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REVIEW

Current Options in the Treatment of COVID-19: A Review

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Azadeh Teimury
Elahe Mahmoodi Khaledi

Department of Cell and Molecular Biology, Faculty of Chemistry, University of Kashan, Kashan, Iran

Abstract: Novel Coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in December 2019 in China and spread rapidly all around the world infecting many people. To date, no specific vaccines and drugs have been developed for this disease. Also, due to the COVID-19 pandemic and high prevalence of the infected patients, the drugs and the therapies of other past viral epidemics have been used for this disease. Many studies have been performed on the specific treatments to find whether or not they are effective on COVID-19 patients. In this review, we collected information about the most widely used drugs to treat COVID-19 (coronavirus disease 2019) belonging to groups of antivirals, antibiotics, immune modulators, and anticoagulants. Some of these compounds and drugs were used directly by inpatients, so researchers have examined others in laboratory conditions. This study considered the pros and cons of using these treatments separately and together and compared their results. By studying this review, we hope to provide useful information for researchers.

Keywords: SARS-CoV-2, COVID-19, antiviral drugs, antibiotics, immune modulators, anticoagulants

Introduction

The first cases of the new coronavirus infection were reported in December 2019 in Hubei Province of China, during which a wave of people was infected by pneumonia.[1] Today, SARS-CoV-2 has officially become a pandemic whose clinical symptoms can affect the respiratory system and may eventually lead to death.[2,3] To date, no definitive vaccine or drug has yet been developed to treat SARS-CoV-2 infection. Therefore, drugs used in clinical trials for COVID-19 patients are the ones employed for other viral diseases.[4] For example, there is an overlap between SARS-CoV-2 pathogenesis and MERS-CoV (the Middle East Respiratory Syndrome Coronavirus) and SARS-CoV diseases.[5] The recurrence of drugs used to treat the mentioned diseases is the fastest way to solve clinical problems in COVID-19 patients, particularly those with mild to moderate severity.[6] Many drugs used in this field have been active against the SARS virus in laboratory conditions, and some have been licensed.[7]

A few years ago, when the Ebola virus became a pandemic, randomized trials were conducted, and many patients were not treated. Today, with the spread of SARS-CoV-2 around the world, researchers are reluctant to repeat past mistakes.[8] During these days, in which different countries are at this crisis, many researchers have studied the effects of multifarious drugs on patients with COVID-19,

Correspondence: Elahe Mahmoodi Khaledi
Department of Cell and Molecular Biology, Faculty of Chemistry, University of Kashan, Kashan, Iran
Tel +9831-55913042
Fax +9831-55511121
Email e.mahmoodi_kh@kashanu.ac.ir

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belonging to groups of antivirals, antibiotics, immune modulators, and anticoagulants. Some medical centers conduct plasma therapy along with these drugs. In this review, we presented the results of several studies on the effectiveness or ineffectiveness of these drugs. Table 1 briefly outlines the known uses of these drugs and the results of their current applications for COVID-19.

Main Drugs and Therapeutic Compounds in SARS-CoV-2 Infection

Antiviral Drugs

Lopinavir-Ritonavir (LPV-RTV)

LPV-RTV is a protease inhibitor used for a variety of treatments, including the initial treatment of HIV (Human Immunodeficiency Virus) infected adults.[9] One study used a combination of Chinese and Western therapies, including LPV-RTV, arbidol, and Shufeng Jiedu Capsule (SFJDC), which improved the patients significantly.[10] In another study, the interaction was investigated between LPV-RTV and oseltamivir as a neuraminidase inhibitor. As a result, these drugs were found to function more effectively when used together than when used separately.[11]

Two separate studies conducted in Korea achieved reduced viral loads and improved clinical symptoms during the LPV-RTV treatment. LPV-RTV is helpful to relatively high-risk patients with COVID-19 pneumonia who have underlying diseases, especially in the early stages of the disease.[12,13] By observing the improvement of patients, another study suggested the possibility of using LPV-RTV as a treatment option for COVID-19.[14] However, one report suggested that LPV-RTV was more effective when combined with ribavirin and interferon beta-1b than when used alone.[15]

