Review

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Current Therapeutic Interventions for COVID-19

Güncel Bilgiler Işığında COVİD-19'da İlaç Tedavisi

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 is an important infectious agent that was first detected in China, causing the pandemic and death of thousands of people. Although the clinic of this disease, called coronavirus disease-19 (COVID-19), is variable, cytokine storm and different mechanisms can cause increased mortality as a result of progressive and serious clinical presentations. Since it belongs to a well-known group of viruses, researchers have gained momentum after the isolation and the identification of the features of the virus. Although specific drugs began to be developed, the first potential candidate drugs were drugs such as broad-spectrum antibiotics, antiviral agents, anti-parasitic agents, and interferon, which were planned to be used with similar indications before pandemic. Trials on all steps such as prophylactic and supporting therapies, as well as care for critically ill patients and vaccine investigation studies are still ongoing. The drugs used in the light of the guidelines were frequently updated and some changes were made as a result of reports on side effects and efficacy evaluations. Especially in some drug combinations, side effects like prolonged QT interval, drug-drug interactions, and restrictions on the use of some drugs in the pediatric age group or pregnancy limit the specific, evidence-based and reliable treatment. Although there are many drugs in the trial phase for COVID-19 treatment, the most promising and most effective drugs are discussed and summarized under the light of national guidelines and clinical evidences with all aspects of the literature.

Keywords: SARS-CoV-2, 2019-nCoV, COVID-19, drug treatment

ÖZ

Şiddetli akut solunum sendromu koronavirüs-2, ilk defa Çin'de tespit edilmiş, pandemiye ve binlerce insanın ölümüne yol açmış önemli bir enfeksiyon ajanıdır. Koronavirüs hastalığı-19 (COVİD-19) adı verilen hastalığın kliniği değişken olmakla birlikte neden olduğu sitokin fırtınası ve farklı mekanizmalar, ilerleyici ve ağır klinik tablolar sonucunda ölümle sonuçlanabilir. Virüsün izolasyonundan sonra özelliklerinin tanımlanması ve iyi bilinen bir virüs ailesine ait olması nedeniyle araştırmalar hız kazanmıştır. Hedefe yönelik uygun ilaçlar geliştirilmeye başlansa da ilk potansiyel aday ilaçlar, pandemiden daha önce benzeri endikasyonlar ile üretilmiş olan geniş spektrumlu antibiyotikler, antiviral ajanlar, anti-parazit ajanlar ve interferon gibi ilaçlardır. Profilaksi, destekleyici tedaviler, kritik hasta tedavisi ve aşı üzerine çalışmalar devam etmektedir. Kılavuzlar ışığında önerilen ilaçların kullanımı sonrasından ortaya çıkan yan etkiler ve etkinlik değerlendirmeleri sonucunda tedavi algoritmaları sıkça güncellenmiş ve bazı değişiklikler yapılmıştır. Özellikle bazı ilaç kombinasyonlarında QT süresinin uzama potansiyeli taşıması gibi yan etkilerin olması, ilaç-ilaç etkileşimleri, çocuk yaş grubu ya da gebelik döneminde kullanımıyla ilgili kısıtlamaların olması, özgün, kanıta dayalı ve güvenilir bir tedavinin olmasını kısıtlamaktadır. COVİD-19 tedavisi için deneme aşamasında birçok ilaç olmasına rağmen, en umut verici ve en etkili ilaçlar literatürdeki tüm yönleriyle ulusal kılavuzlar ve klinik kanıtlar ışığında tartışılmakta ve özetlenmektedir.

Anahtar Sözcükler: SARS-CoV-2, 2019-nCoV, COVİD-19, ilaç tedavisi

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Introduction

Coronavirus disease-2019 (COVID-19) is a pandemic and worldwide growing public health problem. There is currently no described specific established treatment for this disease. The beneficial and appropriate drug should be specific, effective in its highest level, proven with trials and suitable for pharmacological treatment. As the pandemic spreads rapidly and causes deaths, therapy is urgently becoming essential.

Some medicines which are utilized for other diseases, could potentially be beneficial for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection without definitive evidences. At this point, the therapeutic approach should be based on infections coming from similar backgrounds with similar effects.

Structural parts of coronavirus (e.g. trimeric spike (S) protein, viral DNA) or some parts from life circle (e.g. proteases, hemagglutinin esterase, NTPase/helicase, and endosomal pH challenges) are important target points for developing drugs (1) (Figure 1).

The objective of this study is to examine drugs with a higher level of evidence, which are recommended or started to be used in COVID-19 treatment. Some of these medicines are known in literature with similar indications from the past. Under the light of current guidelines, these drugs are examined according to their recommendation level and effectiveness in use.

General Palliative/Supportive Treatment

Since there is no specifically defined treatment for SARS-CoV-2, the designated therapy should be appropriate for the clinical levels specific to the condition of the patients. Symptomatic treatment includes controlling high fever or pain with an antipyretic patch or antipyretic-analgesic drug treatment. The treatment regimen could be revised to comprehend a broad perspective. Supportive therapy is vital in these patients. General supportive treatment strategies for patients with mild symptoms are shown in Table 1 (2,3).

