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Potential treatment of COVID-19

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Abstract:

Following the first reported cases of pneumonia of unknown etiology at the end of 2019 in Wuhan city, Hubei province, China, the causative agent was demonstrated to be a new coronavirus that has not been defined in humans before. The World Health Organization (WHO) named this virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by the virus as coronavirus disease-19 (COVID-19). The disease spread rapidly to other countries through human-to-human transmission, and WHO declared a pandemic on March 11, 2020. As of April 2020, the number of individuals infected with SARS-CoV-2 and COVID-19 related deaths continue to increase rapidly worldwide. The main reason for the increase in the rate of infection is person-to-person transmission, while the main reason for the increase in mortality rate is the lack of a proven medical treatment specific to COVID-19 and the severe course of the disease in the elderly with low immunity. While a vast majority of individuals infected with SARS-CoV-2 are asymptomatic or recover after displaying mild symptoms, hospitalization is required in 14% of cases and severe disease requiring intensive care admission is seen in 5% of the infected individuals. WHO and national guidelines do not make clear recommendations regarding treatments for symptomatic patients. Currently, there is no vaccine or specific antiviral treatment for COVID-19, however supportive care, isolation and protective measures and experimental drugs/treatments are being used for the management of COVID-19. Medical treatments being used for COVID-19, aim to prevent the entry of the virus into the cell, to inhibit or reduce its replication, and to suppress the increased inflammatory response. In addition, "convalescent" plasma, which includes antibodies of patients who were completely recovered from the infection, is among the treatment options.

Keywords:

Coronavirus disease-2019, potential treatment, severe acute respiratory syndrome-coronavirus 2

Introduction

In December 2019, pneumonia cases caused by a new β-coronavirus turned into a pandemic that affected the whole world, starting from Wuhan, China. The genomic sequence of this new coronavirus was demonstrated to be 96% similar to the bat-coronavirus and 79.5% similar to the severe acute respiratory syndrome-coronavirus (SARS-CoV), the causative agent of the SARS, which also appeared in China in 2003.[1] Therefore, the World Health Organization (WHO) defined this virus as SARS-CoV-2, and the disease caused by the virus as coronavirus disease-2019 (COVID-19).[2]

As of April 2020, the number of infected people with SARS-CoV-2 worldwide surpassed two million and deaths related to COVID-19 exceeded 150,000, and the numbers continue to increase rapidly. The main cause of increased infection rate is transmission from person to person, while the main cause of increased mortality rate is the lack of availability of a proven medical treatment specific to COVID-19 and the

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severe course of the disease in the elderly with low immunity. Therefore, the main purpose of pandemic control is the detection and isolation of people infected with SARS-CoV-2.

A majority of infected people (81%) are asymptomatic or recover after displaying mild symptoms. Despite the fact that the WHO and national guidelines have classified the symptoms as mild, intermediate, severe, acute respiratory distress syndrome (ARDS), and shock, they have not come up with clear recommendations concerning treatment methods to be used at different stages of the disease.[2] Unfortunately, COVID-19 treatment is planned experimentally, taking into account the clinical experiences in the 2003 SARS and the 2012 MERS outbreaks and the antiviral efficacy of some drugs. Therefore, it is necessary to know the physiopathogenesis of the virus to understand why certain drugs are used for treatment.

CoV is enveloped, single-stranded positive-sense RNA virus that can be classified under four groups as alpha-, beta-, gamma-, and delta-CoV. SARS-CoV-2 is a member of the *Betacoronavirus* family. The single-stranded RNA genomes of SARS-CoV-2 include 6–11 open reading frames encoding nonstructural proteins (nsp1–nsp16). Other viral genomes encode four structural proteins, including the S glycoprotein, the small envelope (E) protein, the matrix (M) protein, and nucleocapsid proteins 3–5 (N).[3] The S protein in SARS-CoV is responsible for attachment of the virus to the host cell receptor. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE 2), which is present as a host cell receptor in the epithelial cells, alveolar macrophages, and monocytes. After being attached to the receptor, the virus is taken into the cell by endocytosis where it undergoes replication, and it is then released from the cell to infect other target cells.[4] The new viruses that are released activate CD4 + T-lymphocytes and cause the formation of pathogenic T-helper (Th) 1 cells. Active pathogenic Th 1 cells aggravate inflammation by causing the secretion of interleukin-6 (IL-6) from monocytes and macrophages through Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), and other inflammatory cytokines. The activated immune system cells enter the pulmonary circulation and play a key role in the immune damage that develops, especially in patients with severe pulmonary syndrome.[5]

The medical treatments, currently used in COVID-19, are the treatments for preventing the entry of the virus into the cell, inhibiting or reducing its replication, and suppressing the increased inflammatory response in line with this physiopathogenesis. The use of "convalescent" plasma (CP), which contains antibodies of patients who were infected and then completely recovered, is also among the current treatment options.