A clinical trial was conducted on 199 patients with COVID-19 divided into two groups and treated with LPV-RTV and standard treatment. The results showed that LPV-RTV treatment was associated with lower mortality, shorter stay in the intensive care unit, and fewer gastrointestinal side effects, although it did not significantly improve the treatment of the patients. This issue is related to the patient selection process because the patients were late during the infection, which caused damage to their tissues.[16] What encourages the use of LPV-RTV for COVID-19 treatment is its availability in large quantities with approved licenses and the fact that many reports suggest it for COVID-19 treatment.[17]

In one study, COVID-19 patients treated with LPV-RTV were at increased risk of bradycardia. In the study, the heart rate dropped to less than 60 beats per minute for more than 24 hours. Bradycardia was resolved in the patients when the LPV-RTV dose was reduced or stopped. According to this result, it was reported that RTV-LPV could increase the risk of bradycardia when used in inflammatory injury conditions and during critical stages of the disease.[18]

Remdesivir (RDV)

RDV is another antiviral drug that can change to its active form (GS-441524). It causes to obscure the RNA polymerase, and eventually, prevents its replication. RDV was developed in 2017 to treat Ebola, and has a wide spectrum of antivirus activities.[19] In an experiment, a recombinant MERS-CoV was used to express a reporter nanoluciferase (MERS-nLUC) on a mouse laboratory model to measure RDV, LPV-RTV, and interferon beta antiviral activity. Interferon beta had little effect on the virus, and the performance improvement was not significant with LPV-RTV. However, treatment with RDV could improve the disease outcomes and reduce the virus proliferation in mice infected with MERS-CoV. The treatment with RDV could also reduce acute lung injury in the studied mice.[20] RDV has also been shown to improve pulmonary function and reduce viral load in chimeric virus-infected mice, making it a suitable candidate for COVID-19 treatment.[21]

In one study, the RDV effectiveness was evaluated in COVID-19 patients using statistical methods. The results showed that RDV was effective in patients who were not in the severe stage of the disease.[22] In a trial in China, COVID-19 patients over the age of 18 accidentally received RDV. There was no significant difference in terms of clinical benefits between the group receiving RDV and the control group. However, a numerical decrease was observed in the recovery time of the treatment group.[23]

In a randomized trial, more than 1000 adult patients with COVID-19 were treated with RDV for 10 days. The recovery time was shorter in patients receiving RDV than in controls, and RDV was reported to be effective in shortening the recovery time in the patients.[24] In one study, 397 COVID-19 positive patients were randomly divided into two groups receiving RDV for 5 or 10 days. At baseline, the clinical condition was significantly worse