Medical Treatment with Drugs

There is a large number of drugs, which are still in the clinical trial phase to be used in the treatment of COVID-19 disease.

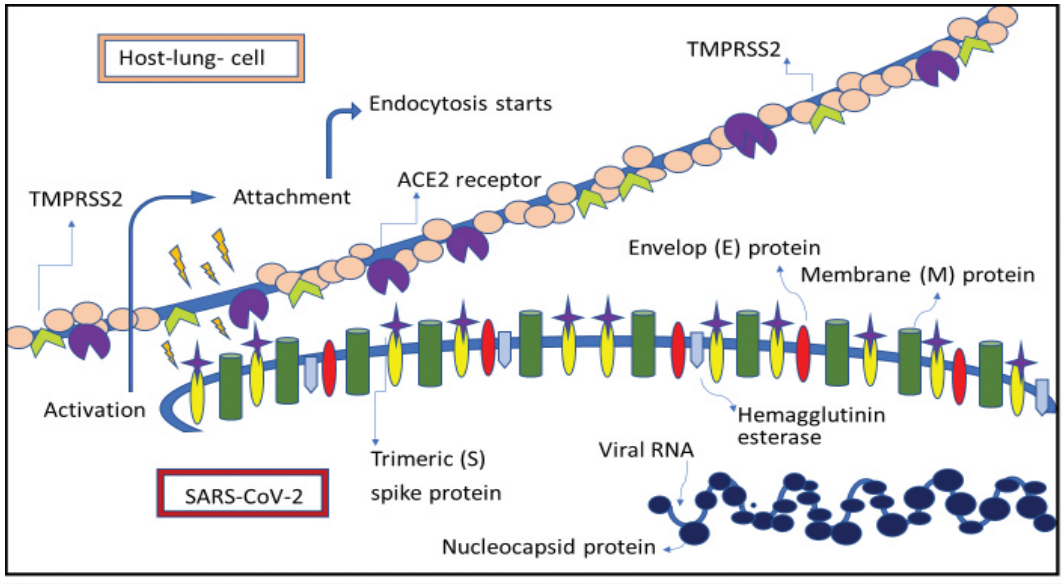

Figure 1. The structural parts of SARS-CoV-2
ACE-2: Angiotensin converting enzyme-2, TMPRSS2: Transmembrane serine protease 2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Table 1. Supportive treatment options other than specific medications (3)

General treatment strategies	Supportive care steps in critical illness
Bed resting	Prevent and treat complications, underlying diseases
Ensuring sufficient calory	Secondary bacterial or fungal infection treatment
Adequate water intake	Complete fluid resuscitation
Paracetamol	Lung protective ventilation strategy, O_2 support
İbuprofen	Prone position ventilation, lung recruitment
C vitamin	Vasoactive drugs
N-aceytil cysteine	ECMO

ECMO: Extracorporeal membrane oxygenation

Table 2. Classification of various drugs tried in COVID-19 (4,5)

Protease inhibitor	Interferon	Monoclonal antibody
-Lopinavir/ritonavir (/+ ribavirin)		-Tocilizumab
-Nelfinavir	-Interferon beta 1A	-Sarilumab (anti-IL6R)
-Camostat mesilate NI-03	-Interferon beta 1B	-SAB-301
-ASCO9 (/+ oseltamivir)	-PEG Interferon Lambda	-CDC2-C2
-ASCO9 (/+ ritonavir)	-Interferon Alpha 2A	-IFX-1
-Darunavir/cobicistat	-Interferon Alpha 2B	-M336
-Flavopiridol	-Interferon Alpha N3	-REGN3051 /+REGN3048
-Relacatib		
Anti-protozoal	RNA polymerase inhibitor	Immunemodulator
-Hydroxychloroquine	-Favipiravir	-Colchicine
-Chloroquine	-Favipiravir + interferon-α	-Hiltonol (poly-IC)
-Emetin		-Rintatolimod
Nucleoside analogue	Nucleoside analogue + reverse transcriptase inhibitor	Endonuclease inhibitor
-Remdesivir	-Emtricitabine + tenofovir	-Baloxavir morboxil
-Galidesivir		
Immunosuppressant	Fusion inhibitor	NMDA inhibitor
-Mycophenolate mofetil	-Arbidol (Umifenovir)	-Ifenprodil
Kinase inhibitor	Steroid	Neuraminidase inhibitör
-Baricitinib	-Hydrocortisone acetate	-Oseltamivir
Ribonucleoside analogue		
-Ribavirin		

Table 3. Various combination therapies in COVID-19 disease (4,5)

1. Drug		2. Drug		3. Drug
Corticosteroid	+	Rapamycine		
Hydroxychloroquine	+	Azithromycin		
Favipiravir	+	Oseltamivir		
Favipiravir	+	Tocilizumab		
Indinavir	+	Ritonavir		
Interferon beta	+	Mycophenolate mofetil		
Lopinavir/ritonavir	+	Ritonavir	+	Ribavirin
Lopinavir/ritonavir	+	İnterferon beta		
Ribavirin	+	İnterferon beta		
Ruxolitinib	+	Mesenchymal stem therapy		

Classification of drugs according to their effect mechanisms and possible combination therapies being utilized are given in Tables 2 and 3 (4,5).