Treatment Methods Inhibiting the Virus Entry into the Cell

Chloroquine/hydroxychloroquine

Chloroquine (C) and hydroxychloroquine (HC) are the drugs that are used for the treatment of malaria. HC is a more soluble and a less toxic metabolite of chloroquine, and its potential side effects are lower.[6] C and HC were used for the treatment of HIV and SARS-CoV for their antiviral efficacy. However, controversial results were obtained for both viruses.

In their studies conducted on SARS-CoV, Keyaerts *et al*.[7] found chloroquine to be effective against SARS-CoV infection by inhibiting intracellular SARS-CoV replication in newborn mice. However, Barnard *et al*.[8] reported on the contrary, stating that chloroquine did not inhibit virus replication in mice. Vincent *et al*.[9] reported that chloroquine decreased the attachment of the virus to the ACE receptor, thus decreasing viral transmission.

There are not many studies regarding the use of chloroquine and HC for the treatment of COVID-19. *In vitro* studies have demonstrated that chloroquine and HC decreased viral activity.[10,11] Concerning *in vivo* studies, a data review of > 100 cases in 10 hospitals in China has demonstrated that chloroquine was more effective in preventing the progression of pneumonia and improving radiological findings without any significant adverse effects compared to the control group. It also reduced the duration of the disease and polymerase chain reaction (PCR) negativization time.[12] Following this review, C/HC treatment was included in the Chinese guideline. However, the reliability of this study has been questioned since the method of review; the control group and treatment protocols were not presented in the publication. The effect of 400 mg HC/day administration for 5 days on PCR negativization time of the nasopharyngeal swabs was not demonstrated on COVID-19 patients who have positive nasopharyngeal swab PCR. On the other hand, in another study involving mild cases, PCR negativization rates were significantly higher on the 7th day in patients who were administered 200 mg HC three times daily (600 mg/day) for 10 days when compared to the control group (70% vs. 12.5%).[13,14] However, HC treatment showed no effect on mortality rate and revealed no improvement on the lymphocyte count and the neutrophil/lymphocyte ratio in hospitalized PCR + COVID-19 pneumonia cases. In addition, the cases treated with HC were also found to have an increased necessity for respiratory support. Despite its antiviral efficacy in some *in vivo* studies, there is no case of acute SARS-CoV-2 infection in humans who have been treated successfully with chloroquine and HC.[15]

It is disputable whether chloroquine or HC is more effective in the treatment of SARS-CoV-2. HC is preferred as the first-line treatment since its rate of adverse effects is lower.[6,11] However, the WHO has made no clear recommendations on the selection of patients, dose, and duration of the treatment, while various suggestions have been published in other studies.[16] The American Thoracic Society (ATS) has suggested the use of HC in selected patients with pneumonia alone, while chloroquine phosphate has been recommended for fewer than 10 days in a 500 mg twice daily dose (300 mg twice daily for chloroquine) in the Chinese guidelines.[17,18] The International Pulmonary Diseases Specialists COVID-19 Consensus recommends 200 mg HQ twice daily after a loading dose of 400 mg twice daily for 5 days only in hospitalized patients with intermediate level pneumonia and with dyspnea and hypoxia.[19] C/HC treatment is recommended in intermediate and severe patients in the European guidelines, other than those of France.[20] The Republic of Turkey Ministry of Health National guideline recommends 200 mg HC twice daily after an initial loading dose of 400 mg twice daily, for 5 days. HC use in asymptomatic outpatients has been left to the preference of the physician according to benefit and risk status of the patients.

It has been suggested that the treatment might be extended to 10 days in patients with progression under HC treatment.[21] The treatment recommendations in the guidelines are summarized in Table 1.