Table 1 Available Drugs for the Treatment of Patients with COVID-19

Groups	Drugs	Applications	Results Related to COVID-19
Antivirals	Lopinavir–ritonavir (LPV-RTV)	HIV[9]	Reducing the disease symptoms in the early stage,[12–14] not accelerating the disease treatment,[16] increasing the risk of bradycardia[18]
	Remdesivir (RDV)	Ebola[19]	Accelerating the patient's recovery, having no specific side effects[22–24]
	Favipiravir (FPV)	Influenza[26,27]	Accelerating the patient's recovery, having few side effects[28,29]
	Arbidol (ARB)	Influenza[30]	Having proper performance,[34–37] having no specific side effects[34]
	Ribavirin	Lassa[40]	Having no clear benefit, having no treatment advantage,[41] having in vitro antiviral effects against SARS-CoV-2[43]
	Chloroquine, Hydroxy chloroquine (CQ/ HCQ)	Viral and autoimmune diseases[46,47]	Effectively controlling the disease with or without azithromycin, reducing mortality, having no high-risk side effects[49–52,54,57]
Antibiotics	Azithromycin	Many types of bacterial infections[60,61]	Having good performance in combination with HCQ, reducing mortality, having no special side effects[63–67,69]
	Teicoplanin	Ebola[70,71]	Having inhibitory effects on viral infection[70–72]
Immune modulators	Baricitinib	Inflammatory diseases, rheumatoid Arthritis[90,91]	Reducing inflammatory responses,[90,91] having a greater efficiency in combination with RDV and LPV-RTV,[93] having the possibility of creating anemia[95,96]
	Corticosteroids (CSs)	Inflammatory diseases[98]	Reducing mortality,[102] having short-term or long-term side effects
	Anakinra	Inflammatory diseases[108]	Having good performance, reducing mortality,[110–112]
	Tocilizumab (TCZ)	Inflammatory diseases, rheumatoid arthritis[116]	Showing significant clinical progress, reducing inflammatory markers, reducing mortality, reducing the risk of invasive mechanical ventilation, improving oxygen delivery in patients, having few side effects[117–123]
Anticoagulants	Heparin	Coagulation problems[130]	Reducing mortality,[129] having side effects including drug resistance and heparin-induced thrombocytopenia (HIT)[130,131]
	Nafamostat mesylate	Coagulation problems[134]	Having the ability for in vitro inhibition of SARS-CoV-2 S protein-mediated cell fusion and its infection,[132–134] improving clinical conditions in patients in need of supplementary oxygen therapy.[135]

in the 10-day group than in the other group. Side effects such as nausea and respiratory problems were observed in these patients.[25]

Favipiravir (FPV)

FPV, in previous years and various studies, was proved to be able to inhibit different strains of influenza virus resistance to drugs such as amantadine, zanamivir, and rimantadine. The FPV function involves a variety of activities against viruses resistant to various drugs. FPV directly inhibits influenza virus transcription, and the drug inhibits the virion M2 ion channel.[26,27] A study in the Third People's Hospital of Shenzhen examined clinical results in people with COVID-19 treated with FPV and in those treated with LPV-RTV. They found that patients treated with FPV recovered faster, and the chest radiography of both groups showed more changes in the FPV group than in the LPV-RTV group.[28]

In a clinical trial with COVID-19 confirmed patients, the results showed a rapid antiviral response with FPV. Side effects observed in the patients included those previously reported in patients taking FPV. However, it is recommended to use this drug in patients with respiratory and immunological problems, only in combination with drugs that have proven effectiveness.[29]

Arbidol (ARB)

Umifenovir, under the brand name ARB, is used as a drug against the flu virus.[30] It can inhibit the fusion of the virus to the cell membrane.[31] ARB can have more inhibitory effects on a variety of viruses, such as RNA viruses. It can also be effective before or during a virus infection.[32] A study on the comparison between different types of drugs used to treat Lassa (LasV) and Ebola (EboV) infections showed that ARB could control two viruses.[33]

In a study on 50 patients, the LPV-RTV and ARB efficacy was evaluated, and the treatment was followed for 14 days. Side effects did not occur in either group, but the study data showed that no viral load was observed in the ARB group, whereas the problem persisted only in some patients in the LPV-RTV group. Finally, it was reported that ARB monotherapy might be superior to LPV-RTV in the COVID-19 treatment.[34] In another study, adult COVID-19 patients treated with ARB and LPV-RTV had a better clinical response than patients treated with LPV-RTV alone.[35]

Treatment with arbidol and interferon alfa-2b has proven to be effective in treating patients with mild disease.[36] ARB can reduce the hospitalization duration; moreover, it has been suggested that the use of this drug in combination with adjuvant therapy can somewhat speed up treatment time.[37] In another study, 1052 patients were included in an ARB and a control group to determine the efficacy of ARB in COVID-19 control. Finally, the results showed that there was insufficient evidence to support the use of this drug for recovering COVID-19 patients.[38]

