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CURRENT TREATMENT OPTIONS FOR COVID - 19

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Abstract

The current pandemic of Coronavirus Disease 2019 (COVID-19) caused about 350 000 deaths in world. Currently, there are no proven effective vaccines or therapeutic agents against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Current clinical management includes supportive treatment and infection prevention and control measures. Research and clinical data regarding suggest a potential list of repurposed drugs with appropriate pharmacological effects and therapeutic efficacies in treating COVID-19 patients. In this review, we will update and summarize the most common and plausible drugs for the treatment of COVID-19 patients. These drugs and therapeutic agents include antiviral agents (favipiravir, remdesivir, hydroxychloroquine-chloroquine, lopinavir/ritonavir) and immunomodulatory agents (tocilizumab, tnf alpha inhibitors, corticosteroids, mesenchymal stem cell), among others.

Keywords: COVID-19**,** antiviral treatment.

Резюме

ТЕКУЩИЕ ВАРИАНТЫ ЛЕЧЕНИЯ COVID - 19

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Нынешняя пандемия коронавирусной болезни 2019 года (COVID-19) вызвала около 350 000 смертей в мире. В настоящее время не существует проверенных эффективных вакцин или терапевтических средств против тяжелого острого респираторного синдрома коронавируса 2 (SARS-CoV-2). Текущее клиническое ведение включает поддерживающее лечение и меры профилактики и контроля инфекции. Исследования и клинические данные в отношении этого предполагают потенциальный список перепрофилированных лекарств с соответствующими фармакологическими эффектами и терапевтической эффективностью при лечении пациентов с COVID-19. В этом обзоре мы будем обновлять и обобщать наиболее распространенные и вероятные препараты для лечения пациентов с COVID-19. Эти лекарственные средства и терапевтические агенты включают противовирусные агенты (фавипиравир, ремдесивир, гидроксихлорохин-хлорохин, лопинавир / ритонавир) и иммуномодулирующие агенты (тоцилизумаб, ингибиторы TNF-альфа, кортикостероиды, мезенхимальные стволовые клетки) и другие.

Ключевые слова: *COVID-19, противовирусное лечение.*

Түйіндеме

АҒЫМДАҒЫ COVID - 19 ЕМДЕУ ЖОЛДАРЫ

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2019 жылғы коронавирустық аурудың қазіргі пандемиясы (COVID-19) әлемде 350 000-ға жуық өлім тудырды. Қазіргі уақытта 2 коронавирустың ауыр жіті респираторлық синдромына (SARS-CoV-2) қарсы тексерілген тиімді вакциналар немесе дәрілер жоқ. Ағымдағы клиникалық жүргізу демеуші емді және инфекцияның алдын алу және бақылау шараларын қамтиды. Бұған қатысты зерттеулер мен клиникалық деректер COVID-19 бар пациенттерді емдеуде тиісті фармакологиялық әсерлері мен терапиялық тиімділігі бар қайта бейіндегі дәрілердің тізімін ұсынады. Бұл шолуда біз COVID-19 бар пациенттерді емдеуге арналған ең көп таралған және ықтимал препараттарды жаңартып, жинақтаймыз. Бұл дәрілік заттар мен терапевтік агенттерге вирусқа қарсы агенттер (фавипиравир, ремдесивир, гидроксихлорохин-хлорохин, лопинавир / ритонавир) және иммуномодуляциялық агенттер (тоцилизумаб, TNF-альфа тежегіштері, кортикостероидтар, мезенхимальды бағаналы жасушалар) және басқалар кіреді.

Негізгі сөздер*: COVID-19, вирусқа қарсы ем.*

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Introduction

Coronaviruses are zoonotic viruses that may transmit the infection from animals to humans. Subtypes of coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63 and HKU1-CoV) cause mostly common cold and upper respiratory tract infections in humans (1). Recently, Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV) are also occurred as severe pneumonia outbreaks caused by coronaviruses (2). At the end of 2019, a novel coronavirus was recognized as the cause of a cluster of viral pneumonia cases in Wuhan, China. Since the 2019 Novel Coronavirus (2019-nCoV) genome has 70% similarity to the SARS-CoV, it was named SARS-CoV-2 and the disease was called COVID-19. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. The disease spread rapidly and was declared as a pandemic by the World Health Organization (3, 4).