Chloroquine

Chloroquine (CQ), a compound from class 4-aminoquinoline, has been used to treat malaria effectively as a cheap treatment based on its clinical safety.

CQ is also used for amebiasis, lupus erythematosus, Sjogren's syndrome and rheumatoid arthritis. Against rheumatoid arthritis, it acts by inhibiting lymphocyte proliferation, phospholipase A2, antigen presentation in dendritic cells, the release of enzymes from lysosomes, reactive oxygen species from macrophages, and production of interleukin (IL)-1 (6).

Lately, it was administered in CoV infections, SARS-CoV and Middle East respiratory syndrome-CoV (MERS-CoV). It has an effect on the immune system as an immunomodulating agent, inhibits cytokine production by suppressing T-cell activation, autophagy and lysosomal activity in antigen-presenting cells by preventing antigen processing and major histocompatibility complex class II-mediated autoantigen presentation to T-cells, and diminishes viral replication. There are ongoing and finished clinical trials on the use of CQ in COVID-19 disease because the efficacy and safety of CQ is still unsatisfactory (7).

Impaired terminal glycosylation of angiotensin-converting enzyme-2 (ACE-2) (the cellular receptor of SARS-CoV) may diminish the binding efficiency between ACE-2 on host cells and the SARS-CoV spike protein. Consequently, the binding of the virus to the receptors on the cells is interrupted and infection is averted. CQ also acts as a zinc ionophore, that permits of extracellular zinc insertion through the cell and inhibits viral RNA-dependent RNA polymerase (7).

Chloroquine vs Hydroxychloroquine?

CQ is used as phosphate and sulfate salt and it is stored in high concentrations in the liver, kidney, spleen, lungs and leukocytes. The half-life varies between 70 and 120 hours depending on the dose. It is slowly excreted from the body (8). The EC50 of CQ for SARS is 4.4 to 8.8 μM in *in vitro*, indicating that CQ could be more potent against COVID-19 than SARS (9).

In a study including 100 patients, CQ inhibited the exacerbation of pneumonia, promoted the conversion of the polymerase chain reaction test to a negative and shortened disease period however more detailed data were not reported (10).

Hydroxychloroquine, is an analogue of CQ, diverges from CQ with a single hydroxyl group attached to the end of the chain, by the way it provides low ocular toxicity. Nowadays, it is used more frequently due to the much lower side effects. Hydroxychloroquine has been shown more potent in vitro activity against SARS-CoV-2 than CQ. EC50 of Hydroxychloroquine is 0.72 μM for SARS-CoV-2 (8,11).

Although there are many data streams from all over the world, some of them indicate efficacy and acceptable safety for CQ in COVID pneumonia (5,10). In addition to that 23 trials are continuing, all in China. The trials are differed in study design, the severity of COVID-19 in the target group and application route and duration of the treatment (8).

A Chinese single center clinical trial (ChiCTR2000030417) which is not recruiting yet (n=30, 15/15); is comparing CQ phosphate as an aerosolized inhalation solution to water for atomized inhalation group (12).

In a clinical trial of 36 patients; a significant reduction of the viral carriage has been evidenced at day 6th after inclusion compared to controls with much lower average transfer duration compared to that of reported untreated patients in literature. This trial also shows decreased SARS-CoV-2 shedding with hydroxychloroquine treatment. The combination of hydroxychloroquine and azithromycin has a synergistic effect with a more efficient virus elimination, which, also provides viral carriage reduction. The clinical outcome is good (13).

In a limited study, 368 African American veteran males of different severity stages of COVID-19 disease were retrospectively evaluated. In all 3 groups; application of hydroxychloroquine and azithromycin, alone each or in combination, did not cause a significant decrease in the need for respiratory support and the number of deaths after ventilation. The increased risk of mortality was observed in the hydroxychloroquine group compared to the groups without hydroxychloroquine administration (14).

A study analysis with a multinational registry that was later retracted in June due to insufficient data advocated the restriction of hydroxychloroquine and CQ administration because of increased cardiovascular mortality detected in COVID-19 patients (15).

Dosing of Chloroquine

Dose arrangement is necessary between CQ phosphate and CQ base since 250 mg of the first one corresponds to 150 mg of the second. Based on pharmacokinetic modeling, a study recommends a dose for hydroxychloroquine 400 mg twice daily for the first day, then 200 mg twice daily for 4 days in the treatment of COVID-19, as it reached three times the potency of CQ phosphate when given 500 mg twice daily for 5 days (8).

Italian Society of Infectious and Tropical Disease, advises using CQ 500 mg twice a day or hydroxychloroquine 200 mg/day for 10 days and suggests adjusting treatment duration from 5 to 20 days, in line with the clinical severity (4).