Ribavirin

Ribavirin is a guanosine analogue with a wide range of antiviral activities associated with the proliferation of RNA and DNA viruses.[39] Ribavirin is recommended for the control of Lassa hemorrhagic fever, especially when there is a high risk of the disease.[40] In a study on 115 patients with severe COVID-19, ribavirin treatment was evaluated. The results showed that the ribavirin therapy of the patients did not reduce the mortality rate compared with the control group.[41]

A few years ago, there was a study on the RNA-dependent RNA polymerase (RdRp) as one of the components involved in catalyzing the synthesis, transcription, and proliferation of RNA as well as the pathogenesis of the virus.[42] One study investigated drugs inhibiting the effects of the RdRp component of the HCV (Hepatitis C Virus) after analysis, as a model for SARS-CoV-2. According to this study, ribavirin, IDX-184, RDV, and sofosbuvir could be effective in treating SARS-CoV-2.[43] In another study by the same researchers, the RdRp component of SARS-CoV-2 was remodeled, and the effect of several drugs with anti-polymerase activity was investigated. According to the findings, IDX-184, YAK, and sofosbuvir were more successful in binding to RdRp than other drugs, and thus, they could be used to treat COVID-19.[44] Studies on the HCV have shown that the drug IDX-184 as an adenosine derivative is the most effective drug in the control of this virus. Further, IDX_184 was more effective than ribavirin in treating MERS-CoV.[45]

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

The next drug is CQ and some of its analogues. CQ and HCQ are weak bases that can interfere with the multiplication of viruses by interacting with a virus entry mediated with endosomes. They can be useful in the treatment of viral diseases due to many reports on their inhibitory effects.[46] HCQ and CQ are used in the treatment of autoimmune diseases to prevent the multiplication of many viruses.[47] HCQ and CQ are well-distributed throughout the patient's body, especially inflamed tissues.[48]

In France, a clinical trial investigated the effect of HCQ on patients with COVID-19. A higher percentage of people, treated with HCQ, improved in comparison with the control group. After a while, azithromycin was prescribed for both groups. The results showed that HCQ and azithromycin were effective in most patients for 3 to 6 days. Finally, it was suggested that HCQ and azithromycin could be used to treat SARS-CoV-2 infection.[49] Another study showed that treatment with HCQ alone or in combination with azithromycin reduced mortality in patients with COVID-19.[50] It has also been shown that low doses of HCQ reduce mortality in patients, even in the early stages of COVID-19.[51] However, it should be noted that the prolonged use of HCQ has been implicated in the development of drug-induced cardiomyopathy.[52]

In Italy, CQ and LPV-RTV are being tested on patients with COVID-19.[53] Various studies and observations suggest that HCQ and CQ activity are very close. Since HCQ is a more common medication, it is a priority in some COVID-19 treatments.[54] Moreover, the antiviral and anti-inflammatory activities of CQ have been effective in SARS-CoV-2 treatment. Since CQ has no high-risk side effects, it has been used to treat related diseases for years.

According to many reports, chloroquine phosphate (CQP) has a major role in the control and inhibition of pneumonia, although incompatibility with this drug has not been reported in treated patients.[55] However, it should be determined that only CQP has this effect, or other HCQ and CQ salts can have the same application.[56] One study investigated the in-vitro effects of seven drugs, including nafamostat, nitazoxanide, penciclovir, ribavirin, CQ, RDV, and FPV, on SARS-CoV-2 isolated from patients. The findings showed that CQ and RDV could control the infection effectively and treat the new coronavirus.[57]

In a randomized trial, adults exposed to COVID-19 due to occupational conditions received HCQ as a prophylaxis, and a control group was considered. There was no significant difference between the control group and the HCQ group in terms of the disease prevalence.[58] In one study, the effect of the HCQ plasma concentration was investigated on COVID-19 patients admitted to the intensive care unit. These results suggest that HCQ administration will not be useful for the recovery of COVID-19 patients with severe symptoms.[59]

Antibiotics

Azithromycin

Azithromycin is an antibiotic derived from the macrolide erythromycin. This antibiotic has shown better performance than erythromycin against gram-positive and gram-negative pathogens.[60,61] In one study, the relationship was investigated between macrolides and mortality in MERS-CoV patients. The results showed no significant relationship between macrolide treatment in the patients and reduced mortality.[62] However, the treatment of COVID-19 patients with azithromycin cannot be avoided because the number of studies with similar results is small.