The most common symptoms of patients with COVID-19 are fever, cough and dyspnea. Patients may have severe pneumonia, which lead to acute respiratory distress syndrome (ARDS) and may die from respiratory failure. On the other hand, infected people may be asymptomatic carriers (5-7).

Nucleic acid-based polymerase chain reaction (PCR) test is used for diagnosis of disease. The sensitivity of this test is found higher in lower respiratory tract samples. False negative results may occur due to technical reasons inherent in the test, for example, if very small amount of the respiratory specimen is collected, obtaining the sample too early or late during the infection. It has also been shown that the virus cannot be detected in respiratory samples after 12 days. Computed tomography (CT) plays important role for the diagnosis of COVID-19 pneumonia (8, 9). Ground glass opacity and bilateral irregular shade are characteristic findings in thorax-CT (10). The most common laboratory findings are lymphopenia, high C-reactive protein (CRP), Lactate dehydrogenase (LDH), ferritin and D-dimer levels (8).

Bacterial or fungal infections can be seen secondary or as co-infection. Current therapeutic options are very limited and controversial. Supportive treatment and prevention of secondary infections is the important components of the treatment (11).

Several trials are currently investigating the efficacy and tolerability of some antiviral (Favipiravir, Remdesivir, Lopinavir/ ritonavir, Chloroquine-Hydroxychloroquine) and immunomod immunomodulatory ulator drugs (Corticosteroids, IL-6 and TNF alpha antagonists, Mesenchymal stem cell, Convalescent plasma). Here we presented an overview of treatment options.

Antiviral Treatment of COVID-19

Favipravir

Favipiravir is an antiviral drug that inhibit the RNA-dependent polymerase RNA (12). It is a broad-spectrum antiviral approved in Japan for the treatment of influenza in 2014 (13). Besides its anti-influenza virus activity, it is also able to inhibit the replication of flavi-, alpha-, filo-, bunya-, arena-, noro, and of other RNA viruses (12). During the 2014-2015 Ebola virus outbreak in West Africa, an increase in survival was reported in patients treated with favipiravir (14). The dosing regimen of favipiravir for influenza includes a 3,200 mg oral loading dose (1,600 mg every 12 hours) on day 1, followed by 600 mg twice daily on days 2–5 in Japan. According to the results of a preclinical study and a clinical study from China, the regiment of 3,200 mg (1,600 mg twice daily) loading dose on day 1 followed by 1,200 mg maintenance dose (600 mg twice daily) on day 2 to day 14 is effective. Favipiravir is metabolized in cytosol in the liver but not by enzymes. Anemia, neutropenia, hyperuricemia and QT prolongation are known side effects (13). Favipravir increases the blood level of acetaminophen. Therefore, acetaminophen should be used no more than 3 gr/day in patients receiving favipiravir (15).

Favipiravir is considered as one of the potential candidates for COVID-19 treatment. Preliminary studies have found that COVID-19 is superior to Lopinavir/ritonavir in the treatment of COVID-19. A shorter viral clearance time was found for the favipiravir versus the

Lopinavir/ritonavir. Also favipiravir showed a significantly higher improvement rate in chest imaging (median (interquartile range, IQR), 4 (2.5–9) d versus 11 (8–13) d, $P < 0.001$). Additionally, fewer adverse events were found in the favipiravir group than lopinavir/ritonavir group (16). Currently, clinical studies are continuing for COVID-19 patients. These trials include non-randomized and randomized controlled trials evaluating the efficacy and safety of favipiravir alone (ChiCTR2000030113, JPRN-jRCTs031190226, and JPRNjRCTs041190120) or in conjunction with interferon-α (ChiCTR2000029600), tocilizumab (ChiCTR2000030894, NCT04310228).

