infection. Such antibiotic includes macrolide, tetracycline, fluoroquinolones, rifampin, fosfomycin, clindamycin, they all have anti-inflammatory and immunomodulating effects. They decrease cytokines, TNF, and T-cells activity.²⁶ Fosfomycin also decreases the release of histamine from basophils.²⁶

NICOTINE

WHO discourage the use of any nicotine product in the treatment of COVID-19, as there is insufficient data? However, some ongoing research and clinical trials show some beneficial effects of nicotine in decreasing the inflammatory response associated with COVID-19. The theory behind the use of nicotine is the stimulation of the cholinergic system and its association with decreasing the inflammatory response.²⁷ Nicotine does have beneficial effects in inflammatory.

bowel disease and could have immunomodulating effects in COVID-19.²⁸ At this time, ongoing research is

continued, and there is not enough information available to comments on its uses in COVID-19.

MOUTH WASH

There are various stages of COVID-19. Initially, the virus infects mucosa of nose and throat, and then as the disease progress, the SARS-Cov-2 virus moves down to the lung. Rinsing and gargle at initial stage with the mouth wash having antiviral activity, especially ethanol base make sense. It might decrease the viral load and severity of the disease. However, it is interesting to know that it has not been used in any clinical trials. Recently, some clinical trials are started in some countries.

SUMMARY

Since the outbreak of COVID-19, a lot of drugs have been tasted. The combined effort of the countries all over the world resulted in a lot of information about the pandemic and the possible treatment options in a short period. There are many ongoing clinical trials all over the world, but there is not enough data to recommend any particular regimen over others for the treatment of COVID-19. Look like we are running out of options in the fight against COVID-19. New ideas would become the essence of continue to fight against the disease or infection. We are all hoping to have some kind of treatment option before the second wave of COVID-19 hits. The development of vaccines is about 8 to 12 months from now, and we do not know how effective it would be! Preliminary results from phase I and II trials clinical trials are encouraging, but it is too early to say anything.

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