For pediatric patients, it was also recommended in COVID-19 guideline of the Turkish Ministry of Health in different dosing regimens, 6.5 mg/kg/dose twice for the first day [maximum (max) 400 mg] and 3.25 mg/kg/dose twice for 2-5 days (16).

Side effects of CQ and some clinical conditions to be considered are shown in Tables 4 and 5, respectively (16,17).

Chloroquine in Pregnancy and Lactation

CQ has not been found to increase the risk of adverse fetal events or any harmful effects on the fetus when used in recommended doses for malarial prophylaxis, according to the American Centers for Disease Control and Prevention (CDC) guidelines. CQ and its metabolites pass the breast milk and placenta. It can be noticed in the cord blood and urine of the newborn infants (18).

There is not certain assigned pregnancy category by the Food and Drug Administration (FDA).

For children infected by SARS-CoV-2, there is no recommended dosage of CQ thus far. A dose of 50 mg/kg CQ refers to an acute poisoning and it can be fatal. In a report CQ serum concentration >25 μmol/L was considered as a predictor of lethality (18).

Mefloquine

As positive results have been published regarding the use of anti-malarial drugs in the treatment of COVID-19, recommendations began to emerge about another anti-malarial drug, mefloquine.

Mefloquine was found to have anti-viral activity against both MERS-CoV and SARS-CoV. The EC50 value of mefloquine is 7,416 for SARS-CoV and hydroxychloroquine sulfate is 7,966, CQ diphosphate is 6,538 (19).

Pangolin coronavirus GX-P2V is a workable model for SARS-CoV-2 research and the study has shown that mefloquine hydrochloride is a potential drug for treating SARS-CoV-2 infection (20).

Table 4. Side effects of chloroquine (17)

Unwanted/uncontrolled movements (including tongue and face twitching)
Deafness or tinnitus
Nausea, vomiting, diarrhea, abdominal cramps
Headache
Shortness of breath
Swelling legs/ankles, muscle weakness
Mental/mood changes (such as confusion, personality changes, unusual thoughts/behavior, depression, feeling being watched, hallucinating)
Signs of serious infection (such as high fever, severe chills, persistent sore throat)
Skin itchiness, skin color changes, hair loss, and skin rashes
Unpleasant metallic taste
Electrocardiographic changes*
Chloroquine retinopathy**
Pancytopenia, aplastic anemia, reversible agranulocytosis, low blood platelets, neutropenia, severe hypoglycaemia

*Electrocardiographic changes include conduction disturbances (bundle-branch block, atrioventricular block) or cardiomyopathy. Hypertrophy, restrictive physiology, and congestive heart failure often accompany the conditions which may be irreversible. Only two cases have been reported requiring heart transplantation, suggesting this particular risk is very low. Electron microscopies of cardiac biopsies show pathognomonic cytoplasmic inclusion bodies (67).
**Generally, chloroquine accumulates in retinal pigment cells and corneal epithelium. Accumulation in the cornea cause blurred vision; however, when the treatment is stopped, this effect will disappear but retinopathy tends to progress and can lead to permanent vision loss.

Table 5. Note some clinical situations before or simultaneously or afterwards proposing use of chloroquine (17)

Rule out the development of anemia, thrombocytopenia or leukopenia
Serum electrolyte disturbances
Hepatic and renal function dysfunction
Routine electrocardiography were recommended (rule out the development of QT interval prolongation or bradycardia)
Patient interviews to seek the appearance of visual and/or mental disturbance/deterioration
Avoid concurrent administration of other drugs known to prolong the QT interval (i.e. kinolones, macrolides, ondansetron) as well as various antiarrhythmic, antidepressant and antipsychotic drugs
Drug-drug interactions
Ask about G6PD deficiency; hepatic impairment, porphyria, seizure disorder*

*Use with caution in these patients; may exacerbate disease symptoms

Also, clinical trials are ongoing, about prophylaxis, efficacy, and safety of mefloquine. CDC suggests the anti-malarial drug mefloquine for pregnant women based on the recent FDA re-categorization of mefloquine from a pregnancy category C drug to category B.

Remdesivir

Remdesivir (GS-5734) is a mono phosphoramidate prodrug of an adenosine analog and it is manufactured by Gilead Sciences. It inhibits viral RNA polymerases activity of RNA virus families. It inhibits SARS-CoV and MERS-CoV replication in multiple *in vitro* systems, including primary human airway epithelial cell cultures at submicromolar IC_{50} values. This drug has also shown activity in a rhesus macque model of MERS-CoV infection. Remdesivir has been currently in clinical trials for the treatment of Ebola virus disease (11).

There has not been yet clearly stated any evidence of safety, optimal dosing, or effectivity for the treatment of COVID-19 disease, only *in vitro* activity against SARS-COV-2 has been shown (11). Under the light of the latest literature data, FDA has approved the use of this drug in COVID-19 on 1st of May, 2020 (emergency use authorization). The extensive guide published by the FDA provides detailed information about administration and side effects due to elevated transamine levels in the blood and infusion site reactions (21).

