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REVIEW: Drugs Using for COVID-19 Treatment: A Narrative Review

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ABSTRACT

The Novel Coronavirus Disease 2019 (COVID-19) was identified firstly in CHINA. Manifestation of this disease can be in wide range from asymptomatic to severe critical disease. All gender and ages are at risk for Covid-19 infection in other hand, COVID-19 was known as respiratory infectious disease but this infection may present with other organ injury.
Although effective drug for COVID-19 treatment not approved but some antiviral agents and immune modulating treatments may be beneficial. The aim of this study is to evaluate the medications using for treatment patients with Covid-19 infection. Although effective treatment not approved for covid-19 but Remdesivir, as antiviral agent, and dexamethasone are recommended for use in hospitalized patients.

Introduction

In December 2019, the new coronavirus was recognized in China's Hubei province. The Coronavirus Disease 2019 (COVID-19) caused Pneumonia and lung infection and expanded quickly in all of the world (1). In The February 2020, World Health Organization (WHO) Announced infectious coronavirus disease 2019 officially. Until the end of December 2020, 75 Million Infection to COVID-19 and One and about half million death reported in the world (2).

Every individual may exposure to sever infection of coronavirus but the risk is the highest in people older than 60 years old with chronic disease. Hospitalization and mortality rate in patients with chronic disease increased 6 times and12 times than health people Respectively (3).
COVID19 respiratory disease may be pretend without symptom or respiratory illness mild to moderate disease (80%), sever symptoms (15%) and even critical illness (5%) (4)

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Table 1. Classification of COVID-19 severity

Asymptomatic	Positive PCR test for SARS-CoV-2 No clinical signs or symptoms Lung CT-scan: without changes
Mild	Positive PCR test for SARS-CoV-2 Clinical manifestations: fever, chills, cough, sore throat, muscle aches, diarrhea, headache, myalgia, loss of smell, nausea, vomiting Lung CT-scan: usually without changes
Moderate	Positive PCR test for SARS-CoV-2 Clinical manifestations: fever and pneumonic findings with abnormal Respiratory sounds such as Wheezing and Crackles Lung CT-scan: less than 50% lung involvement with bilateral ground-glass changes and consolidation Saturation of oxygen (SPO2) is above 94%
Severe (15%)	Positive PCR test for SARS-CoV-2 Clinical manifestations: shortness of breath, dyspnea, nausea, vomiting, diarrhea Lung CT-scan: more than 50% lung involvement with bilateral ground-glass changes, consolidation and pleural effusion Saturation of oxygen (SPO2) is less than 94%.
Critical (5 %)	Positive PCR test for SARS-CoV-2 Clinical manifestations: shortness of breath, involvement of other organs such as kidney, heart, liver with acute respiratory failure and septic shock Lung CT-scan: more than 50% lung involvement with bilateral ground-glass changes, consolidation and pulmonary nodules Saturation of oxygen (SPO2) is less than 94%.

Table.1 demonstrated severity illness of COVID-19.

COVID-19 often spends Incubation period during 2 to 14 days. This infection including early and late stages. In early phase, the virus replication. In later stage the host inflammatory response leads to organ damage (5).

Recent study demonstrated that 15 percent of patients suffer of severe symptoms and 2 percent is hospitalized in intensive care unit (ICU). Common symptoms reported including: Fever, chills, cough, muscle aches, shortness of breath, headache, loss of appetite and gastrointestinal symptoms (6).

Laboratory findings demonstrated blood disorders such as Leukopenia, leukocytosis and lymphopenia. Other laboratory disturbance positive CRP (C-reactive protein), high ESR (Erythrocyte sedimentation rate), high Hepatic transaminases (AST, ALT), elevated Lactate dehydrogenase (LDH) Increased levels of ferritin, positive D-dimer have been reported (7). Chest CT scan demonstrated bilateral consolidation or ground glass opacity in the lungs of all the patients with Covid-19 that compatible with viral pneumonia (8).

