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A REVIEW OF COVID-19 TREATMENT

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ABSTRACT

This review mainly focusing on antivirals and drugs with immune-modulatory, anti-inflammatory properties, against COVID-19, their pharmacological features and achievement in term of patients' clinical outcomes. The global pandemic of novel corona virus disease 2019 (Covid-19) caused by SARS-CoV-2 began in Wuhan, China, in December 2019, and has since spread worldwide. At the time of this review, COVID-19 has been diagnosed more than 6,485,526 cases and 386,704 death. A large number of antiviral agents, including lopinavir/ritonavir, favipiravir, remdesivir, many of which are used for the treatment of hepatitis, human immunodeficiency virus (HIV) and flu symptoms are currently using as off-label for the worldwide patients. The viral lifecycle, viral entry, and immune regulation pathway providing potential targets for drug therapy.

KEYWORDS: Covid-19, cytokine storm, ARDS, Favipiravir, Remdesivir, Tocilizumab.

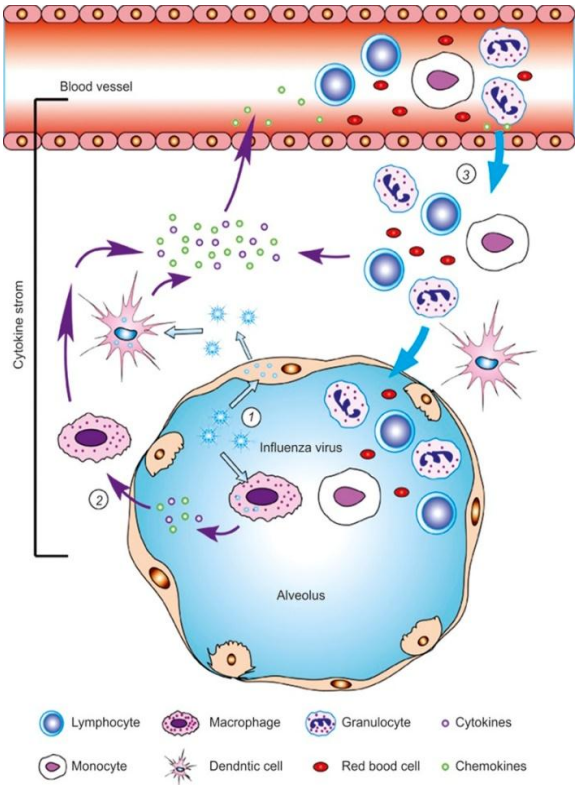
INTRODUCTION

Coronaviruses are medium-sized enveloped positive-stranded RNA viruses, that belong to the beta coronavirus cluster, whose name is derived from the Latin “corona” meaning crown or halo, referring to their image under electron microscopy with crown like spikes on their surface similar to the solar corona.

In December 2019, several patients in Wuhan, Hubei, China were diagnosed with pneumonia secondary to an unknown virus, the WHO announced COVID-19 outbreak a pandemic as of 13th of March 2020. The virus that causes COVID-19 is also known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019- nCoV. Most of the critically ill and dead patients did not develop severe clinical manifestations in the early stages of the disease. Some of the patients only showed mild fever, cough, or muscle soreness. The conditions of these patients deteriorated suddenly in the later stages of the disease or in the process of recovery.

COVID-19 pathogenic Mechanism

The receptor binding domain of S protein on the surface of SARS-CoV-2 binds to the ACE2 receptor on the cell surface to facilitate the virus entering the host cell, then the virus exposes its RNA, translate its RNA replicase, and form an RNA replicase transcriptase complex. Through transcription and replication, the complex forms RNA negative strands that will be translated for the structural proteins of the virus later. Then the structural proteins and RNA in the cytoplasm assemble into new viral particles, which are released from infected cells by exocytosis to infect other cells. Each infected cell produces thousands of novel viral particles that spread to bronchi, eventually reach the alveoli, and extrapulmonory organs, causing pneumonia and targeted organic infections.



Cytokine Storm: Cytokine storm is an excessive immune response to external stimuli. The pathogenesis of the cytokine storm is complex. The disease progresses rapidly, and the mortality is high. Certain evidence shows that, during the coronavirus disease 2019 (COVID-19) epidemic, the severe deterioration of some patients has been closely related to the cytokine storm in their bodies.