Immediately after remdesivir was approved by Japan on May 7, some trials like National Institute of Allergy and Infectious Diseases (NIAID) trial have resulted in some data as the drug helped patients heal faster than standard care, indicating it could become the first efficient therapy for the illness (22).

In a mouse model of SARS-CoV pathogenesis, the prophylactic and early therapeutic use of remdesivir markedly decreased lung viral load and improved clinical condition besides respiratory functions (11).

Airway resistance or accumulation of debris in the airway was markedly ($p<0.05$) elevated in vehicle-treated animals (mice) as compared to those treated with GS-5734. Prophylactic

administration of GS-5734 mitigated lung virus titers, improved lung function, and ameliorated symptoms of COVID-19. On the other hand, therapeutic post-exposure administration of GS-5734 appeased illness in this wide spectrum trial (23).

In an unpublished trial, which consists of 12 infected rhesus macaques with SARS-CoV-2, the treated group with remdesivir was significantly healthier than the untreated group and had a less viral load and less damage in lungs (24).

Fifty-three patients' data from multicenters were involved in a trial of compassionate use of remdesivir without any control groups. There were 2 deaths because of adverse effects resulting in liver and renal failure. Thirty-two patients (60%) were developed adverse events during the treatment period. The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. Generally, adverse events were more severe in critical cases such as -multi-organ-dysfunction syndrome, septic shock, and hypotension (25).

There is an evidence of *in vivo* administration of remdesivir for prophylactic and therapeutic use against MERS-CoV infections in mice. Remdesivir improves pulmonary function and severe lung pathology, as well as reduces viral titers in the lung (26). Further, experiments in mice using remdesivir showed higher efficacy than lopinavir/ritonavir + interferon (IFN)-β (27).

Moderate or severe ill COVID-19 cases with respiratory problems who received remdesivir, recovered quickly than similar patients who received placebo, according to a preliminary data analysis from a randomized, controlled trial including 1063 hospitalized patients (28).

In contrast, in a double-blind randomized trial including 237 Chinese patients with severe COVID-19 (hypoxia and radiographically confirmed pneumonia), duration to clinical healing was not statistically different with remdesivir compared to placebo for 10 days (29).

NIAID investigates therapeutics, as there is not a clear dose regimen schema for adults and adolescents with acute Ebola virus disease, it suggests as following; single remdesivir 200 mg IV loading dose on the first day of treatment followed by 9th to 13th day (if virus has still been detectable in plasma) once daily 100 mg IV maintenance dose. It has an intracellular half-life of longer than 35 hours.

For pediatric patients with body weight <40 kg, a body weight-based dosing regimen of one loading dose of remdesivir 5 mg/kg IV (max 200 mg) on day 1, followed by 2.5 mg/kg/dose IV once daily (max 100 mg) was used in 41 pediatric patients involving 2 neonates who were in a phase 3 Ebola trial (30).

Ribavirin

Ribavirin, a guanine analogue, which inhibits viral RNA-dependent RNA polymerase in other coronaviruses, is also a candidate for COVID-19 treatment. Nowadays, only *in vitro* data is available regarding the activity of ribavirin on SARS-CoV-2. Ribavirin seems to be less potent *in vitro* than CQ and remdesivir (11). In a systematic review of ribavirin treatment in patients infected with SARS-CoV, 26 trials were inconclusive, and 4 showed potential harm as in Canada 2003. Additionally, it decreased the amount of hemoglobin as a side effect in cases needing respiratory support (27,31).

An open-label study resulted in 2004, compared a historical control group of 111 cases who were administered only ribavirin with 41 cases who were received a combination of lopinavir/ritonavir (400 mg/100 mg) and ribavirin. Ribavirin alone had no significant beneficial effect in reducing adverse clinical outcomes such as death and reducing the viral load of SARS-CoV (32).

Interferons

Interferons have antiviral properties and they have been evaluated as a potential treatment for COVID-19 disease but with lack of data in this regard. Some clinical trials have not been yet published or concluded, support of using interferons, alone or in a combination.

A clinical trial of 350 critically ill patients with MERS-CoV was evaluated. Mortality rates were higher in patients who received ribavirin and interferon than compared to the group without any medication (33). In 301 patients with ARDS, intravenous IFN-β1-α administration had almost same ventilation time and mortality rate compared to placebo (34). IFN-β is better tolerated in terms of its side effects than IFN-α.

Lopinavir/Ritonavir

Lopinavir, a repurposed drug for the treatment of MERS-CoV and SARS-CoV, is an antiretroviral medicine primarily used for human immunodeficiency virus (HIV) infection (27,32). Lopinavir is combined with ritonavir, which inhibits the cytochrome p450, by the way plasma half lifetime of lopinavir is extended.