C/HC is a safe drug. Retinal and cardiac toxic effects have been reported in long-term use, but these are very rare. Rare gastrointestinal side effects have been observed in short-term use. Cautious usages for the patients who have kidney and liver failure are recommended. The effect of its individual use on QT interval has not been demonstrated to be significant.[22,23]

In conclusion, evidence demonstrating the *in vitro* activity of C/HC against SARS-CoV-2 is limited. Current *in vivo* studies are limited to low numbers of cases, methodological errors, and data with contradictory results. Based on the preliminary results of ongoing clinical studies, some countries have included C/HC in the treatment protocols for some COVID-19 patients. However, no medium- or long-term follow-up data to support this approach are present.[22]

Umifenovir (arbidol)

Arbidol is an antiviral drug that is used especially in China and Russia for the treatment of influenza with no major side effects. It inhibits the fusion of viral membranes with host cells.[24] To date, there is only one study on the use of arbidol for the treatment of COVID-19. The study compared the combination of arbidol + lopinavir/ritonavir (LPV/r) with LPV/r alone in COVID-19 patients who are not under invasive respiratory support. The combination group revealed higher negativization of the nasopharyngeal swab on the 7th day (75% and 35%, respectively) and improvement in radiological findings.[25]

Use of arbidol is recommended in the Chinese COVID-19 guideline for a maximum period of 10 days as doses of 200 mg, three times per day (600 mg/day). However, the data on which this recommendation is based were similar to a news report, rather than a scientific publication, and this has raised questions.[18]

Oseltamivir

Oseltamivir is a neuraminidase inhibitor used for the treatment of influenza, and it effects by blocking the release of viral particles from the cell, thus inhibiting their spread.[26] Oseltamivir was used as a treatment method during the MERS outbreak, to treat the accompanying influenza infections in up to 30% of the cases.[27] However, simultaneous influenza infections were detected in only 4.3% of the patients with COVID-19,[28] so the use of oseltamivir for the treatment of COVID-19 is controversial. To date, there have been no studies in the literature demonstrating the efficacy of oseltamivir in COVID-19 patients, except a study demonstrating the effect of lopinavir, oseltamivir, and ritonavir combination on the control of virulence within 48 h in COVID-19 patients.[29]

The routine use of oseltamivir is not recommended in the WHO and other national guidelines if there is no suspicion of influenza. The International Pulmonologists Consensus on COVID-19 recommends its administration for 5 days in a daily dose of 150 mg only for hospitalized patients with intermediately severe disease and patients who have pneumonia with dyspnea and hypoxia, for the prevention of influenza progression.[19] The Republic of Turkey Ministry of Health recommended the use of oseltamivir in all symptomatic patients for 5 days in a dose of 75 mg twice daily in the first version of the COVID-19 guidelines; however, in the updated version, oseltamivir use was recommended in patients with suspicion of influenza and not combined with favipiravir.[21]

Camostat

Camostat is a commercial serine protease inhibitor. Along with the ACE 2 receptor, it has been demonstrated that the S protein bound entry of SARS-CoV into the host cell is associated with also TMPRSS2, a cellular serine protease. The inhibition of TMPRSS2 with camostat in mice has been shown to inhibit the spread of the virus by blocking its entry into the cell.[30] In the only study on

Table 1: Medical treatment recommendations in the guidelines for coronavirus disease -19[20]