Remdesivir

Remdesivir is an adenosine analogue that inhibits viral RNA polymerase. It has broad-spectrum activity against members of filoviruses (e.g., Ebola) and coronaviruses (17). It is currently under clinical development for the treatment of Ebola virus infection (18). Antiviral efficacy of remdesivir was demonstrated in an in vitro study with SARS-CoV-2 (19). It was used for the first time against SARS-CoV-2 in the USA as a compassionate use. Rapid clinical and microbiological recovery was observed in the first patient

using remdesivir. According to the results of first international observational study, clinical and microbiological improvement was achieved in 68% of 48 patients requiring oxygen support (20, 21). On the other hand, in a study in China, it was found that intravenous remdesivir did not significantly improve clinical recovery, mortality or clearance time of the virus compared to placebo in patients with severe COVID-19 (22).

According to the recently published preliminary report of the double-blind randomized trial, remdesivir is superior to placebo in patients with lower respiratory tract infection due to SARS-CoV-2. The risk of death was reduced by 30% in groups other than the severely ill group who need mechanical ventilation or extracorporeal membrane oxygenation (23).

Due to poor oral absorption of remdesivir, it is administered intravenously. Hypokalemia, hypoalbuminemia, anemia and thrombocytopenia are the most common adverse effects of remdesivir. Other reported side effects include gastrointestinal distress, elevated transaminase levels (liver enzymes), and infusion site reactions (24).

Lopinavir/ ritonavir

Lopinavir / ritonavir (LPV/r) is an antiretroviral drug combination inhibits protease enzyme.

It was used in MERS-CoV and SARS-CoV outbreaks because it has antiviral effects against coronaviruses. In the SARS outbreak, patients who received LPV/r (usually in combination with ribavirin and corticosteroids) had lower mortality rates, lower mechanical ventilation requirements, and lower viral loads after treatment (25,26). Based on this information, it was thought that LPV/r might be effective on SARS-CoV-2.

LPV/r (400 mg and 100 mg, respectively) twice daily for 14 days vs standard care were compared in a trial in 199 hospitalized patients with COVID-19 in China. According to the results of this randomized, controlled, open-label study, there was no difference between LPV/r and standard care groups in terms of mortality and viral load (*27.).* Drug interactions are the most important side effects of LPV/r due to inhibition of CYP3A4. Gastrointestinal toxicities, including diarrhea, nausea and vomiting, and hepatotoxicity, increased liver enzymes are other known side effects (28).

Chloroquine and Hydroxychloroquine

Chloroquine, an antimalarial and antirheumatic drug, acts by increasing the pH of intracellular vacuoles (29). Due to Hydroxychloroquine has an N -hydroxyethyl side chain in place of the N -diethyl group of chloroquine, hydroxychloroquine has less side effects than chloroquine. It has recently been reported as a potential broad-spectrum antiviral drug. Chloroquine has been found effective against SARS-CoV-2 in vitro (19). Besides, chloroquine has immuno-modulating effect. A clinical study in China found that chloroquine reduces the duration of symptoms, accelerates radiological recovery in pneumonia, and accelerates viral clearance.

Based on these findings, it started to be used in COVID-19 therapy (30).

There are several study results on the use of hydroxychloroquine in COVID-19 treatment. In a prospective randomized trial in China, 15 patients who received only conventional treatment were compared 15 patients who received conventional treatment and Hydroxychloroquine. Viral clearance on day 7, mean viral clearance time, fever response, and CT progression were not different between the groups (31).

In another study, 62 patients with mild pneumonia and no hypoxia were evaluated. The duration of symptoms has been reported to be shortened in the hydroxychloroquine group. Azithromycin is suggested to act in combination with chloroquine/hydroxychloroquine against SARS-CoV-2 (32).

