An Overview of COVID-19 Medicines in Current Guidelines

Güncel Kılavuzlardaki COVİD-19 İlaçlarına Bir Bakış

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ABSTRACT

An acute respiratory disease caused by a new coronavirus (Severe acute respirotary syndrome-coronavirüs-2, previously known as 2019-nCoV), coronavirus disease 2019 (COVID-19), appeared in December 2019 and then has spread rapidly throughout the world starting from China, Japan and South Korea. As of January 30, 2020, the World Health Organization has officially declared the COVID-19 outbreak. Considering the clinical symptoms of COVID-19, it has many symptoms such as high fever, cough, and fatigue. It is reported that this disease is very severe and causes serious consequences such as cytokine storm and acute respiratory distress syndrome in the elderly and those with chronic diseases. Currently, scientists are trying to find a specific antiviral treatment strategy. Various medications such as hydroxychloroquine, lopinavir/ritonavir, ribavirin, remdesivir and favipiravir are currently being applied in clinical trials to test their efficacy and safety worldwide in COVID-19 treatment, and some promising results have been achieved so far. In this review, agents with potential efficacy against COVID-19 are presented in summary.

Keywords: COVID-19, antivirals, treatment, SARS-CoV-2

ÖZ

Yeni bir koronavirüsün (daha önce 2019-nCoV olarak bilinen Şiddetli akut solunum enfeksiyonu-koronavirüs-2) neden olduğu akut solunum yolu hastalığı, koronavirüs hastalığı 2019 (COVİD-19) Aralık 2019'da ortaya çıkmış ve daha sonra Çin, Japonya ve Güney Kore'den başlayarak Dünya genelinde hızlı bir yayılım göstermiştir. 30 Ocak 2020 itibariyle de Dünya Sağlık Örgütü COVİD-19 salgınını resmi olarak ilan etmiştir. COVİD-19'un klinik semptomlarına bakıldığında yüksek ateş, öksürük, yorgunluk gibi birçok semptomu vardır. Yaşlılarda ve kronik hastalıkları olanlarda bu hastalığın çok ağır geçtiği ve sitokin fırtınası ile akut solunum sıkıntısı sendromu (ARDS) gibi ciddi sonuçlara neden olduğu bildirilmektedir. Şu anda bilim insanları tarafından spesifik antiviral tedavi stratejisi bulunmaya çalışılmaktadır. Hidroksiklorokin, lopinavir/ritonavir, ribavirin, remdesivir ve favipiravir gibi çeşitli ilaçlar şu anda Dünya çapında COVİD-19 tedavisinde etkinliklerini ve güvenliklerini test etmek için klinik çalışmalarda uygulanmaktadır ve şimdiye kadar bazı umut verici sonuçlar elde edilmiştir. Bu derlemede, COVİD-19'a karşı potansiyel etkinliği olan ajanlar özet halinde sunulmaktadır.

Anahtar Sözcükler: COVİD-19, antiviraller, tedavi, SARS-CoV-2

Introduction

The Severe acute respirotary syndrome-coronavirus-2 virus (formerly 2019-nCoV) appeared in Wuhan, Hubei province of China in December 2019, and then spread very rapidly across the world, starting from China, Japan and South Korea. To date, more than 3 million cases and more than 200 thousand deaths have been reported worldwide (1). The first COVID-19 case was confirmed in Turkey on March 10, 2020 and a total of 107,773 cases were approved as of April 25th 2020, and it was reported that a total of 2,706 patients died (2). Considering the lack of effective antiviral therapy against COVID-19, current treatments

are predominantly for symptoms (3). That is why, scientists have recently intensified their work rapidly on drug therapy for COVID-19 treatment. We can use some treatment strategies against coronaviruses based on the experience of struggling in SARS-CoV and Middle East Respiratory Syndrome corona virus (MERS-CoV) outbreaks (4). Some agents have been quickly tested in clinical trials and have been reported to show activity against COVID-19 (5). The summary of current adult and pediatric patient medication guideline published by the Republic of Turkey Ministry of Health dated April 14, 2020 is shown in

