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Research Article

An Update on the Pharmacological Treatments of COVID-19

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ABSTRACT
Researchers have tried many therapeutic agents in their experimental studies since the first pandemic time of COVID-19; these studies have been virus-based or host-based. Major therapeutics agent's regimens evaluated in this review. Antiviral agents such as remdesivir, and Umifenovir should be used before the viral peak of replication to obtain the best clinical outcome. Dexamethasone is FDA approved in the treatment of certain cases of Covid-19. Immunoglobulin, and Interferon effectiveness in the treatment of this pandemic disease is not clear due to inconsistent outcomes data obtained in many studies. Several studies that used chloroquine and hydroxychloroquine as a therapeutic agent in COVID-19 showed that these agents have in vitro inhibitory activity against SARS-CoV-2, but failed to show a significant effect in many clinical studies. For patients who develop cytokine storm the interleukine-6 inhibitors like Tocilizumab could be effective.

Keywords: COVID-19, Pharmacological Treatments of COVID-19

INTRODUCTION

Coronavirus disease 2019 is a global pandemic virus caused by severe acute respiratory syndrome coronavirus-2, that is started in China, Wuhan city, in the year of 2019, after that the virus expanded to the worldwide. More than 1.2 million reported cases on April 5, 2020, and approximately 69000 patients were dead in up to 200 countries (1). The similarity of Beta-coronavirus to the SARS-CoV-1 was firstly reported in 2003and to the Middle East respiratory syndrome coronavirus reported in 2012, genetically, COVID-19 that is reached to humans through an unclear type of intermediate mammal host is likely created from a bat-derived form of coronaviruses. SARS-CoV-2 possesses a novel genome character represented by a virus quickly sequenced which interferes with diagnostic testing, and with therapeutic strategies designing [1]. According to the patient's vast majority, COVID-19 is represented as a mild viral infection disease 80% but in individuals with underlying diseases and the elderly, this novel virus may cause several complications like severe pneumonitis and also may cause disseminated endotheliosis [2]. Approximately, twenty percent of the patients that are infected with COVID-19 need hospital admitting, and 5% of these admitted patients require intensive care. There is a correlation between case severity and viral load [3].

COVID-19 infection Clinical Symptom Spectrum

Fever, cough, fatigue, and myalgia, these symptoms are represented as a common COVID-19 infection symptom. Diarrhea and nausea are initial symptoms that may appear on patients in several days prior to a fever development. Headache or hemoptysis symptoms noted also in a small number of patients and some patients be relatively asymptomatic (4). Severe alveolar damage which leads to respiratory failure had been more likely seen in older men with comorbdities. The COVID-19 infection disease is a rapid progression disease that may cause organ dysfunction like shock, syndrome of acute respiratory distress, heart injury, and also an injury of the kidney which may lead to a patient's death in severe infection (5). COVID-19 infected

patients may show white blood cell normal or low counts, also showing thrombocytopenia, accompanied by a significantly increasing in the level of C-reactive protein (6).

Diagnosis of Novel COVID-19 Virus

Real time reverse transcription polymerase chain reaction technique has been developed for COVID-19 diagnosis which is used in most clinics, though the RT-PCR technique represented as a reference standard for COVID-19 infection clinical diagnosis, the unavailability and the high rate of a false negative for an RT-PCR technique in the disease early stage restricted prompts diagnosis for patients with infection (7). Thin slice chest is one of the radiological examinations, which plays a major role in fighting COVID-19 infectious disease. The early phase of a lung infection can be identified by chest CT. In Hubei, China, chest CT is one of the most important pieces of evidence to confirm the clinical diagnosis of COVID-19 (8). There are many laboratory observations for patients with pneumonia infected with COVID-19 such as elevation in plasma D-dimer concentration level in synchronicity with an elevation of cardiac markers, which include brain natriuretic peptide, troponin-T, and creatine kinase. Estimation of troponin-T at hospitalization is represented as one of the best indications for the patients' poor prognosis (9).