In a very recent study in Lancet, a multicenter study evaluating data from six continents published results of a study evaluating hydroxychloroquine and chloroquine effects and side effects. Treatment was started within the first 48 hours after diagnosis and patients were taken to one of the four treatment groups: I) only chloroquine, II) chloroquine plus a macrolide, III) only hydroxychloroquine, IV) hydroxychloroquine plus a macrolide. According to the results of this study, there was no difference between the four groups for recovering. There was not any benefit of hydroxychloroquine or chloroquine (when used alone or in combination with a macrolide) on in-hospital outcomes. In addition, each of the chloroquine or hydroxychloroquine drug regimens, alone or in combination with a macrolide, was associated with increased risk of ventricular arrhythmias and increased hospital mortality with COVID-19 (33). The most important factor restricting the use of hydroxychloroquine is cardiac side effects. Serious cardiac events, sudden cardiac arrests, prolonged QT and arrhythmia have been reported frequently. Due to increase in hospital mortality depending on cardiac side effects, WHO halts hydroxychloroquine trial for coronavirus amid safety concern (34).

Immunomodulatory agents for the treatment of COVID-19

Tocilizumab

Tocilizumab (TCZ) is an antiinterleukin-6-receptor (IL-6R) monoclonal antibody used in rheumatological diseases. Severe COVID-19 patients are known to be in cytokine storm. IL-6, IL-2, IL-7 and IL-10 and tumor necrosis factor (TNF) levels are very high in patients who need intensive care. Especially IL-6 levels correlated with poor clinical status and SARS-CoV-2 RNAaemia in severely ill patients (*35*). On 16 February 2020, the first case in which tocilizumab was effective has been reported, in China *(36).* The first retrospective observational study was reported from Wuhan. In this study, TCZ was applied to 15 patients infected with COVID-19 from January 27 to March 5, 2020 in Wuhan, Tongji Hospital. Two of the patients (13.3%) were moderate patients, six (40.0%) were severe patients and seven (46.7%) were critical patients. Ten patients (66.7%) had one or more comorbidities. The dose of TCZ used in patients was between 80 mg and 600 mg each time in combination (eight patients) with methyl-prednisone. The authors concluded that single-dose TCZ is not effective in combination with glucocorticoids in critically ill patients. However, they think that the use of TCZ in repeated doses may be effective in critically ill patients (37).

TNF alpha inhibitors

TNF alpha is a pro inflammatory cytokine involved in autoimmune and immune-mediated disorders. TNF alpha

inhibitors, which act by suppressing the physiologic response to TNF alpha may be used in the treatment of the autoimmune disorders.

Inhibition of TNF alpha can be achieved with a monoclonal antibody, such as infliximab (Remicade), adalimumab (Humira), or with the receptor fusion protein etanercept (Enbrel).

Two studies have been identified so far. The first study was a research letter that suggested that TNF alpha has been implicated in the severe immune-based pulmonary injury caused by SARS coronavirus, suggesting that TNF alpha inhibitors could be a potential treatment for the acute respiratory disease syndrome caused (38). The second study utilized 22 piglets to assess the efficacy of an anti-TNF alpha therapy for endotoxin respiratory diseases and observed that TNF alpha blockage was not associated with decrease in disease severity (*39*). Anti-TNFs enhance the risk of bacterial, viral and fungal infections. Therefore, their use in COVID-19 should be supported with randomized clinical studies.

Corticosteroids

Increased inflammatory responses in the lungs may lead to acute lung injury and ARDS. Corticosteroids are used to prevent this high response. Some clinicians suggest that systemic corticosteroid therapy may be beneficial for patients with COVID-19 who have elevated levels of pro-inflammatory cytokines and lung damage (40,41).

In Hubei, Liu et al showed that, 30-80 mg/day prednisolone was not beneficial in pneumonia patients (42). Wu et al. evaluated 201 pneumonia, 84 ARDS patients. Administration of methylprednisolone reduced the risk of death (P = 0.003) in subjects having ARDS for COVID-19 (43).