Table 1. Current guideline for adult and child patient drug treatment

Name of drug	Dosage	Administration way	Time
Treatment recommendations for asymptomatic definite COVID-19 cases to be monitored as outpatient and for uncomplicated patients or patients with mild pneumonia-possible COVID-19			
Hydroxychloroquine	2x200 mg	Oral	5 days
Recommendations for COVID-19 Patients with indication for hospitalization			
Treatment in uncomplicated possible/definitely diagnosed COVID-19 Cases			
Hydroxychloroquine	2x200 mg	Oral	5 days
-/+ Azithromycin	1st day 500 mg +250 mg x4 days	Oral	5 days
Treatment in possible/definitely diagnosed COVID-19 cases with severe pneumonia			
Hydroxychloroquine	2x400 mg loading dose +2x200 mg	Oral	5 days
-/+ Favipiravir	2x1,600 mg loading dose +2x600 mg maintenance dose	Oral	5 days
-/+ Azithromycin	1st day 500 mg +250 mg x4 days	Oral	5 days
Treatment in patients whose pneumonia findings have progressed while receiving hydroxychloroquine treatment			
Favipiravir (Hydroxychloroquine treatment should be completed within 10 days and stopped)	2x1,600 mg loading dose +2x600 mg maintenance dose	Oral	5 days
Treatment in pregnants with the definite diagnosis of COVID-19			
Hydroxychloroquine	2x200 mg	Oral	5 days
-/+ Lopinavir 200 mg/ Ritonavir 50 mg	200 mg/50 mg twice a day	Oral	10-14 days
Dosages and administration ways of drugs that can be used in the treatment of children			
Hydroxychloroquine	6.5 mg/kg/dose of Hydroxychloroquine for twice on the first day; maximum dose on the first day: 400 mg/dose; on the 2nd-5th days, 3.25 mg/kg/dose of Hydroxychloroquine for twice a day: maximum dose 200 mg/dose	Oral	5 days
-/+ Azithromycin	**1-5 month children** 10 mg/kg/dose (max dose 500 mg/dose) **>6 month children and adolescents** 10 mg/kg single dose on the first day (max dose 500 mg/dose), Then, continuing with 5 mg/kg single dose a day for 2-5 days (max dose 250 mg/dose) totally 5 days	Oral	5days
-/+ Lopinavir 200 mg/ Ritonavir 50 mg	**Between 14 days-6 months:** Lopinavir 16 mg/kg PO BID **Between 6 month-old-18 year-old:** 15-25 kg: 200 mg-50 mg PO BID 26-35 kg: 300 mg-75 mg PO BID >35 kg: 400 mg-100 mg PO BID	Oral	10-14 days

COVID-19: Coronavirus disease 2019, max: Maximum

Table 1 (6,7). In the most current version of the guideline, the use of antimicrobials such as hydroxychloroquine lopinavir/ritonavir, azithromycin and favipiravir is recommended for the treatment of COVID-19 (Table 2).

Hydroxychloroquine is an antimalarial widely used in malaria, which was discovered to be a potential broad-spectrum antiviral in 2006 (8,9). Although the mechanism of action of hydroxychloroquine is not fully understood, it appears to block viral entry into cells by inhibiting the glycosylation of host receptors, proteolytic processing and endosomal acidification. This drug has also been shown to suppress cytokine production, such as interleukin (IL)-6 and tumor necrosis factor-α, and has immunomodulatory effects in host cells through the inhibition of lysosomal activity and autophagy (10,11). Chloroquine has the ability to inhibit replication cycles against human immunodeficiency virus (HIV) and other inflammation-related viruses (12).

Hydroxychloroquine has blocked SARS-CoV-2 infection at a low micromolar concentration with a semi-maximum effective concentration (EC_{50}) of 1.13 μM and a semi-cytotoxic concentration (CC_{50}) greater than 100 μM (13). Currently, there are some randomized clinical trials that examine their role in COVID-19 therapy (14). Chloroquine is known to inhibit pH dependent steps of replication of various viruses (11). Hydroxychloroquine studies are planned for post-exposure prophylaxis after chloroquine prophylaxis (NCT04303507) and high-risk exposures (NCT04308668) in healthcare professionals (15). Although the antiviral properties of chloroquine treat people with the disease, it should be remembered that this will change depending on the disease, chloroquine concentration and duration of treatment (16). Chloroquine is still the first drug that comes to mind because it leads to rapid fever reduction and an immediate improvement in lung computed tomography findings, and at least 10 clinical studies are currently being performed (17).