Pharmacologic Treatments for COVID-19

Pharmacological treatment that is used in SARS management and also for MERS has been chosen as a potent therapy for COVID-19 treatment. Meta-analysis studies found that the therapy that used in the management of SARS and MERS has no evident advantage as a regimen for virus treatment (10).

Chloroquine and Hydroxychloroquine

These agents have previous history in malaria management and the management of other inflammatory diseases like systemic lupus Erythematous and the disease of rheumatoid arthritis (11). Chloroquine also hydroxychloroquine by its inhibitory effect on host receptors glycosylation which leads to stopping virus entering to the host cells, endosomal acidification mechanism, and proteolytic processing. These two agents have effects as immunomodulatory via inhibition of the production of cytokine and Autophagy process, also the lysosomal activity in host cells (12). In vitro, Chloroquine inhibits COVID-19 with EC50 in a low range, in vitro effectiveness of hydroxychloroquine which has low EC50 for COVID-19 disease when compared with chloroquine, 24 hours after growth (EC50 for hydroxychloroquine equal to 6.14 μM while EC50 for chloroquine equal to 23.90 μM) (13). Modeling hydroxychloroquine pharmacokinetic study in the management of SARS-CoV-2 recommended a loading dose of the drug as 400 mg two times a day for one day after that dose of 200 mg two times a day also as an optimal dosing regimen (13). Chloroquine showed no significant adverse effects at these doses and durations during COVID-19 treatment. Chloroquine and hydroxychloroquine recommended as a safe drug when using during pregnancy (14).

Lopinavir/Ritanovir

A combination agent of oral Lopinavir/Ritanovir approved by Food and Drug Administration as a typical choice for immunodeficiency virus management, thus, described in vitro combination therapy activity against other novel coronaviruses by inhibiting 3-chymotrypsin-like protease (15). For using lopinavir/ritanovir in the treatment of COVID-19 treatment, there is no data published yet (16). The administration timing of lopinavir/ritanovir in the first seven to ten days which is the early viral replication peak is very important due to the delayed this combination therapy did not affect clinical outcomes (17). The most commonly used lopinavir/ritanovir dosing regimen in the treatment of SARS-CoV-2 is 400mg/100mg tow times a day for more to fourteen days (18). Concerning the side effect of lopinavir/ritanovir which includes gastrointestinal distress adverse effects like nausea, vomiting, and like diarrhea, which may be more than 28% and about hepatotoxicity from two to ten percent. In COVID-19 patients, lopinavir/ritanovir adverse effects may be exacerbated when these agents combined with other therapy or by a viral infection; this refers to that the twenty to thirty percent of patients show elevated transaminase at COVID-19 infected patient presentation (19).

Ribavirin

Ribavirin had a previous history in the management of other types of nCoVs, thus give a priority to this agent in SARS-CoV-2 management. Ribavirin is one of the guanine analog agents, which have an inhibitory effect on RNA-dependent RNA polymerase of the virus. It has a limit in vitro effect toward SARS CoV and it needed high doses to block the virus replication, requiring a high oral dose such as 1.2 grams to 2.4 grams each eight hours and may combine with other therapy (20). There is no evidence in nCoV management for inhaled ribavirin use, and

the data with the respiratory syncytial virus suggest that the inhalation route administration has no benefit over the other route of administration like entreat or intravenous (21). About the adverse effects of ribavirin such as the toxicity of the liver and hematologic toxicity which is dose dependent adverse effect. Sixty percent of the patients that used ribavirin for the management of SARS infection showed the hemolytic anemia (20).

Other Antiviral managements

Oseltamivir: Neuraminidase inhibitory antiviral agent that is approved as a typical therapy in influenza management, in the treatment of SARSCoV-2, there is no evidence documented for the use of oseltamivir. In China, the initial outbreak happens for COVID-19 during the peak season of the influenza virus, due to that, most of the patients had been taken empirical oseltamivir until the time of SARS-CoV-2 discovering as the source of COVID-19 (22). It has no specific role in COVID-19 management the moment that influenza has been eliminated. Clinical trial studies used oseltamivir mainly in comparison groups but not used it as a suggested therapeutic intervention (23).