Azithromycin has been used in many reports examining the effects of HCQ. In a study on 80 patients, azithromycin and HCQ were used to treat COVID-19, which significantly reduced the viral load in the patients.[63] In the United States, a retrospective study was conducted on the history of hospitalized patients with COVID-19. Mortality was lower in the group receiving HCQ with azithromycin than in the group receiving HCQ alone.[64] In another study, the use of HCQ with azithromycin was implicated in reducing the mortality of COVID-19 patients.[65] Moreover, adding azithromycin to the medication regimen of patients taking HCQ and LPV-RTV improved the general condition of the COVID-19 patients.[66]

In a systematic study using meta-analysis, there was no significant difference between HCQ recipients and the control group; however, in some cases, HCQ consumption along with azithromycin reduced the progression of lung disease. In five studies, the use of both HCQ and azithromycin was associated with improved outcomes.[67] Nevertheless, in a controlled trial, COVID-19 patients were treated with HCQ alone or with azithromycin. Compared to the control group, no improvement in clinical status was observed in mild to moderate patients who took HCQ alone or with azithromycin.[68] A study on 1061 patients in France, in which a group of patients received HCQ and azithromycin, showed that the use of these drugs could be safe when the complications of COVID-19 did not occur in the patients. In this case, a reduction in mortality occurred in the patients.[69]

Teicoplanin

In 2016, a study found that glycopeptide antibiotics were suitable for diseases such as Ebola, SARS-CoV, and MERS-CoV due to their low toxicity. In another study, teicoplanin functioned as an inhibitor of Ebola to advance the healing process. In fact, teicoplanin inhibits the virus entry by inhibiting cathepsin L.[70,71] Teicoplanin, which is suitable for infectious cases, was recommended in a study for COVID-19 treatment.[72] However, the role of teicoplanin in inhibiting novel coronavirus remains to be clarified.

Immune Modulators

Following the exacerbation of the disease in COVID-19 patients, complications such as worsening of cellular immune responses and increased cytokines have been reported.[73] Researchers in China have found that there are very high levels of cytokines in the plasma of patients with COVID-19, which is interpreted as a cytokine storm or cytokine release syndrome (CRS).[1] It means that the release of high-level cytokines cannot be controlled. This usually occurs in severe infectious diseases, when the body's immunity reaches a very high level.[74] The high serum concentrations of cytokines, especially IL-6, were also observed in MERS-CoV infection.[75,76] If CRS occurs, problems such as macrophage activation syndrome (MAS) and cytopenia may also occur.[77] Secondary haemophagocytic lymphohistiocytosis (sHLH) can occur in hyperinflammatory conditions and can be caused by a severe viral infection that can be detected with manifestations such as cytopenia and CRS.[78]

It has been reported that a protein called angiotensin-converting enzyme 2 (ACE2) functions as the main receptor for SARS-CoV-2 virus on the surface of many types of human cells. Following the binding of the spike-like protein of the virus to this receptor, the entry of the virus and its RNA into the cytoplasm is facilitated.[79] The ACE2 receptor is expressed in various tissues of the body as well as in the immune system cells such as macrophages and monocytes.[80] It can be concluded that the receptor expression increases in special immunological conditions caused by COVID-19.[81] To improve this situation, treatments such as convalescent plasma, interleukin inhibitors, and other inflammation inhibitors, were suggested.[82]