Severity of disease	Turkey (21)	Italy (20)	France (20)	Netherlands (20)	Belgium (20)	IPCC (19)	China (46)	WHO (2)	ATS (17)
Asymptomatic patient	No routine treatment HC 2×200 mg 5 days (physician's discretion)	No	No	No	No	No	No	Does not recommend any antiviral treatment	Does not recommend any antiviral treatment other than HC treatment in hospitalized patients with severe pneumonia
Mild and intermediate patients with no risk factors	HC 2×400 mg loading dose, 2×200 mg maintenance dose for 5 days –/+ AZT 500 mg/day on day 1, 250 mg/day for the following 4 days	No	No	No	No	No	No		
Mild and intermediate patients with risk factors	HC 2×400 mg loading dose, 2×200 mg maintenance dose for 5 days and/or FVP 2×1600 mg loading dose, 2×600 mg maintenance dose for 5 days –/+ AZT 500 mg/day on day 1, 250 mg/day for the following 4 days	LPV/r+HC/C 5-7 days	LPV/r can be considered (duration is dependent on viral clearance time)	C may be considered for 5 days	HC may be administered as 2×400 mg loading dose, 2×200 mg maintenance dose (5 days)	OST 2×75/150 mg HC may be considered LPV/r, if progression is present			
Severe patient	HC 2×400 mg loading dose, 2×200 mg maintenance dose for 5 days and/or FVP 2×1600 mg loading dose, 2×600 mg maintenance dose for 5 days –/+ AZT 500 mg/day on day 1, 250 mg/day for the following 4 days	RDV+HC/C 5-20 days Or LPV/r+C	RDV (duration is dependent on viral clearance time)	C 600 mg/day loading dose followed by 300 mg/day maintenance dose, total 5 days or LPV/r 10-14 days	HC 2×400 mg loading dose, 2×200 mg maintenance dose (5 days) or LPV/r 14 days	Severe patient treatment not defined	No treatment was recommended according to the course of the disease. Treatments that can be administered in hospitals were recommended Int A 2×5 million+LPV/r 200 mg/50 mg 2×2 tb 10 days, ribavirin 2 or 3×500 mg IV (combined with Int A or LPV/r) 10 days, C 2×500 mg 7 days Arb. 3×200 mg 10 days		
Critical patient (ARDS)	HC 2×400 mg loading dose, 2×200 mg maintenance dose, max 10 days and/or FVP 2×1600 mg loading dose, 2×600 mg maintenance dose, 5 days –/+ AZT 500 mg/day on day 1, 250 mg/day for the following 4 days For appropriate patients TZP 400 mg (repeat within 12-24 h if necessary) or 800 mg (single dose) in 100 cc saline, 1 h infusion CP 200 ml each time, preferably single dose (max 600 mg if necessary, 48 h between applications) CS 1-2 mg/kg/day for 5-7 days	RDV+HC/C 5-20 days or LPV/r+C	RDV (duration is dependent on viral clearance time) or LPV/r	RDV (10 days) + C (5 days)	HC+for appropriate patients TZP	RDV+for appropriate patients TZP, In case of progressive disease LPV/r+HC+Inf B1	For appropriate patients TZP 400 mg (repeat within 12-24 h if necessary) or 800 mg (single dose) in 100 cc saline, 1-h infusion CP CS 1-2 mg/kg/day for 3-5 days	Does not recommend any antiviral treatment	Does not recommend any antiviral treatment

COVID-19: Coronavirus disease-19, IPCC: International Pulmonologists Consensus on COVID-19, WHO: World Health Organization, ATS: American thoracic society, C: Chloroquine, HC: Hydroxychloroquine, FVP: Favipiravir, AZT: Azithromycin, TZP: Tocilizumab, CP: Convalescent plasma, CS: Corticosteroid, Lpv/r: Lopinavir/Ritonavir, RDV: Remdesivir, Arb: Arbidol, Inf A: Interferon alpha, Inf B: Interferon B, OST: Oseltamivir, IV: Intravenous

SARS-CoV-2, camostat was demonstrated to be effective on blocking the entry of the virus into the cell; however, no clinical use has been reported, to date.[31]

Treatments Inhibiting or Decreasing Viral Replication

Remdesivir

Remdesivir is an adenosine analog that was developed for the treatment of the *Ebola* virus. It causes premature ending of the virus by involving in the new viral RNA strands.[32] In a mice study, remdesivir had a more powerful activity against MERS-CoV than lopinavir and ritonavir, and in addition, it showed decrease in the viral load and severe lung damage and improvement in pulmonary functions.[33] In another *in vitro* study, the authors showed that remdesivir blocked the SARS-CoV-2 virus after entering the cell.[11] Holshue *et al*.[34] found that their patients with COVID-19 pneumonia responded well to remdesivir.

The WHO currently has no recommendation regarding the use of remdesivir for the treatment of COVID-19, although they consider the drug to be the most promising agent for the treatment of this disease. Furthermore, in the guidelines of ATS and other countries, no recommendations have been made for the use of remdesivir in the treatment of COVID-19.[2,17] Remdesivir use was recommended in the guidelines of Italy and France for intermediate and severe cases and the guidelines of Holland in only critical cases as a 10-day treatment after an initial dose of 200 mg daily, continuing with a 100 mg daily dose.[20] The results of a Phase III study, involving a 10-day protocol of remdesivir for the treatment of COVID-19 after an initial dose of 200 mg daily, continued with 100 mg daily dose, are expected to become a reference for the recommendations for the guidelines currently.