Umifenovir: Has an individual antiviral mechanism of drug activity that selecting the viral S protein/host cell ACE2 interaction and interfering with virus fusion to the membrane. In Russia and China, Umifenovir is clinically approved as a management and as a prophylaxis therapy for influenza which gives attention to this drug as a medication for COVID-19 depending on in vitro data that supposed the activity of this agent in SARS treatment (24). An oral dose of 200mg every eight hours used for the treatment of influenza is being discussed as management for COVID-19. In China, there is a limited clinical experience described using Umifenovir in COVID-19 treatment (25).

Miscellaneous Agents

Interferon-α and-β

the use of these agents for the treatment of nCoVs have been studied, also has activity against MERS with interferon-β. The studies that were published for Interferon-α and -β reported that these agents combined with ribavirin and/or lopinavir/ritanovir for maximum activities. As other agents that using in COVID-19 treatment, the effectiveness of these agents depends on the time of treatment so, delayed treatment may limit the effectiveness. Clinical trial studies absence and relying on data from animal and in vitro studies, interferon's using in COVID-19 management is not recommended (26). Interferon is listed as an alternative and may combine with other therapy regimens in the Chinese guidelines. Traditionally, other agents that have an immunomodulatory effect is indicated for a non-infectious indication that demonstrates in vitro effectiveness or may have mechanisms of action purported to inhibit SARS-CoV-2, such as baricitinib, Imatinib, dasatinib, and cyclosporine (27). However, for the use of these agents in SARS-CoV-2 management, there is no animal or human data exist, and it stays to be seen whether these agents give preservation for patients already using these agents for other indications.

Nitazoxanide

Anti-helminthes therapy, which has a broad antiviral effect with a relatively profile of safety. It has displayed in vitro activity as antiviral for the management of MERS also for SARS-CoV-2 management. Until new other evidence, the Nitazoxanide activity as antiviral, immunomodulating activity, and the drug safety properties warrant its other study as a COVID-19 management option (28).

Camostat mesylate

In Japan, this agent approved as a typical therapy for pancreatitis, blocks in vitro nCoV cell entry by suppression of the host serine protease, TMPRSS2. Camostat mesylate has a unique mechanism which gives attention to the drug as a target for further research (29). This discovery has enhanced a discussion for whether ACE inhibitors agents or agents that block the angiotensin receptor may treat COVID-19 or may worsen the case. These agents can enhance the receptors of ACE2 and may worsen the outcomes if it increases the ability of the virus to enter the host cells. Besides that, the drugs that block the angiotensin receptor agents have a clinical advantage by its activity on ACE2 receptors (30).

Remdesivir

Also named as GS-5734, which is a prodrug of monophosphate, as a prodrug this agent undergoes the metabolism process to yield its active metabolite which is an active analog of C-adenosine nucleoside triphosphate. This drug has antimicrobial effects by its activity toward the RNA of the virus, like Coronaviridae and also Flaviviridae. One study developed on remdesivir which suggests the activity of this drug during the outbreak of the Ebola virus, due to the remdesivir specific characteristics like low EC50 and its selectivity to the host polymerase against the Ebola virus (31). Remdesivir as a drug is a potent therapy in COVID-19 management because it has a broad spectrum effect toward many kinds of nCoVs, like SARS-CoV-2 and the EC50 equal to 0.77 μM. Remdesivir prevented lung hemorrhage, in murine lung infection models of