As it has been used for the treatment of HIV-positive pregnants, there is a wide experience for good safety. Although lopinavir is found in the breast milk at a much lower amount, according to World Health Organization (WHO) guidelines, several safer treatment options are recommended to treat HIV-infected mothers (35). It was also recommended by Turkish Ministry of Health, COVID-19 guidelines for use in pediatric patients (16).

According to a clinical trial of the combination of lopinavir/ritonavir with ribavirin or IFN-α, viral load was reduced, and survival improved among SARS and MERS patients (32,36).

Retrospective comparative analysis in MERS, lopinavir/ritonavir ensured ARDS or death reduction from 28% to 2.4% (27).

A randomized clinical trial was compared lopinavir-ritonavir therapy and standard-care therapy in hospitalized SARS-CoV-2 infected patients. There was no clinical improvement or difference in mortality at 28 days or detectable viral RNA load at various time points. Nevertheless, gastrointestinal adverse events were more common. Although skin eruptions, QT prolongation, pancreatitis, drug interactions due to CYP3A inhibition was observed in the lopinavir-ritonavir group, serious adverse

events/complications such as ARDS or acute kidney injury and pneumothorax was more common in the standard-care group (37).

Favipiravir

Favipiravir (T705) is a purine nucleic acid analog of pyrazine carboxamide derivative (6-fluoro - 3-hydroxy - 2-pyrazinecarboxamide), which is an antiviral drug developed for the treatment of influenza and it was used during the Ebola virus outbreak. It increased the survival rate and reduced viral load in Ebola virus-infected patients. Nowadays, it is being evaluated for the safety and efficacy in patients with COVID-19 (38). So far registered clinical trials are expected to be beneficial. Clinical trials are ongoing about different dosing regimens of favipiravir alone or combined with tocilizumab, CQ, IFN-α and, other antiviral treatments for the use of COVID-19 disease. In a clinical trial, no evidence of difference in the improvement of patients' condition between favipiravir and arbidol treatment has been shown (39).

For dosing there is a preliminary *in vitro* and preclinical data from China that the regiment of 3,200 mg/day loading dose on day 1, followed by 1,200 mg maintenance dose on day 2 to day 14 is effective or, a loading dose is recommended (2400 mg to 3000 mg every 12 hours, 2 doses/day) and followed by a maintenance dose (1200 mg to 1800 mg every 12 hours). The half-life of favipiravir is approximately 5 hours (40).

Corticosteroids

ARDS is the major lethal clinical picture due to SARS-CoV-2 infection**.** Corticosteroids can reduce the host inflammatory responses in the lungs with potent anti-inflammatory effects and a potential therapeutic role in suppressing cytokine-associated lung damage with acute lung injury.

During community-acquired pneumonia, the effect of corticosteroid treatment was investigated through the systematic review and meta-analysis of randomized trials. Reduced parameters were found to be mortality (3%) and mechanical ventilation support (5%), and length of hospital stay (about 1 day) (41).

Generally, there is no certain data came up to expect that COVID-19 disease will benefit from corticosteroids. On the other hand, their harmfulness must not be ignored. Some authors conclude that corticosteroid treatment should not be administered for COVID-19-related lung injury treatment or shock without conducting clinical trials. WHO guideline also recommends not to use systemic corticosteroids for the treatment of any viral pneumonia except during clinical trials (42).

The Chinese Thoracic Society has published an expert consensus declaration involved fundamental principles when utilizing corticosteroids in SARS-CoV-2 pneumonia: the benefits and harms should be weighed prior to administering corticosteroids, corticosteroids should be used carefully in advanced stages of illness with SARS-CoV-2 pneumonia, for patients with hypoxemia due to COVID-19 or who regularly use corticosteroids for chronic diseases for further use of corticosteroids should be cautious, and the dose regimen should be low-to-moderate (≤0.5-1 mg/kg/day methylprednisolone or equivalent) and the therapy period should be less than almost 7 days (43).

Infectious Diseases Society of America Guidelines recommends corticosteroid administration in the patients who hospitalized with ARDS due to COVID-19, not all the hospitalized COVID pneumonia (44).

In contrast, different meta-analysis results of 528 patients showed that prolonged corticosteroid therapy is more effective in severe community-acquired pneumonia to reduce the mortality and risk of ARDS (45). In a systematic review consisting steroid use in 29 COVID-19 patients, 25 were inconclusive and 4 were categorized as causing possible harm (31).

In addition, increased mortality was observed due to the early administration of corticosteroids in 241 patients with Influenza-associated ARDS (46).

Corticosteroid administration should be evaluated on a case-by-case basis, based on the patient's disease status and severity, indication and underlying medical condition. More clinical research and data are needed.

Vitamin C

Beyond antiviral and antioxidant properties, vitamin C has effects on immune system response. It avoids epithelial water-channel damage due to the limitation of active neutrophil migration to alveolar medium and support for the development of more channels. It is caused by the enhancement of alveolar fluid clearance. Also, it abates lipopolysaccharide-induced acute lung injury.