Although effective treatment not approved for covid-19 (9) but Antiviral agents and immune modulating treatments may benefit to improve hospitalize patient. In other hand, COVID-19 was known infectious respiratory disease but this infection may present with heart problems, kidney and liver failure and neurological injuries caused to death. In this study, the most important drugs that used to COVID-19 treatment was investigated.

Methods

Our goal is to presentation medications used to COVID-19 treatment. Drugs used for COVID-19 in English articles and guidelines were searched. Biomedical databases comprised PubMed, Scopus, Web of Science and Google Scholar. Authors performed the searches and imported each article into

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the bibliographic software EndNote X20 (Thomson Reuters). The records were evaluated and Classify based on the type of drug used. Eventually, the full text of the selected articles and guidelines was reviewed.

Results

1 Antiviral therapy for coronavirus disease 2019

As mentioned, the COVID-19 consists of early and late phases. Replication of the virus in the early stage lead to development of clinical symptoms (10). So, antiviral drugs are effective at the beginning of the disease and before the illness progresses.

1.1 Kinase Inhibitors: Baricitinib and Other Janus Kinase Inhibitors, and Bruton's Tyrosine Kinase Inhibitors

The kinase inhibitors especially Baricitinib can prevent phosphorylation of crucial proteins involved in the signal transduction. Baricitinib use with approved dose for treatments in COVID-19 patient Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins. Baricitinib have antiviral effect through interference with viral endocytosis, potentially preventing to progress infection. In rare case, when corticosteroids cannot be used recommends Baricitinib in combination with Remdesivir for the treatment of COVID-19 in hospitalized patients (11).

1.2 The use of Chloroquine / Hydroxychloroquine for Coronavirus Disease 2019 (COVID-19) Treatment

The mechanism of CQ is inhibiting the virus life cycle at different stages(12).CQ and HCQ with three activity ,control the cell life process such as glycosylation of ACE2, endosomal alkalization and increasing lysosomal proteins (13). In the current COVID-19 pandemic, wear a mask, isolation, quarantine and social distancing are the preventive approach that have been effective in COVID-19. CQ and HCQ were used to prevent SARS-CoV-2 infection but a few researches demonstrated that CQ&HCQ cannot effective in treatment and prevention of covid-19 And the use of this drug in the treatment of COVID-19 is very controversial(14).In this studies, excluded individuals with glucose-6-phosphate dehydrogenase deficiency, retinal disease, or substantial cardiac disease who were allergic to hydroxychloroquine (15).

1.3 Remdesivir

Remdesivir is one of the best broad-spectrum antiviral drug, which was used against SRAS-CoV and MERS-CoV. As well as, the lung function of mice infected with SRAS-CoV-2 in animal study significantly improved by Remdesivir .patients who suffered of severe COVID-19 infection Remdesivir cause Clinical improvement (16). Remdesivir has known one of the most useful drugs for the treatment of COVID-19 and so was approved by US FDA(14). Liver damage is the most important adverse effect in patients treated by Remdesivir (17)

Remdesivir is a prodrug of a nucleotide analogue that neutralizes viral RNA polymerases and prevent of transcription and proliferation viruses. Antiviral effect of this drug including members of several virus families, including filoviruses (Ebola) and coronaviruses (SARS-CoV)and Middle East respiratory syndrome coronavirus [MERS-CoV]) and effective on covid19.This drug received FDA approved in individuals with upper 12 years old and at least 40kg.In hospitalize patient ,when O2saturation become lower than 94% use of Remdesivir indicated(18).

Remdesivir Adverse effects including: high blood glucose, increased ALT, AST& bilirubin level, acute kidney injury (AKI), increase serum creatinine, decreased glomerular filtration rate (GFR).

1.4 Lopinavir/Ritonavir+ Ribavirin

Recent clinical trial reported COVID-19 patients receiving treatment of combined IFN-1b, LPV/r, and ribavirin (triple antiviral therapy) have faster recovering in comparison with LPV/r treatment alone and

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exhibited improvement clinical injuries in patients with mild to moderate COVID-19(19).