Convalescent Plasma

Convalescent plasma is a therapy currently used in many countries around the world for patients with COVID-19. It is suggested that convalescent plasma obtained from people who had recovered from COVID-19 is promising treatment without adverse events.[83] In 2014, it was used to treat patients with EboV.[84] In a study at the Third People's Hospital of Shenzhen, five people with COVID-19 and acute respiratory distress syndrome (ARDS) were treated with convalescent plasma. As a result, the condition of the patients was improved clinically. However, given the number of people examined, further analysis is required for more accurate results.[85] In another study, plasma therapy was evaluated in six COVID-19 patients. The results showed a reduction in disease-related symptoms with no side effects. Finally, it was suggested that this treatment could be effective, specific, and promising.[86]

The effectiveness of convalescent plasma transfusion (CPT) treatment was evaluated in another study. The results showed that plasma with a suitable concentration of SARS-CoV-2 immunoglobulins could reduce mortality in patients with severe COVID-19 and had beneficial effects in safe patients.[87] In a more comprehensive study, 20,000 COVID-19 patients receiving CP were examined. The results showed that this treatment was safe and effective.[88] On the contrary, another study found that CP treatment in patients with severe disease could not reduce mortality, and suggested that effective treatment should start earlier.[89]

Baricitinib

Baricitinib is a selective inhibitor of Janus kinase (JAK) and works by disrupting the activation of proinflammatory mediators. It is effective in inflammatory diseases and patients with rheumatoid arthritis.[90,91] Baricitinib is another drug that can block the infection process and does not appear to allow viruses to spread the infection to the lungs.[92] In one study, a group of drugs was targeted to prevent clathrin-mediated endocytosis. Baricitinib is a compound that can regulate clathrin-mediated endocytosis. It was found that this drug could be used to treat COVID-19 because inflammatory responses to the disease could lead to death. In addition, the drug was effective in combination with other direct-acting drugs, including RDV and LPV-RTV, which reduces viral infections and inflammatory responses.[93]

In an uncontrolled retrospective study at Atlanta Veterans Affairs Medical Center, 15 COVID-19 confirmed patients were treated with baricitinib and HCQ. Nevertheless, no significant relationship was observed between treatment with these two drugs and clinical improvement.[94] According to some reports, baricitinib may lead to anemia, and even, in severe cases, may associate with leukopenia, lymphocytopenia, and thrombocytopenia. Accordingly, a review showed that treatment with baricitinib could lead to anemia in patients with severe COVID-19.[95,96] However, in another study examining the use of baricitinib in patients with rheumatoid arthritis, problems such as anemia were not reported compared to the control group.[97]

Corticosteroids (CSs)

By considering the inflammatory conditions caused by the infection, these drugs with anti-inflammatory properties are used in treating severe infections.[98] CSs bind to their receptors in the cytoplasm of target cells and exert their effects. These receptors are widely found in the lungs, and thus, CSs are mostly used in the control of inflammatory lung diseases.[99,100] It has been reported that ACE2 expression decreases with the use of inhaled corticosteroid (ICS).[101]

Administration of CSs in the treatment of COVID-19 patients has led to anti-inflammatory responses. In a controlled trial on a high number of COVID-19 patients, glucocorticoids were used for treatment. In this study, the patients received oral or intravenous dexamethasone for 10 days. The mortality rate in the dexamethasone group, which also had invasive mechanical ventilation, was very low compared to the control group.[102] However, due to the role of CSs in suppressing the immune system, there are concerns about the use of these drugs by patients with COVID-19.[103]

In another study, to evaluate the efficacy of CSs, 31 COVID-19 patients were surveyed. Contrary to expectations, no significant correlation was found between patients receiving CS and the control group concerning recovery.[104] Consistent with this study, 309 patients with MERS were studied for the correlation between treatment with CS and mortality. In 151 patients receiving CS showed no difference compared to the control group in terms of mortality rate. However, in the main group, the viral RNA clearance was observed with a slight delay.[105] It should be emphasized that the role of CSs is undeniable in modulating hyperinflammation; however, due to immunosuppression and side effects associated with these drugs, it is recommended that appropriate precautions must be taken during treatment.[106]