Lopinavir and ribavirin

Proteinase inhibitors have been used for the treatment in SARS and MERS outbreaks. LPV/r is a proteinase inhibitor that includes a combination of lopinavir and ribavirin. LPV/r is considered to be effective by inhibiting the 3CLpro proteinase, which is responsible for processing the polypeptide product in the RNA genome of CoV into protein components. The antiviral activity of LPV/r is similar to the activity of LPV alone, which suggests that the effect is directed by LPV to a major extent. Therefore, ribavirin is used simultaneously with lopinavir and interferon in the treatment of SARS but not used individually.[35,36]

The use of LPV/r as an initial treatment method in severe acute respiratory failure due to SARS (lopinavir 400 mg/ritonavir 100 mg every 12 h for 10–14 days) has been demonstrated significantly decreased mortality rates (15.6% vs. 2.3%, respectively), intubation requirement (11% and 0%, respectively), and required doses of steroid, compared to standard treatment methods. However, the addition of LPV/r formerly as a rescue therapy neither altered the mortality rate nor decreased the requirement for intubation and use of steroids, when compared to the standard therapy in the same group of patients. Therefore, LPV/r has been suggested as an initial treatment method in the early phase of the disease in patients with severe acute respiratory failure.[37]

In their study comparing the LPV/r with individual ribavirin treatment as an initial treatment modality, Chu *et al*.[38] demonstrated that LPV/r in the serum concentrations of 4 μ/ml and 50 mg/ml, respectively, inhibited SARS-CoV activation within 48 h. In the same study, LPV/r treatment was demonstrated to significantly decrease the mortality rate and the development of ARDS (2.4% and 28.8%, respectively). PCR positivity was decreased to a great extent at the end of 21 days in the treatment-receiving group (2.4% and 67%, respectively).

The number of publications regarding the use of LPV/r in COVID-19 patients is limited. A LPV/r/arbidol combination was demonstrated to provide improvement of symptoms of four patients with COVID-19.[39] In a study in which an arbidol + LPV/r combination was compared with LPV/r alone in COVID-19 patients with no invasive respiratory support, the negativity of the nasopharyngeal swab on the 7th day (75% vs. 35%, respectively) and radiological improvement differed significantly, in favor of combination group.[25] However, in another retrospective study comparing LPV/r and arbidol alone, no difference was found between the groups in terms of improving symptoms and decreasing viral load.[40]

The positive effect of LPV/r as an initial treatment in patients with SARS has yet to be demonstrated in COVID-19 patients. However, this may be due to lack of publications on the use of LPV/r in COVID-19 patients. The results of randomized controlled studies assessing the efficacy of LPV/r in COVID-19 patients are yet to be published. Nevertheless, the Chinese guidelines recommend LPV/r use for up to 10 days in combination with arbidol in a dose of 2 capsules each time, twice daily (200 mg/50 mg/capsule).[18] The International Pulmonary Disease Specialists COVID-19 Consensus recommends LPV/r use only in hospitalized patients with an intermediate-level disease in the presence of signs of progression, while the European guidelines recommend its use in intermediate and severe cases. On the other hand, the guideline of the Republic of Turkey Ministry of Health recommends two capsules each time, twice a daily, for 10–14 days in pregnant patients.[19-21]

Favipiravir

Favipiravir is a purine analog that is an RNA-dependent RNA polymerase inhibitor (RDRI) and has been used against influenza in Japan. It has also been demonstrated to be effective against many RNA viruses, such as *Ebola*, *Norovirus*, and *Enterovirus*. The fact that SARS-CoV-2 viruses are known to contain RDRI in a similar structure to SARS and MERS led its use in the treatment of SARS-CoV-2 virus.[41]

In a study comparing COVID-19 patients using favipiravir + interferon alpha with Lpv/r + interferon alpha, radiological improvement rates were higher (91.43% and 62.22%, respectively) and viral clearance time was shorter (4 and 9 days, respectively) in the group using favipiravir.[42] In another study comparing favipiravir with arbidol, despite the fact that there was no difference between the groups in terms of clinical recovery on the 7th day, the reduction of cough and body temperature occurred in a shorter time. The most common side effects in the favipiravir group were behavioral disorders, gastrointestinal complaints, and elevated liver enzymes and uric acid levels.[43]