MERS-CoV, which decreased the virus titers in the lung in proportion to comparator agents (32). Remdesivir pharmacokinetics and safety were estimated in single also in phase of multiple dose of the clinical trials. Intravenous infusions from (3mg to 225mg) were safely tolerated with no evidence for liver toxicity or the toxicity of the kidney, which showed pharmacokinetics linear activity in the range of dose and within intracellular estimated half-life up to 35 hours, elevation both of aspartate aminotransferase and also the alanine transaminase following multiple-dose administrations of remdesivir (33). The investigational dose of remdesivir is 200-mg as a loading dose, then by the dose of 100-mg every day as an infusion. During this agent treatment time, there is no need to adjust hepatic or kidney function, but as initial therapy, it is not liable for patients which have an estimated glomerular filtration rate of lower than (30 mL/min). Clinically, remdesivir used at the beginning as a therapy for Ebola management, even more, the using of remdesivir as a therapy in SARS-CoV-2 management have been reported (34). Many clinical trials are estimated the remdesivir safety profile and its activity against viruses in patients that infected with the virus of SARS-CoV-2, in mild, moderate, and severe stages of virus (NCT04292899, NCT04292730, NCT04257656, NCT04252664, NCT04280705) (35).

Favipiravi

named T-705, it is a prodrug of a Purina nucleotide, ribofuranosyl-5′-triphosphate, Favipiravir mechanism of action via RNA polymerase inhibition, stopping the viral replication. The preclinical Favipiravir data are obtained from its activity on the influenza virus and Ebola; also, it showed a broad effectiveness toward other RNA types of viruses (36). The EC50 in vitro value for Favipiravir during COVID-19 managements was 61.88 μM/L, according to the type of infectious indication. The dosing regimens have been designed. The reason for Favipiravir dosing variations is the low values of EC50 which used in influenza when compared with the dose that used in Ebola and SARS-CoV-2 (37). Favipiravir loading dose is 2400 mg - 3000 mg every twelve hours as two doses then the maintenance dose as 1200 mg - 1800 mg every twelve hours. Half-life of Favipiravir is about five hours, and the adverse effects are mainly mild, which is a well-tolerated drug (38).

Adjunctive Therapies

Corticosteroids

Agents that are mainly used to reduce inflammatory responses in the lungs of the host may lead to acute injury in the lung and acute respiratory distress syndrome. Corticosteroids risk against benefit including delaying in virus clearance and stimulating the harmful activity of secondary infection. Although the direct corticosteroids evidence in the treatment of SARS-CoV-2 is restricted or maybe as clinical outcomes survey in other viral types of pneumonia (39). Observational studies reported that there is no relationship between corticosteroids and improved survival in patients with SARS and MERS, but showed a relationship to the delayed of the virus clearance from the patient respiratory tract and also from the blood with high complications rates such as an increase in blood sugar level, and necrosis in the blood vessels (40). Chinese retrospective study on two hundred one patients, these patients progressing to acute respiratory distress syndrome when infected with a virus of SARS-CoV-2, which discovered that there is a decrease in the risk of death after patients receiving to methylprednisolone therapy, reduction percent is 46% when using steroids versus 62% without steroids using (41).

Immunomodulatory Agents

Monoclonal antibodies are adjunctive therapies for COVID-19 which is directed against cytokines (cytokines are inflammation key) or against other aspects of the innate immune response. The immune response in COVID-19 amplified which leads to enhancing cytokine release which is called "cytokine storm "this describes the pathophysiology mechanisms of organ damage like lungs and another organ damage (42). Based on the early series case from China, IL-6 is represented as the key driver of the inflammation dysregulation. Therefore, the monoclonal antibodies improve clinical outcomes by its damping effect against IL-6 (43).

Tocilizumab

Monoclonal antibody which has an antagonism effect against the interleukin-6 receptor. It is one of FDA approved therapy that used in the management of rheumatoid arthritis disease also used for the syndrome of cytokine release that is followed by chimerical therapy of antigen specific for T-cell receptor, in order that, it is used in severe cases of COVID-19 disease. In one study which includes 21 patients that received Tocilizumab as (400mg) dose during COVID-19 infection, from total patients about 91% showed clinical improvement after receiving management, by measuring the respiratory function improvement, with successful discharge, noted that most patients in this study receiving only one dose (44). In China, there are many randomized controlled trial studies underway on

Tocilizumab, which used this drug as monotherapy or combine it with other agents for treatment of COVID-19 infected patients and these patients progress to severe pneumonia (NCT04310228, and ChiCTR200002976), also in these studies the current Chinese national treatment guidelines included (27).