Anakinra

In addition to CSs, interleukin inhibitors are used to control immunological conditions caused by COVID-19, such as CRS and its complications. Patients with immune-mediated inflammatory diseases (IMID) who typically use cytokine-inhibiting drugs have been reported to be less susceptible to SARS-CoV-2-induced infection than IMID patients who do not use these drugs.[107] Most reports highlight the use of IL-6 and IL-1 inhibitors in the treatment of this disease, which will be described below.

Anakinra (Kineret®) is an IL-1 receptor antagonist (Ra) that can block its activity in the regulation of inflammatory responses.[108] It has been reported that anakinra is effective in treating conditions such as sHLH and MAS.[109] In one report, eight patients with COVID-19 pneumonia and complications such as sHLH were treated with anakinra. The data showed that the use of anakinra by patients with such symptoms is beneficial.[110] Further, it has been reported that anakinra reduces mortality in patients with severe COVID-19.[111] During a course of treatment with this drug, a large percentage of COVID-19 patients improved significantly.[112] Anakinra, like CSs, is involved in suppressing the immune system, and thus, great precautions and considerations are necessary for its administration.[113]

Tocilizumab (TCZ)

TCZ is a human monoclonal antibody and an IL-6 inhibitor. TCZ plays this role by inhibiting the binding of this cytokine to its receptors, thereby inhibiting the pro-inflammatory activity of IL-6.[114,115] This drug has been shown to be effective in treating inflammatory diseases such as rheumatoid arthritis.[116] It has been reported that TCZ reduces mortality in patients with severe COVID-19.[117] A study was conducted in Italy on 100 patients with COVID-19 and ARDS to evaluate the effect of TCZ. Patients with complications such as lymphopenia and high levels of cytokines received an intravenous injection of TCZ. The results showed that the use of TCZ could lead to significant clinical progress.[118] In another study in Italy, adult patients with severe COVID-19 were treated with common medications such as HCQ. One group of patients received TCZ intravenously or subcutaneously. The results showed that the use of this drug, both intravenously and subcutaneously, was effective in reducing mortality as well as reducing the risk of invasive mechanical ventilation.[119]

In a retrospective study, the therapeutic response was evaluated using TCZ in COVID-19 patients. The observations revealed that TCZ therapy could be effective in patients at risk of cytokine storms, especially high levels of IL-6.[120] Twenty-five COVID-19 patients were included in a study with TCZ treatment and followed for 14 days. It was shown that TCZ reduced inflammatory markers and the patients' need for ventilation. However, in most of the patients, side effects such as anemia, alanine aminotransferase increase, etc., were observed during the treatment.[121] It is recommended to use TCZ when the D-dimer level, inflammatory markers, and the need for oxygen supply are high in patients.[122]

To control CRS, COVID-19 patients were treated with TCZ in a study. Although side effects were observed in a number of patients and IL-2 levels increased after using TCZ, oxygen delivery in the patients and inflammatory markers were significantly improved.[123] IL-6 has many roles in inducing the final maturation of B cells into antibody-producing cells, involving in the differentiation of cytotoxic T cells, and regulating acute-phase response proteins like C-reactive protein with the liver. However, inhibition of its functions in the control of COVID-19 requires more comprehensive studies.[124]

Anticoagulants

In addition to the mentioned inflammatory conditions, abnormal coagulation parameters are worth considering when treating COVID-19 patients. In fact, coagulation problems occur in many of these patients, especially in the severe stages of the disease and later. In a study at the Tongji Hospital, 183 patients with positive NCP (novel coronavirus pneumonia) were evaluated for coagulation status. The results of this study showed that abnormal

coagulation outcomes and existence of disseminated intravascular coagulation (DIC) were common in deaths with NCP.[125] Infections actually disrupt the function of endothelial cells, resulting in high levels of thrombin production, inactivation of fibrinolysis, and conditions occurring with high level coagulation.[126] Therefore, it is critical to gather accurate data to show that thrombosis prevention or thromboprophylaxis in COVID-19 patients will lead to better outcomes, including improved survival, without serious complications such as bleeding.[127]