Another study showed that the duration of viral RNA detection for oropharyngeal swabs and feces in the corticosteroid treatment group was longer than that in the non-corticosteroid treatment group, which were 15 vs. 8.0 days (P = 0.013) (44).

According to a study conducted in two centers in China, the use of corticosteroids did not affect virus clearance time, hospital stay or duration of symptoms in patients with mild COVID-19 (45).

In the light of all this information, corticosteroid use may benefit survival in patients with ARDS or severe pneumonia. But there is no benefit in mild pneumonia or adding COVID-19 to standard therapy. Also, routine use is not recommended due to potential side effects such as impaired glucose regulation.

There are several case reports claiming that inhaled corticosteroids may also be beneficial. For example, ciclesonide is an inhaled corticosteroid that has antiviral activity against MERS-CoV. It has been reported three patients using ciclesonid have recovered (46). However, efficacy cannot be discussed with only this limited number of observational cases.

Convalescent plasma

Passive immunotherapy is a very old procedure. It used in many epidemics since 1890. The evidence of efficacy of these practices are based on studies of varying size and quality describing the clinical experience in treating viral infections, including those due to SARS-CoV, 2009 pandemic influenza A (H1N1), MERS epidemic in 2012, and against Ebola in 2015 (47-50).

All these clinical experiences were evaluated in a systematic review and meta-analysis by Mair-Jenkins et al. According to the analysis, convalescent plasma therapy reduced the mortality (51). Publications about plasma treatment in COVID-19 are case series. In addition, in 21 patients with severe pneumonia, clinical findings were reported to have improved (52).

Convalescent plasma therapy is a well-tolerated treatment and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases. The optimal dose and time point of application, as well as the clinical benefit of convalescent therapy, needs further investigation in larger well-controlled trials.

Mesenchymal Stem Cell (MSC)

Currently, stem cell therapy has become one of the promising agents in difficult-to-treat diseases. It has been shown to be effective in resistant infections that are difficult to manage. MSC treatment has some advantages;

I) They are easily accessible and can be isolated from a variety of tissues such as umbilical cord, bone marrow and adipose tissues;

II) They are multipotent stem cells;

III) It can easily expand to clinical volume in a suitable period of time;

IV) MSC can be stored for repetitive therapeutic usage, safety and effectiveness of MSC have been obviously documented in several clinical trials (53).

It has been reported with preclinical and clinical studies that MSC can regulate cytokine storm developing with immunomodulatoryy effects in sepsis and septic shock (54).

MSC show antiviral activity by suppressing viral replication, viral shedding and virus-induced lung epithelial cell damage. It has been shown to have antiviral effect against influenza, hepatitis B, herpes simplex virus (HSV), cytomegalovirus (CMV) and measles virus (55-59). MSCs reduce the expression of growth factor-beta (TGF-y), interferon-gamma (IFNy), macrophage anti-migration factor, and tumor necrosis factor-alpha (TNF-α) with immunomodulatory effects and prevent the development of lung fibrosis (60).

MSC is thought to be one of the promising agents due to these effects in the treatment of COVID-19. Leng et al. reported clinical improvements with intravenous administration of umbilical cord-MSCs into seven patients with COVID-19. All of the selected patients were positive for SARS-CoV-2 and have pneumonic infiltration on chest CT. One patient was critical type, four patients had severe type and two had milder disease symptoms. Prior to MSC infusion, all of the patients displayed high fever, shortness of breath, low oxygen saturation and pneumonia. When symptoms worsened, the patients received 1 x106 UC-MSCs/kg by intravenously and were closely followed for 14 days. Virtually all symptoms subsided within 2-4 days subsequent to MSC infusions with no adverse effects. The majority of patients tested negative for the SARS-CoV-2 nucleic acid test at a week or two after MSC infusion. They found that MSC could significantly improve the functional outcomes of seven patients without any observed adverse effects (61).

MSC treatment and cell-based treatments seem to be one of the potential treatments for COVID-19. Randomized, well controlled studies are needed in this regard.

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The authors have no conflicts of interest to declare

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