1.5 Famotidine

Famotidine, a specific histamine type 2 receptor antagonist that appropriate candidate for coronavirus disease 2019 (COVID-19) treatment. Famotidine has long history safe use that may benefit immune modulation. Recent study demonstrated in patient with sever COVID -19 release of pathological histamine occurred that may induce acute respiratory distress syndrome. Use of famotidine in these patients caused the level of inflammatory cytokines (IL12,1L10, TGFb) become low with inverse agonism of histamine type 2 receptors. Famotidine inhibits the 3-chymotrypsin-like protease, these proteins essential for viral replication (20).

1.6 Bromhexine

Recent studies showed, SARS-CoV virus imported to human cell through human cell protease such as Transmembrane serine proteases (TMPRSS) and elastases. As well as, presence of the ACE2 receptors have essential for lung cells infection. TMPRSS& ACE2 play essential role in expanded virus in human lung cells. Bromhexine hydrochloride and famotidine could also be used as an inhibitor of TMPRSS2 for the treatment of coronavirus infections because with inhibiting TMPRSS2, The virus entering to the lung cells significantly reduced (21).

2 Immunomodulators

2.1 Interferon (Alfa, Beta)

Interferon is derived its name from virus interference that make anti-inflammatory and antiviral effects. IFN-α, IFN-β& IFN-γ are the most important interferon in human. Type 1 IFNs have been divided into two groups: IFN-α, which is secreted largely by leukocytes, and IFN-β which is produced by fibroblasts. Type II IFN, is known as IFN-γ, is synthesized primarily by T lymphocytes and natural killer (NK) cells. Interferon stimulate to produce protein kinase enzyme and in following inhibiting virus proliferation and induce anti-inflammatory effect(22).

Only in early stage to corona virus infection, interferon induce antiviral effect but in progressive and critical form of infection not recommend use of interferon(15).

Fever, nausea & vomiting, headache, Anorexia body aches, chest pain, flu symptoms; pale skin, easy bruising, unusual bleeding (nose, mouth, vagina, or rectum), purple or red pinpoint spots under your skin; swelling, bruising ,depression, elevate AL&AST Enzyme are the important side effects of Interferon.

2.2 Interleukin-6 Inhibitors

Tocilizumab is a recombinant humanized interleukin-6 receptor blockade .IL-6, involved in the inflammatory cascade with well-known Commercial brand RoActemra® or Actemra®. Tocilizumab and Sarilumab are IL-6 receptor blockade drugs that inhibit production of cytokine and prevent acute phase reaction. Recent study demonstrated Tocilizumab in dose-dependent process decreases in neutrophils. serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides elevated moderately in tocilizumab recipients. AS well as, hepatic transaminases (ALT&AST) high increased (23).

interleukin-6 receptor blockade might useful to improve the hypoxemic respiratory failure, and decrease the necessity of supplemental oxygen (4) and so, recommend in combination with a course of dexamethasone therapy. In recent study demonstrated, tocilizumab improved in-hospital survival (15).Serious infections became low in patients who received tocilizumab. In ill hospitalized patients with Covid-19, single dose of either tocilizumab (8 mg per kilogram of body weight and up to a maximum 800 mg per dose) Tocilizumab was not operative for preventing intubation or death(24).

2.3 Interleukin-1 Inhibitors

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to

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treat rheumatoid arthritis .Recent study demonstrated that in patients with COVID-19 Endogenous IL-1 is high and anakinra at a daily dose of 100 mg subcutaneously in adult patients, suppress the activity of pro inflammatory cytokines IL-1α and IL-1β that useful for control sever lung inflammation (25) .