Heparin

The therapeutic effect of this drug has been previously reported on SARS patients.[128] Another study at the Tongji Hospital examined the mortality rate of 449 patients with severe COVID-19, of whom 99 used heparin. The results showed that the 28-day mortality was lower in heparin users than in nonusers in patients with elevated sepsis-induced coagulopathy score or D-dimer criteria.[129] However, there is evidence that taking heparin in COVID-19 patients may lead to drug resistance and complications such as heparin-induced thrombocytopenia (HIT).[130,131]

Nafamostat Mesylate

This drug is known as an existing treatment used for DIC. It was previously reported that nafamostat mesylate was able to effectively inhibit the S protein-mediated cell fusion of MERS-CoV. A new study conducted by the same research team showed that nafamostat mesylate potently inhibited the SARS-CoV-2 S protein-mediated fusion in a cell fusion assay system, and also, inhibited SARS-CoV-2 infection in vitro in a cell-type-dependent manner.[132–134] It has also been reported that the use of this safe drug has improved clinical conditions in COVID-19 patients needing supplementary oxygen therapy.[135]

Conclusion

To date, no definitive medication or vaccines have been reported for the new coronavirus. Given the spread of this virus and the increased number of infected people, it is necessary to evaluate some known drugs for other viral epidemic diseases such as Ebola or diseases with similar symptoms to COVID-19. This review aimed to present current treatment options in combating SARS-CoV-2. Based on many studies and by considering many aspects, it can be concluded that remdesivir and hydroxychloroquine with or without azithromycin are still effective treatment options for COVID-19 patients in the mild to moderate stages of the disease. By its rapid antiviral response, favipiravir, manufactured under the brand name avifavir in Russia, also has a promising effect in these stages of COVID-19. In severe cases of the disease, in addition to convalescent plasma therapy, the use of interleukin inhibitors such as tocilizumab appears to be effective. However, in COVID-19 patients with abnormal coagulation parameters, nafamostat can be an appropriate treatment option that provides improved conditions. Therefore, in the current situation, the use of a specific single drug may not be sufficiently effective to control all stages of the disease. On the other hand, side effects of taking these drugs alone or in combination with other drugs should not be underestimated. We hope that researchers will discover a definitive treatment for this disease as soon as possible.

Abbreviations

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ACE2, angiotensin-converting enzyme 2; ARB, Arbidol; CQ, chloroquine; CQP, chloroquine phosphate; CP, convalescent plasma; CPT, convalescent plasma transfusion; COVID-19, coronavirus disease 2019; CSs, Corticosteroids; CRS, cytokine release syndrome; DIC, disseminated intravascular coagulation; EboV, Ebola virus; FPV, favipiravir; HIT, heparin-induced thrombocytopenia; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HCQ, hydroxychloroquine; IMID, immune-mediated inflammatory diseases; ICS, inhaled corticosteroid; JAK, Janus kinase; LasV, Lassa virus; LPV-RTV, Lopinavir-ritonavir; MAS, macrophage activation syndrome; MERS-CoV, Middle East respiratory syndrome coronavirus; nLUC, nanoluciferase; NCP, novel coronavirus pneumonia; Ra, receptor antagonist; RDV, remdesivir; RdRp, RNA-dependent RNA polymerase; sHLH, secondary haemophagocytic lymphohistiocytosis; SIC, sepsis-induced coagulopathy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFJDC, Shufeng Jiedu Capsule; TCZ, Tocilizumab.

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Disclosure

The authors declare that they have no competing interests in this work.

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