Acute respiratory distress syndrome (ARDS) and multiorgan dysfunction are the leading cause of death in critically ill patients with COVID-19. The elevated inflammatory cytokines suggest that a cytokine storm, also known as cytokine release syndrome (CRS), may play major role in the pathology of COVID-19. SARS-CoV-2 targets the lungs and likely other organs leading to multiorgan damage by binding to the angiotensin converting enzyme 2 receptor[1] a cell surface protein highly expressed in the lung.[2]

CRS or cytokine storm is a supraphysiologic response to immune therapy that activates immune effector cells. The systemic reaction is associated with increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells.

Many of the clinical manifestations of CRS are caused by release of cytokines. Severe COVID-19 are linked with increased levels of IL-6, IL-10, and TNF-α.[16] Cardiomyopathy, activation of coagulation cascades, vascular leakage are caused by IL-6, while IFN-g is associated with fever, chills, headache, dizziness and fatigue. Flu-like symptoms, malaise, watery diarrhea, lung injury, and production of acute phase proteins are mainly associated with release of TNF-a.[14, 15]

Compared with COVID-19 patients from general wards, patients in the intensive care unit (ICU) display increased serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF-α. Suggest that the cytokine storm is positively correlated with disease severity.[22]

In COVID-19, the inflammatory cytokine storm is closely related to the development and progression of ARDS. The serum levels of cytokines are significantly increased in patients with ARDS, and the degree of increase is positively correlated with mortality rate.[23]

In summary, the new-type coronavirus infection causes an inflammatory cytokine storm in patients. The cytokine storm leads to ARDS or extra pulmonary multiple-organ failure and is an important factor that causes COVID-19 exacerbation or even death.

Antiviral Agents

Many studies have focused on repurposing established antiviral therapies, especially those that showed prior efficacy against SARS-CoV and MERS-CoV. A large number of antiviral agents, many of which are used to treat HIV, Hepatitis, Ebola, and flu symptoms are currently administered worldwide in patients with COVID-19 (off-label) are under clinical evaluation for the treatment of the disease.

Favipiravir

Favipiravir, previously known as T-705, is a prodrug of a purine nucleotide, a pyrazine carboxamide derivative, is a novel broad spectrum antiviral drug was authorized 2014 in Japan for the treatment of influenza virus infections. It is selectively inhibit the influenza viral RNA- dependent RNA polymerase, thereby blocking the process of replication by negatively acting on genetic copying. Due to its activity against RNA viruses, it has been tested against several RNA viruses including H1N1, Ebola, Lassa viruses and approved for few indication in Japan and France. It is known to be active in vitro against Oseltamivir-resistant influenza A, B and C viruses.[3]

Favipiravir was administered during a clinical trial to 200 patients with COVID-19 at hospitals in Wuhan and Shenzhen. The results of these studies showed that patients who received the drug tested negative in a relatively short time (4 days compared to 11 days in the control group), while the symptoms of pneumonia were significantly reduced.

Recently preliminary results of clinical studies have shown Favipiravir to have promising potency in treatment of Chinese patients with SARS-CoV-2 infection.[5]

Another clinical study carried out in Wuhan showed that favipiravir-treated patients recovered from fever after an average of 2.5 days compared to 4.2 days in other patients. Chang Chen et al. (2020) recently published the results of a randomized clinical trial (Chictr.org.cn, n. ChiCTR200030254), which compared the efficacy and safety of favipiravir versus umifenovir in the treatment of 240 patients with COVID-19.

Lopinavir/ ritonavir

The combination lopinavir/ritonavir, which is indicated with other antiretroviral medicinal products for the treatment of HIV-1, has raised increasing interest for the treatment of COVID-19, and this (FDA) – approved oral combination agent demonstrated in vitro activity against other novel corona viruses via inhibition of 3-chymotrypsin-like protease.[6, 7]