Sarilumab

Which is an approved therapy in management rheumatoid arthritis by its antagonism activity on IL-6 receptor, in multi-center and double-blind of phase 2/3 trial this agent studied, these studied including hospitalized patients whose infected with severe COVID-19 disease (NCT04315298) (45). Different types of monoclonal antibody and other agents that have immunomodulatory activities studied mainly by Chinese clinical trials or available in the United State for expanded access, these agents like:

Bevacizumab

Clinically, it is an anti–vascular endothelial growth factor agent; NCT04275414.

Fingolimod

With the immunomodulatory activity that was approved as atypical therapy in multiple sclerosis treatment; NCT04280588.

Eculizumab

This agent act as an antibody which inhibits terminal complement; NCT04288713 (35).

Immunoglobulin Therapy

Convalescent plasma which may name as hyper immune immunoglobulin's, acts as an adjunctive therapy that is used in the management of COVID-19. The rationale for using this manganese is the recovered patients' antibodies which have an activity against free virus or for infected cell immune clearance (46). Anecdotal protocols reported that the convalescent plasma act as a salvation agent in the treatment of SARS also for MERS. Giving the convalescent plasma to the COVID-19 infected patients was correlated to mortality rate reduction (47). Theoretically, the convalescent plasma benefits would start in the first seven to ten days of infection, within this time the viremia be at its peak of activity and the primary response of immunity has not occurred. The first report was recently published in China for treating uncontrolled case series designed for five critical illness patients infected with COVID-19 using convalescent plasma to these patients (48). In China, Wuhan city, another case series was published for three patients infected with COVID-19, intravenous immunoglobulin used as a management for these patients in a different dose which ranged from 0.3 to 0.5 g/kg/d in a period of therapy for five days (49). The FDA released guidance On March 24, 2020, for requesting investigations for discovering new drugs and tries to find an application and screening donors for convalescent plasma (50).

Agents under investigation for COVID-19

Theoretically, there are some agents that are investigated and considered as a management line for COVID-19 infective patients. Until now these agents cannot be recommended and should be avoided unless additional supporting evidence will be found.

Anakinra

Act as an antagonism for the receptor of Interleukin-1 which hypothesized to suppress the cytokine storming. There is no data for using this agent in COVID-19 as adjunctive therapy. Also, there are no data from clinical trials until now are registered in China or in the exploring of the United States for the use of this agent in the management of COVID-19 (51).

Arbidol (Umifenovir)

This drug is used in Russia and China as influenza virus therapy, in China, there are many clinical trial studies that used this agent as an oral dose of (200mg) giving three times a daily for a period not exceed ten days in the COVID-19 treatment. No clinical data existing until now, also this agent not available in the United States (51).

Baricitinib

This is an enzyme that inhibits the Janus kinase family, presented as a therapy for COVID-19 infected patients from artificial intelligence. There is no clinical data until now that exists for the use of this agent as a therapy for COVID-19 (52).

Bevacizumab

This is a humanized recombinant monoclonal antibody that inhibits the vascular endothelial growth factor connection with endothelial receptors Flt-1 and with KDR, in the United States approved for multiple cancers. In Chinas clinical trial Bevacizumab evaluated for COVID-19 (NCT04275414) no data that exists until now (51).

Brilacidin

Clinically developed by Innovation Pharmaceuticals as a host defense peptide mimetic. This company recently announced that they will start testing Brilacidin against COVID-19 from the week of March 16, 2020 (51).

Darunavir/cobicistat

Act as inhibitor HIV-1 protease which actually starting evaluation in a clinical trial (NCT04252274), also there is no data that exist at this time for using this agent in COVID-19 management (51).

Disulfiram

Is a thiuram derivative that inhibits the oxidation of alcohol, demonstrated its ability as a

competitive inhibitor for the papain-like proteases of SARS and no existing clinical data for COVID-19 (53).

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