2.4 Statins

Recent studies demonstrated, Statins inhibit the Toll-like receptor (TLR)–MYD88–NF-κB proinflammatory pathway .MYD88 pathway plays important role in inflammatory cascade and antioxidative defense. Through these mechanisms, statins benefit in COVID19 infections(26).Cytokines (such as IL-10) have a vital role in the progression in development of acute respiratory distress syndrome (ARDS), atorvastatin or 25-hydroxycholesterol suppress IL-10 expression and significantly increased the Th1 levels that are beneficial for inflammatory response. Recent study demonstrated, Statins have antithrombotic and anti-inflammatory effect with reduction plasminogen activator inhibitor-1 (PAI-1)such as rosuvastatin and atorvastatin improve vein thrombosis resolution through profibrinolytic and anticoagulant effects (27). statins may cause myotoxicity in some patients. Myalgia is more common to myopathies and rarely rhabdomyolysis. Rhabdomyolysis can induced acute kidney injury patients with COVID-19(28).

3 Corticosteroids

In late stage of Covid-19 infection, Systemic inflammatory response can lead to organ damage and lung injury. Anti-inflammatory effects of corticosteroids might prevent or mitigate these inflammatory damages (29).
Corticosteroids Use for Patients who require supplemental oxygen (non-invasive or invasive) and Mechanically Ventilated Patient. Dexamethasone recommend at a dose of 8 mg once daily for up to 10 days in patients with COVID-19 decreased mortality due to respiratory support(30). Recent studies demonstrated corticosteroids increased the percent of survival in patient severely ill COVID-19(31).

4 Antithrombotic Therapy in Patients with COVID-19

In SARS-CoV-2 infection a lot of cytokines produced especially in lungs, which eventually so-called cytokine storm that caused systemic thrombus formation in pulmonary artery. In this condition, blood levels of D-dimer and a fibrin degradation product measured. Recent study showed D-dimer levels are significantly high in patients with severe COVID-19. Anticoagulant therapy with use of low molecular weight heparin (LMWH)benefit for patients with sepsis-induced coagulopathy (SIC) criteria (32, 33).

5 COMPLMENT THERAPY: Vitamin C, Vitamin D, Zinc Supplementation

In order to the prevention and treatment of COVID-19 or its difficulties, adjunctive therapies with Vitamin C, Vitamin D, and Zinc recommended. This vitamin and mineral supplements compounds potentiality help to immune system become reinfor-cement and was hypothesized to be useful for prevention or treatment of COVID-19(34) .

6 Convalescent Plasma

Passive polyclonal antibody (Ab) available in plasma from donors who have recovered from COVID-19 that may help to improve immune system and reduced inflammation. The patients with a history of severe allergic or anaphylactic transfusion reactions, have been under supervision transfusion medicine specialist .In COVID-19 patients who received convalescent plasma, did not report any significant adverse events (35).

7 Acute Kidney Injury (AKI) and Renal Replacement Therapy (RRT)

Meta-analysis results demonstrated 42.0% patients that died of COVID-19 AKI was common damage. Rates of AKI (12.3%) and RRT use (5.4%) were high among COVID-19 patients, the AKI incidence was high in North America (34.6%) compared to Asia

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(6.9%) &Europe (22.9%). As well as patients admitted to the ICU exhibited very high rates of AKI (39.0%) and RRT use (16.3%).RRT use was known appropriate action to improve the prognosis of patients suffering from AKI (36).

Conclusion

Since the onset of the Covid_19 epidemics, various drugs have been studied to treat this disease. It can almost be claimed that no drug recommended for pre-exposure prophylaxis. In Mild to moderate non-hospitalized patients, Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for Bamlanivimab, etesevimab, Casirivimab and imdevimab monoclonal antibodies.

Of all the drugs was described, only two drugs have strong evidence in COVID-19 treatment. The only drug that is approved by the FDA for the treatment of COVID-19, is Remdesivir. This antiviral drug recommended for use in hospitalized patients who at risk of disease progression (not require supplemental oxygen), or patients require supplemental oxygen (but no invasive mechanical ventilation).

Dexamethasone, a corticosteroid, is used in patients who require supplemental oxygen (even mechanical ventilation) and has been found to improve survival in patients who require supplemental oxygen. Dexamethasone gave greatest effect in patients who require mechanical ventilation.

Conflicts of interest

The authors declare no conflict of interest.

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