Scientists have used protease inhibitors of lopinavir and ritonavir along with other drugs to treat HIV-1-infected adults and children over the age of 14 years (18) and HIV-infected people (19). Chu et al. (20) have confirmed in *in vitro* and clinical

Table 2. Potential antivirals used in the treatment process of COVID-19

Name of Drug	General definition	Mechanism of action	Targeted diseases	Reference
Lopinavir/ritonavir	Protease inhibitor	Inhibition of HIV-1 protease for protein cleavage leading to non-infectious, immature viral particles	HIV/AIDS, SARS, MERS	(19-21)
Chloroquine	9-aminoquinoline	Increased endosomal pH, immunomodulator, autophagy inhibitors	Malaria, autoimmune diseases	(11,13,14,41)
Remdesivir (GS-5734)	Nucleotide analog prodrug	Interaction after entry of the virus into the host	Ebola, SARS, MERS	(42-44)
Nafamostat	Synthetic serine protease inhibitor	It prevents membrane fusion by reducing cathepsin B release; anticoagulant activities	Influenza, MERS, Ebola	(45,46)
Ribavirin	Synthetic guanosine nucleoside	Interfering with viral mRNA synthesis (a broad-spectrum activity against several RNA and DNA viruses)	HCV, SARS, MERS	(46-48)
Oseltamivir	Neuroaminidase inhibitor	Inhibiting the activity of the viral neuraminidase enzyme, preventing proliferation from the host cell, viral replication and infectivity	Influenza, viruses A	(49,50)
Penciclovir/acyclovir	Nucleoside analog	A synthetic acyclic guanine derivative resulting in chain termination	HSV, VZV	(51)
Ganciclovir	Nucleoside analog	Powerful inhibitor of the Herpesvirus family, including cytomegalovirus	AIDS-related cytomegalovirus infections	(52)
Favipiravir (T-705)	Nucleoside analog: Viral RNA Polimerase inhibitor	Influencing viral genetic replication to prevent replication without affecting host cellular RNA or DNA synthesis	Ebola, Influenza, A(H1N1)	(53-55)
Nitazoxanide	Antiprotozoal agent	Modulation of the survival, growth and proliferation of a range of extracellular and intracellular protozoa, helminths, anaerobic and microaerophilic bacteria, viruses	A wide range of viruses, including human/animal coronaviruses	(56-58)

studies that lopinavir/ritonavir has anti-SARS-CoV activity and Arabi et al. (21) have confirmed that they have anti-MERS-CoV activity. They also have demonstrated that they can cure patients.

Early reports of lopinavir/ritonavir for the treatment of COVID-19 are mostly case reports and small-scale retrospective, non-randomized cohort studies, which makes it difficult to detect the direct treatment effect of lopinavir/ritonavir. More recently, Cao et al. (22) have reported open-label randomized clinical trial results comparing the efficacy of lopinavir/ritonavir with standard care in 199 patients with COVID-19. A study conducted in South Korea reported that the viral load of a COVID-19 positive patient decreased with lopinavir/ritonavir treatment (23).

Favipiravir is currently one of the drugs that have undergone clinical trials for the treatment of COVID-19. Favipiravir is a new RNA-dependent RNA polymerase inhibitor. Favipiravir is converted into an active phosphoribosyl form (favipiravir-RTP) in cells and is recognized by the viral RNA polymerase as a substrate, thereby inhibits RNA polymerase activity (24). Therefore, favipiravir is thought to have a potential antiviral effect on SARS-CoV-2, which is an RNA virus. There are a limited number of clinical trials that support the use of favipiravir for COVID-19. In a prospective, randomized, multicenter study, favipiravir (n=120) was compared with Arbidol (n=120) for the treatment of moderate and severe COVID-19 infections. On the 7th day, clinical improvement differences were observed in patients with moderate infection (71.4% favipiravir and 55.9% arbidol, p=0.019). No significant difference was observed in the severe or severe and moderate (combined) arms (25). In another study conducted in China, considering the first results of a total of 80 patients (including the experimental group and the control group), favipiravir was shown to have a stronger antiviral effect than lopinavir/ritonavirin (26).