Different dose schemes have been recommended favipiravir for COVID-19 treatment. In some studies, high doses, such as 1200–1800 mg every 12 h following a loading dose of 2400–3000 mg every 12 h, are recommended. In other studies, similar to the protocol of the Republic of Turkey Ministry of Health, doses such as 3200 mg/day (2 × 1600 mg/day) on the 1st day as a loading dose, followed by a total of 1200 mg/day (2 × 600 mg/day), are recommended.[44,45] Although its use in the treatment of COVID-19 has been approved in China, favipiravir is not mentioned in the treatment guidelines.[46] Use of favipiravir in the European or ATS guidelines has also not been mentioned. The guidelines of the Republic of Turkey Ministry of Health recommended its use in the above-mentioned doses for 5 days in patients with severe pneumonia or progressing patients despite HC treatment.[18,20,21]

Treatment Methods for the Suppression of Increased Inflammatory Response

Tocilizumab

Hemophagocytic lymphohistiocytosis (i.e., cytokine storm) triggered by excess proinflammatory cytokines has been found to be responsible for the development of ARDS and death in COVID-19 patients. Continuous fever, cytopenia, elevated ferritin, and lung involvement are the main characteristics of cytokine storm. There is no absolute definition of the condition; however, some scoring systems have been defined for diagnosis. IL-6 has been shown to be one of the most important cytokines involved in the COVID-19-induced cytokine storms.[47]

Tocilizumab is a monoclonal antibody specific to the IL-6 receptor. Tocilizumab has been demonstrated to be effective in the treatment of cytokine storm in COVID-19 patients. It also stabilizes patients by decreasing the level of acute-phase reactants during the cytokine storm caused by SARS-CoV-2.[48] In another study involving severe and critical COVID-19 patients (patients with a respiratory rate ≥ 30/min and SpO_2 ≤ 93% at room temperature, patients with PaO_2/FiO_2 ≤ 300, and patients with respiratory failure, multiorgan failure, and clinical picture of shock necessitating mechanical ventilation), tocilizumab has been demonstrated to rapidly decrease symptoms, improve hypoxia, and lead to radiological improvement.[49]

Chinese guidelines recommend tocilizumab in severe cases with increased IL-6 levels and diffuse lung lesions. The initial recommended dose according to the Chinese guideline is 400 mg (4–8 mg/kg). This drug dose is recommended to be diluted in 100 ml of physiologic serum and administered over more than an hour and to be repeated after 12 h if there is no response. According to the Chinese guidelines, no > 2 doses or 800 mg should be administered. The use of tocilizumab should be avoided in the presence of active infections such as tuberculosis.[46] The Republic of Turkey Ministry of Health guidelines recommend a single dose of tocilizumab, in a maximum dose of 800 mg according to the severity of the disease. A second dose administration should be applied 12–24 h after the first dose if the initial dose was 400 mg.[21] The International Pulmonary Disease Specialists COVID-19 Consensus recommends tocilizumab treatment in critical patients receiving mechanical ventilation with diffuse lung involvement in the presence of cytokine storm.[19] ATS and other guidelines offer no recommendations associated with tocilizumab.[17,18]

Siltuximab

Another drug used for IL-6 blockage is siltuximab. Different than tocilizumab, siltuximab is a monoclonal antibody that is directly effective against IL-6 (not against the receptor). There is no published study on the use of siltuximab for the treatment of COVID-19. However, the drug was not mentioned in the COVID-19 guidelines; decreased CRP and inflammatory findings in addition to clinical improvement and decreased oxygen requirement are detected in one-third of patients according to the initial results of an ongoing study in Italy.[50]

Interferon

Interferons are proteins which bind to the receptors on the cell surface, thus decreasing intracellular replication of the virus and regulating the immune response of the host. Usually, they are used in combination with other antiviral agents. Although no *in vivo* efficacy of the drug was shown in MERS and SARS, it was recommended in the Chinese guidelines to be administered for a maximum

period of 10 days and in combination with LPV/r and ribavirin in a dose of 5 million units or equivalent, twice a day through inhalation.[46,51] The guidelines of other countries have not recommended its use.