Combination of lopinavir/ritonavir is the most common exploratory antiviral, appearing in 34 investigational studies, both drugs function as protease inhibitors and are used extensively in the management of HIV-1.[8] However, lopinavir has insufficient oral bioavailability for significant therapeutic activity, due to rapid catabolism by the cytochrome P450 enzyme system, ritonavir is given concomitantly to inhibit this, significantly boosting the half-life of lopinavir. This

combination was investigated for efficacy against SARS-CoV in 2004 and found to be effective compared with a historical control.[9] The most commonly used and studied lopinavir/ritonavir dosing regimen for COVID-19 treatment is 400 mg/100 mg twice daily for up to 14 days.[10]

Remdesivir

The antiviral prodrug Remdesivir (GS-5734™) is a nucleoside analogue intracellularly metabolized to an active triphosphate form that acts by inhibiting viral RNA polymerases. Besides its effectiveness against Filviruses (e.g. Ebola) & Nipah Virus; Remedesivir also shows therapeutic & prophylactic efficacy against coronaviruses (e.g. SARS-CoV, MERS-CoV).[17, 18]

Hence the antiviral is currently considered a promising potential therapy especially subsequent to its successful use in the treatment of COVID-19 patient, as per NEJM report of rehabilitation for the first patient with COVID-19 in the US.[20]

In the cohort study of hospitalized severe COVID-19 patients receiving remdesivir therapy, clinical improvements were observed in 68% of the patients.[21] As the specific therapy for COVID-19 evolves, remdesivir is expected to be effective in reducing the number of viral copies in the body hence focus is required on the pharmacokinetics and kinetics data of COVID-19 in the ongoing phase 3 clinical trials.[19]

Several other anti-viral drugs are being investigated, predominantly those with activity against various influenza subtypes and other RNA viruses, these include Umifenovir, triazavirin, and baloxavir marboxil. Many trials are focusing on drugs typically used in the management of RNA viruses, these include danoprevir / ritonavir, azudine, sofosbuvir/ledipasvir, sofosbuvir/ daclatasvir, darunavir/cobicistat, and emtricitabine/ tenofovir.

Additionally there are 26 studies investigating utility of antiviral interferon based treatment, also looking at various different routes of administration including nasal.

Anticytokine or Immunomodulatory Agents

Hyper inflammatory states and cytokine storming, including elevated IL-6, has been reported in severe COVID-19 and were associated with increased mortality in patients in China. Based on this consideration, several drugs with immunomodulatory properties are currently evaluated in patients with COVID-19. These drugs include both synthetic and biological medicines that are able to modulate specific inflammatory pathways through the inhibition of human IL-6 receptor (IL-6R), of the metabolism, motility and chemo taxis of polymorph nuclear cells, of JAK or TNF-α production.

Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, is FDA approved to treat RA and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Given this experience, tocilizumab has been used in small series of severe COVID-19 cases with early reports of success. A report of 21 patients with COVID-19 showed receipt of tocilizumab, 400mg, was associated with clinical improvement in 91% of patients as measured by improved respiratory function, rapid defervescence, and successful discharge.[24, 25]

Corticosteroids: Similar to other severe respiratory tract infections, there is significant interest and controversy surrounding the role of corticosteroids for the management of severe pneumonia due to coronaviruses. Several studies have indicated that the use of corticosteroids in patient with COVID-19is associated with delayed viral clearance, higher risk of secondary infection and increased risk of mortality.[26] Still the use of corticosteroids may be indicated n patient who develop ARDS or refractory septic shock. A study conducted in china found that the use of Methylprednisolone decreased risk of death in patient with COVID-19 who develop ARDS.[27] Corticosteroid may be used if indicated for refractory septic shock or severe ARDS.[28, 29]

Moreover a recent report by Tang et al (2020) demonstrated that anticoagulant therapy with heparin (mainly with low molecular weight heparin) was associated with better prognosis in severe COVID-19 patients. Oxley et al recently reported five cases of large vessel stroke in patients which were positive for COVID-19, all of the were younger than 50 years old, suggesting that the COVID-19 might be the cause.[30, 31]

CONCLUSION

The COVID-19 pandemic represents the greatest global public health crisis of this generation, since the beginning of the outbreak, a large number of clinical studies have been registered worldwide, and several drugs were repurposed to face the new health emergency of COVID-19. While waiting for the development of an effective vaccine, many clinical trials on different types of drugs are currently underway. Their results will certainly bring new knowledge and will help us in defining the best way to treat COVID-19 and reducing its symptoms and complications.

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