Short-term high-dose vitamin C in selected patients may improve hemodynamic parameters, decrease fluid resuscitation requirements, reduce the incidence of perioperative atrial fibrillation, improve pain, and potentially reduce sepsis-associated mortality. High-dose intravenous vitamin C has also been successfully applied to 50 moderate to severe COVID-19 cases. The oxygenation index was healed in real time and all the cases finally cured (47).

On the other hand, the concern that may occur with high-dose vitamin C therapy is osmotic cell death of immune cells, but not apoptosis, which could generate a local inflammation in alveolar space. Accordingly, intravenous glucocorticoid treatment must be performed to limit possible inflammatory damage of high-dose vitamin C therapy (48).

Also, analysis of the CITRIS-ALI study has shown the efficacy of high dose vitamin C (50 mg/kg /6 hrs.) in preventing mortality from acute lung injuries as compared to placebo. This should be considered for evaluation in COVID-19 treatment (49).

Teicoplanin

Teicoplanin is a glycopeptide antibiotic used in the treatment of gram-positive bacterial infections, especially staphylococcal infections. Teicoplanin acts on an early stage of the coronaviruses

and also SARS-COV-2 life cycle by inhibiting the low-pH cleavage of the viral spike protein by cathepsin-L in the late endosomes, thus avoiding the dissemination of genomic viral RNA and proceeding the virus replication cycle. Recently an experiment showed that this activity was conserved against SARS-CoV-2 (the target sequence that serves as the cleavage site for cathepsin L is conserved among SARS-CoV spike proteins) (50). Once these preliminary results have been confirmed in a randomized clinical trial, teicoplanin will be useful for the treatment of COVID-19 (51).

Tocilizumab

Tocilizumab, an IL-6 receptor-inhibiting monoclonal antibody, was first approved by FDA for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and chimeric antigen receptor T-cell-induced severe or life-threatening cytokine release syndrome. The beneficial effect is against the amplified pathological hyperactivity of the immune response observed in COVID-19.

According to a study of 21 patients with severe or critical COVID-19, partial improvement in clinical condition and CT scan image was shown after administration of 400 mg tocilizumab mostly once, in addition to their routine care (52). There are 14 ongoing clinical trials about using tocilizumab for COVID-19 in different dose regimens, alone or in combination, administered intravenously within no less than 60 minutes (53).

The Chinese National Health Commission guidelines suggested using tocilizumab in the management steps of severe COVID-19 with widespread bilateral lung disease and elevated IL-6 (5). The SIMIT Lombardy section guidelines recommended tocilizumab in critically ill patients with ARDS. Side effects can be allergic reactions, fever, chills, increased risk of serious infections, or bleeding, gastritis, liver damage and hepatic failure, leukopenia, neutropenia, thrombocytopenia, muscle weakness, dyspnea, hypertension, etc (4).

Monoclonal antibodies are actively transported across the placenta during the last trimester (pregnancy category C). It is a large protein molecule, the amount in breast milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract (52).

Emetine

Emetine is a protein synthesis inhibitor that was used as anti-protozoan approved for the treatment of ameobiasis, it also inhibits malaria by binding to the ribosomal E site of *Plasmodium falciparum.* However, it has been used less frequently over the years because it has a significant cardiotoxic effect.

Emetine has antiviral efficacy against a wide range of RNA and DNA viruses and inhibits human CoV *in vitro* with EC_{50} reported at low micromolar. Also, emetine was observed at nearly 0.5 μM efficiently interrupting SARS-CoV-2 virus replication in Vero E6 cells (54).

Ivermectin

It is confirmed by the FDA as a broad-spectrum anti-parasitic effect for the treatment of cutaneous larva migrants. In recent studies, ivermectin has been shown to have an *in vitro* effect on SARS-CoV-2 caused by reduction in viral RNA without causing any toxicity raised from the nuclear importin-α/β-mediated transport inhibitory activity. Clinical trials are underway that explore the efficacy of ivermectin alone by real-life experience or combination with hydroxychloroquin and azithromycine, nitazoxanide. Due to their consequential and synergistic manner, ivermectin is recommended as a proposition to use in combination with hydroxychloroquine with no serious drug-related adverse events (55).

In a clinical study 1400 hospitalized SARS-CoV-2 infected patients were treated with 150 mcg/kg of ivermectin once while the second group (control group) adhered to the treatment protocol (not included ivermectin). It was found that there was a decrease in hospitalization period and mortality in the ivermectin group (56).

Oseltamivir

Oseltamivir is a neuraminidase inhibitor that has a proven beneficial effect on prophylaxis and treatment of influenza. It has taken its place among the treatment alternatives of COVID-19 due to its low side effects such as nausea and vomiting. There isn't any identified enzyme or mechanism indicating the effectivity of oseltamivir on coronavirus. Thus, its mechanism of action is not clear. Even so, it has participated in combinations of antiviral therapy in China (57). Trials evaluating only combination regimens are underway.

Intravenous Immunoglobulin and other Immunomodulator Agents

Intravenous immunoglobulin (IVIG) has many indications as a part of combination therapies in treatment of several diseases including adjuvant therapy in a more pathogen-focused (hyperimmune) form.