Corticosteroids

Use of corticosteroids in COVID-19 patients is still a controversial issue. The delayed viral clearance formed by corticosteroids during viral infections is the most important drawback of their use in COVID-19 patients. In patients with SARS, the effects of corticosteroids on the length of hospital stay and mortality rate have not been shown. However, the use of corticosteroids in critical patients has been resulted in positive effects on the length of hospital stay and mortality rate. Moreover, the complications that were developed in those patients were shown to be due to invasive mechanical ventilation rather than side effects of corticosteroids.[52] Mortality rate was found to decrease after corticosteroid use in patients with COVID-19 and ARDS, in comparison with no corticosteroid use (46% and 61%, respectively).[53]

The WHO recommends no routine use of corticosteroids in patients with COVID-19.[2] ATS recommends no use of corticosteroids in patients with COVID-19.[17] The Chinese guidelines recommend methylprednisolone 1–2 mg/kg daily for 3–5 days in patients with rapid progression, while the International Pulmonary Medicine Specialists COVID-19 Consensus recommends corticosteroid use only when an accompanying condition such as septic shock necessitates steroid use.[19,46] On the other hand, the Republic of Turkey Ministry of Health recommends corticosteroid use only in patients with ARDS receiving mechanical ventilation and in a dose of 1–2 mg/kg daily for 5–7 days.[21]

Azithromycin

In addition to their antibacterial properties, macrolides are known to have anti-inflammatory properties such as the downregulation of proinflammatory cytokines and the inhibition of adhesion molecules.[54] Azithromycin has been shown to inhibit the intracellular entry following endocytic activation of the virus. These effects led it to be considered in the treatment of COVID-19.[55]

The mechanism of action of azithromycin on SARS-CoV-2 is unknown. Higher viral elimination rates were shown in COVID-19 patients who received HC (3 × 200 mg daily for 10 days) in combination with azithromycin (500 mg/day for the 1st day and 250 mg/day for the following 4 days), when compared with HC only group (57.1% and 12.5%, respectively).[14]

There is no recommendation regarding the use of azithromycin in the Chinese COVID-19 guidelines; however, the avoidance of broad-spectrum antibiotics is recommended.[19] The International Pulmonary Medicine Specialists COVID-19 Consensus recommends antibiotic treatment compatible with the pneumonia guidelines only in the presence of bacterial pneumonia in intermediate-level patients and makes no comment on the use of azithromycin in antiviral treatment.[46] There are no recommendations regarding the use of azithromycin in the European guidelines.[20] The Republic of Turkey Ministry of Health guidelines recommend combined azithromycin use with HC according to physicians' preferences in hospitalized patients. The recommend schedule is 500 mg daily for the 1st day, followed by 250 mg daily for following 4 days.[21]

Convalescent Plasma

CP treatment is a classical adaptive immunotherapy used for the treatment of infectious diseases for a long period of time. It involves the administration of the plasma containing the antibodies taken from infected and then completely recovered patients, to the recently infected patients. CP treatment is more effective when applied early after the onset of symptoms or as a prophylactic treatment after contact with a patient.[56]

It is shown that CP treatment decreased the viral load significantly and decreased the mortality by 75% in patients with SARS.[57] Due to the SARS-like virologic and clinical properties, CP usage has been considered in the treatment of COVID-19 patients. No serious adverse effects were observed of a single dose of 200 ml CP providing an antibody titer > 1:640, when applied to severe COVID-19 patients in addition to other antiviral and supportive treatments. In those patients, decrease in symptoms, improvement in oxygen saturation, increase in lymphocyte count, and decrease in CRP levels were seen on the 3rd day, and radiological improvement was seen on the 7th day.[58]

Plasma obtained on the 14th day and onward after the recovery of symptoms in COVID-19 patients is demonstrated to contain the maximal amount of antibodies. Individuals who had COVID-19 proven by a PCR test, who showed no symptoms associated with COVID-19 for at least 14 days (fever, cough, dyspnea, etc.), and who had a negative follow-up COVID-19 PCR result are appropriate donors for CP treatment.[56] However, The Republic of Turkey Ministry of Health Guidelines suggest that patients with COVID-19 who were hospitalized and treated can be donors 14 days after the recovery of symptoms, provided that they had two negative PCR results in two swab samples taken 24 h apart after the end of treatment. For outpatient basis recovered, COVID-19 patients can be donors 28 days after the recovery of symptoms, and they must

have a negative PCR in the swab sample before the procedure.[59]

The timing of CP treatment during the COVID-19 disease course is unclear. In general, CP treatment is recommended early after the onset of symptoms. Studies regarding the administration of CP as a prophylactic treatment approach in mild, intermediate, and severe cases are ongoing.[56] Chinese guidelines recommend CP treatment for critical patients or for patients with rapid progression.[46] The Republic of Turkey Ministry of Health guidelines on COVID-19 recommend CP treatment in patients with bilateral diffuse lung involvement identified in a computed tomography, with a respiratory rate of > 30/min, $PaO_2/FiO_2 < 300$, and $PaO_2 < 70$ mmHg or $SpO_2 < 90\%$ in spite of 5 l/min oxygen support, with a need for mechanical ventilation and vasopressor support, and with a progressing SOFA score and laboratory findings.[59]