Azithromycin is an antibiotic from the macrolide group with a wide range of uses, especially for the treatment of gram-positive cocci. Azithromycin has been shown to be active *in vitro* against Zika and Ebola viruses and to prevent severe respiratory infections when administered to patients who have had a viral infection (27-29). Another study reported that the combination of azithromycin-hydroxychloroquine (6/6, 100%) in 6 COVID-19 patients resulted in numerically superior viral clearance compared to hydroxychloroquine monotherapy (8/14, 57%) (30).

In addition to the medicines in the above guidelines, a few more medicines attract attention. Of these, remdesivir, which was developed for Ebola, is an antiviral drug with a nucleoside analog and broad-spectrum anti-RNA (31) and shows broad-spectrum antiviral activity against several RNA viruses. Animal experiments (32) have shown that remdesivir can effectively reduce viral load in lung tissue of MERS-CoV-2-infected mice, improve lung function, and alleviate pathological damage in lung tissue. Based on data collected in the *in vitro* mouse cell culture model, remdesivir has been found to affect NSP12 polymerase in coronaviruses (23). Wang et al. (13) found that remdesivir

strongly prevents SARS-CoV-2 infection at low micromolar concentrations and has a high selectivity index. Holshue et al. (31) reported that remdesivir gave promising results in the treatment of a patient with COVID-19 in the USA. The combination of remdesivir and chloroquine has been proven to effectively inhibit the recently occurring SARS-CoV-2 as *in vitro*. Currently, randomized, placebo-controlled, double-blind phase III studies are being conducted on 761 patients in many hospitals in Wuhan, the first place of outbreak. The results of the trials are expected to be announced in the next few weeks (33). An *in vitro* activity of oseltamivir, another neuraminidase inhibitor, which is normally approved for influenza treatment, has not been documented against SARS-CoV-2. In China, the COVID-19 outbreak initially occurred during the peak influenza season, so a large number of patients underwent empirical oseltamivir therapy, not as a therapeutic intervention, until SARS-CoV-2 was discovered (34). In current guidelines, it is added to the treatment in viral pneumonia seen with COVID-19 (35). Ribavirin is also one of the new drugs added to the guidelines. It is a broad spectrum nucleoside analogue with antiviral effects. One study compared 111 patients with severe acute respiratory syndrome (SARS) treated with ribavirin and 41 SARS patients treated in combination with lopinavir/ritonavir and ribavirin; Acute respiratory distress syndrome (ARDS) and mortality risk were found to be lower in patients treated with combined therapy (20). However, ribavirin was found to have limited *in vitro* activity against SARS-CoV and was shown to require high concentrations to inhibit viral replication, which led to high dose and combination therapy (36). It is thought to have limited use for COVID-19 treatment due to its efficacy data and toxicity without ribavirin for other nCoV types (5). These drugs require more clinical evidence before they are recommended. Other drugs recommended for treatment are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, and plasma of patients recovered from COVID-19 (37-39). Among the candidate drugs to treat COVID-19, repositioning old drugs for use as antiviral therapy is an interesting strategy because information on safety profile, side effects, posology, and drug interactions is well known (40).

Discussion

For COVID-19, which started in December 2019 and spread all over the world, scientists have made great progress in the characterization of the virus, and vaccine-drug research that can actively be effective in combating COVID-19 has also accelerated. There is currently no proven antiviral specific for COVID-19. Other drugs recommended for treatment are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, and plasma of patients recovered from COVID-19 (37-39). Among the candidate drugs to treat COVID-19, repositioning old drugs for use as antiviral therapy is an interesting strategy because information on safety profile, side effects, posology, and drug interactions is well known (40). This indicates that although a pandemic is present, it is necessary to continue the work against the same pandemic with increasing difficulties. At present, more data are needed

to further demonstrate the effectiveness of antiviral treatments against the virus. In addition, studies are needed to investigate the transmission and pathogenicity mechanisms that need to be revealed. The most important issue is to reveal the molecular mechanism of viral entry and viral replication for targeted vaccine-drug studies.

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