Convalescent (immune) plasma is a kind of plasma obtained from the patients recently recovered SARS-CoV-2 infection. It has been accepted as passive antibody therapy in the other CoV infections as well. The issues are regarding its application quantity to appropriate patients. It is recommended to be used in the last-line treatment group, especially in critically ill patients (58). Nevertheless, there are few case reports regarding administration of IVIG for COVID-19 treatment (58). The results of 7 trials of convalescent plasma or IVIG on the SARS-infected patient were inconclusive (31).

During the SARS outbreak, approximately 30% of critically ill patients developed venous thromboembolism despite the prophylactic use of low-molecular weight heparin. It was supposed to be developed due to the IVIG-induced increase of viscosity in hypercoagulable states of SARS patients (59).

Although there are different views about the use of IVIG, a study was conducted in 58 SARS-CoV-2 infected patients. IVIG

administration within 48 hours of admission of the patients to the intensive care unit, has been shown to be effective in reducing the use of mechanical ventilation, hospital length of stay and mortality of patients with severe COVID-19 pneumonia (60).

Immunomodulatory agents can be necessary before multi-organ dysfunction to attenuate systemic inflammation. Corticosteroids may use in compatibly with cytokine inhibitors such as tocilizumab or anakinra (IL-1 receptor antagonist). Generally, recovery from this advanced severe stage of illness is rare, and immediate recognition of condition and administration of such therapy may be the most vital point (61).

Hemophagocytic lymphohistiocytosis (HLH), is a severe and rare condition which can be develop in no more than 0.25-1% of COVID-19 patients during cytokine storm syndrome. Corticosteroids, IVIG, tocilizumab, anakinra, JAK inhibitors and even chemotherapeutics can be used for treatment of HLH. IVIG treatment can be administered for 2 days at the dose of 2 g/kg/day with immunoglobulin level monitoring (should not be used in IgA deficiency) (16).

COVID-19 Treatment Guidelines Panel suggests not to use the following drugs for the treatment of COVID-19: The combination of hydroxychloroquine plus azithromycin because of the potential for toxicities and lopinavir/ritonavir or other HIV protease inhibitors because of unfavorable pharmacodynamics and negative clinical trial data. Except in the context of a clinical trial, the Panel advised against the use of other immunomodulators, such as IFNs, because of lack of efficacy in the treatment of SARS and MERS and their toxicity and Janus kinase inhibitors (e.g., baricitinib), due to their broad immunosuppressive effect (62).

Umbilical Cord Mesenchymal Stem Cell (UC-MSC) Transplantation

According to the clinical data, UC-MSCs and MCS have anti-inflammatory, immunomodulatory and antimicrobial actions, thereby, it can heal damaged tissues. The target tissue for stem cells is where they are caught by the lungs, as this is a favorable condition for COVID-19 treatment.

The clinical condition of elderly patients or patients with secondary comorbidities may progress worse and may not response to conventional treatment. For critically ill patients, infected with SARS-CoV-2, MSC therapy is the last resort and it can save lives. Unfortunately, even if MCS treatment has been previously attempted in different diseases, it is a new and inexperienced treatment method for COVID-19 (63).

In a clinical study presenting positive responses of seven COVID-19 pneumonia patients to MSC, genetic examination showed that MSCs are negative for ACE2 and the cellular protease TMPRSS2, which are known to be exempt from COVID-19 infection. Bone marrow, lymph nodes, thymus, and the spleen, immune cells, such as T and B lymphocytes, and macrophages were consistently negative for ACE2, as well. Therefore, intravenous transplantation of MSCs is likely to be a safe and effective option for the treatment of patients with COVID-19 pneumonia at the critically severe stage (63,64).

Vaccine Developments

It is necessary to overcome various difficulties to succeed in vaccine production. Many vaccine studies are carried out worldwide in accordance with phase 1 through phase 4 trial steps (65).

Moderna, Inc. is manufacturing therapeutics and vaccines for infectious diseases, immuno-oncology, rare diseases and cardiovascular diseases with collaborators as the Vaccine Research Center at the NIAID. mRNA-1273 is an mRNA vaccine, developed by Moderna, against SARS-CoV-2 encoding for a prefusion stabilized form of the Spike (S) protein. mRNA-1273 inhibits viral replication in the lungs of mice in the responding stage to SARS-CoV-2 infection. It is finalizing the protocol for a Phase 3 trial, phase IV "post-approval" studies will probably start in July 2020 (65,66).

Conclusion

Currently, no specific treatment has been approved by the FDA in the treatment or prophylaxis of COVID-19 disease, except for Remdesivir. Despite the claim in medical literature and some clinical studies regarding the achievement of cure in COVID-19 patients using various therapeutics, appropriate clinical research results are needed to identify optimal treatments for COVID-19.

For the current clinical management, supportive care is recommended, including infection prevention and control measures and respiratory support when indicated. As with general patient management, the healthcare provider makes decisions based on the patient's condition and characteristics.

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