Other Treatment Methods

Vitamin C

The intravenous (IV) use of Vitamin C has been shown to have anti-inflammatory and antiviral efficacy in experimental studies. Vitamin C in doses of 15 mg daily for 4 days has been reported to decrease mortality in patients with sepsis-related ARDS.[60] In animal studies of CoV, the use of Vitamin C was demonstrated to increase host cell resistance.[61]

No definitive recommendation of Vitamin C use in patients with COVID-19 is available in the guidelines. The International Pulmonary Medicine Specialists COVID-19 Consensus states that vitamin C can be considered in the treatment of COVID-19 (in a mean dose of 1.5 g IV every 6 h and in conjunction with thiamine 200 mg IV every 12 h).[19] However, the recommended dose in patients with sepsis is far more than this, being 1.5 g/kg daily. Although there are different suggested treatment dosages in patients with COVID-19, a high dose (25 g/daily and higher) is generally recommended. The infusion containing bottle should be wrapped in a dark-colored material during the infusion, and it should be kept in mind that Vitamin C should not be administered to individuals with glucose 6 phosphate dehydrogenase deficiency.

More studies are needed to investigate the use of Vitamin C in the treatment of COVID-19. Currently, there are ongoing studies in China and Palermo regarding the effects of Vitamin C in COVID-19 (NCT 04323514).

Anticoagulant treatment

Patients with COVID-19 with a severe clinical manifestation may be complicated with thrombosis. Data on the thromboembolic risk in patients with COVID-19 are limited. The increased risk of thrombosis is considered to be associated with infection, critical disease, comorbidities, and advanced age. Hypercoagulability secondary to the functional impairment of endothelial cells, excess production of thrombin, fibrinolysin blockage due to infection, and the increased transcription factors and viscosity due to hypoxia observed in patients with COVID-19 have been held responsible for the pathogenesis of hypercoagulability.[62,63]

In the studies conducted on lung dissection materials, vasculitis and findings of small pulmonary occlusion were found at a higher rate in COVID-19 patients than in SARS.[64] In an autopsy series, the two additional pathologies causing death were found to be thrombotic microangiopathy limited to the lungs and small-vessel thrombus formations associated with alveolar hemorrhage foci in the peripheral parts of the lungs. The presence of micro-emboli in the capillary area was demonstrated in the study, although no great vessel thromboembolism was observed. It was suggested that the thrombotic and microangiopathic effects of the virus should be considered in treatment approaches, in addition to the treatment methods targeting directly the viral pathogen in COVID-19 management.[65]

Elevated D-dimer was demonstrated to be associated with a poor prognosis in patients with COVID-19.[66] Seven days or more course of low molecular weight heparin use in COVID-19 patients with high intravascular sepsis-induced coagulopathy scores and D-dimer levels was demonstrated to decrease the risk of mortality.[67]

In the Chinese guidelines, all hospitalized adult patients with D-dimer <10 mg/L are recommended to be administered enoxaparin in a standard prophylactic dose in the treatment protocol, provided that no contraindication is present, while enoxaparin is recommended with dose adjustment based on body weight in all patients with D-dimer ≥10 mg/L. In the event of the verification of a venous thromboembolism in such patients, anticoagulation in the treatment dose is recommended provided that there is no contraindication.[46] On the other hand, the Republic of Turkey Ministry of Health guidelines recommend prophylaxis in all patients. In prophylaxis, enoxaparin in a dose of 40 mg daily according to the body mass index in patients with a D-dimer <1000 ng/ml, and 0.5 mg/kg enoxaparin every 12 h in patients with a D-dimer >1000 ng/ml, is suggested, considering also the GFR.[21]

Conclusion

Currently, there are no treatment recommendations with proven efficacy from large-scale high-quality studies

for COVID-19. Moreover, to date, no vaccine has been developed to overcome SARS-CoV-2. The management of the disease is based more on supportive care, the implementation of isolation and protective measures that will prevent the spread of the disease, and the use of experimental drugs/treatments. Large-scale randomized controlled studies are needed for better control of the disease and to ensure effective treatment.

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Conflicts of interest
There are no conflicts of interest.

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