

Review article

A Comprehensive Review of COVID-19 Treatment

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SUMMARY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus strain that caused coronavirus disease 2019 (COVID-19). This novel coronavirus is an emerging global health threat. It caused approximately 140 million confirmed cases, with about 3 million deaths worldwide until April 18, 2021. Although there are two approved medications for this disease, remdesivir and dexamethasone, numerous studies are underway to investigate more therapeutic options. However, so far, most treatments have been supportive, and the clinical efficacy of the suggested drugs is still under consideration. The purpose of this review is to summarize the ongoing treatments, such as several antivirals, convalescent plasma transfusion, and adjunctive medications, with the intent of serving as a clinical guide for the physician and a resource for further evaluations in various clinical trials.

Key words: COVID-19, SARS-CoV-2, therapeutics, antiviral agents, COVID-19 serotherapy

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INTRODUCTION

Coronaviruses (CoVs), a member of the Coronaviridae family, are enveloped positive-sense RNA viruses that can cause severe infectious diseases in humans and animals (1, 2). They are divided into four genera: alpha, beta, delta, and gamma coronaviruses (3). So far, beta coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have caused significant morbidity and mortality (4 - 6). At the end of December 2019, an unknown pathogen in Wuhan, China, began to cause life-threatening pneumonia, which was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or 2019 novel coronavirus (2019-nCoV) causing coronavirus disease 2019 (COVID-19) (7). Subsequent research has shown that the SARS-CoV-2 genome is about 89% and 80% identity with bat SARS-like-CoVZXC21 and human SARS-CoV, respectively (8). Evidence suggests that COVID-19, similar to SARS-CoV and MERS-CoV, is a zoonotic coronavirus. There are approximately 140 million confirmed COVID-19 cases worldwide, with about 3 million deaths (9). Hundreds of healthcare workers were infected with this virus after close contact with infected cases, indicating interpersonal transmission of the virus.

In this review, we aim to summarize the current evidence on the promising treatments against COVID-19. To this date, only two medications, remdesivir and dexamethasone, were approved for this disease, and the efficacy of several other promising therapeutic agents is still under investigation. Nevertheless, most of the current therapeutic options are supportive care. It is noteworthy that previous studies on antiviral agents effective on SARS-CoV and MERS-CoV are the mainstay of present pre-clinical and clinical evidence on anti-SARS-CoV-2 medications. However, it is unclear how well these treatments can be effective against COVID-19.

Coronaviruses use their spike glycoproteins (S) to bind host cell receptors, mediate membrane fusion, and viral entry into the cells. Spike glycoprotein is trimeric, and each monomer consists of S1 and S2 subunits, mediating attachment and membrane fusion, respectively (10). The fusion process in coronaviruses is similar to human immunodeficiency virus type I (HIV-1). Targeting the spike proteins by developing therapeutic antibodies to treat SARS-CoV is an area of active investigation.

As the similarity of spike proteins among various coronaviruses is relatively high, the efficacy of anti-SARS-CoV antibodies against SARS-CoV-2 is being investigated (11). Moreover, most neutralizing antibodies, such as monoclonal antibodies (mAbs), which are biotherapeutics for passive immunotherapy, may be helpful for therapeutic purposes to fight against viral infection like COVID-19.

Antiretroviral protease inhibitors are being investigated as therapeutic targets for COVID-19. Studies have shown that atazanavir, efavirenz, ritonavir, and dolutegravir, which are antiretroviral medications for treating and preventing HIV, show inhibitory effects against the COVID-19 3c-like protease (12). Other agents, such as lopinavir, ritonavir, and darunavir, also target viral proteases. Therefore, Kaletra, lopinavir/ritonavir combination (LPV/RTV), was thought to be effective in COVID-19 treatment (13). Studies have shown that Kaletra-containing regimens could alleviate clinical symptoms and lower the viral load. Chinese health authorities first included Kaletra in their guidelines for coronavirus treatment. This decision was backed by some early preclinical *in-vitro* studies and anecdotal success in the clinic amid the lack of approved drugs. Kaletra can be administered in high-risk patients, such as the elderly, or those with underlying diseases. Despite the backing of Kaletra, the latest data from clinical studies have been disappointing in mild COVID-19 Chinese patients. Simeprevir, a protease inhibitor, explicitly targets Hepatitis C virus (HCV) replication by inhibiting its NS3/4A protease. It was observed that Simeprevir could work better than Kaletra, and therefore it might be another potential drug against COVID-19 (14, 15). However, updated guidelines advise against Kaletra and other HIV protease inhibitors used in COVID-19 patients in inpatient and outpatient settings (16).

In children, interferon α -2b (IFN α -2b) and Kaletra have been applied and recommended for COVID-19 infection (17). In severe patients, intravenous immunoglobulin (IVIG) at the dose of 1 g/kg QD for two days, or 400 mg/kg QD for five days, has been suggested, but its efficacy needs further evaluation.

Several oncology drugs, such as sunitinib and erlotinib, belonging to AAK1 inhibitors, effectively inhibit viral entry and replication. Thus, they provide an opportunity to treat COVID-19 patients (18). However, these drugs may cause serious side effects. By contrast, baricitinib, a Janus kinase (JAK) in-

hibitor and a regulator of endocytosis, has been recommended to treat this disease (19). Baricitinib's therapeutic effect could be through reducing both viral entry and inflammation in these patients.

Anti-malaria drugs, such as chloroquine, are another top candidate physicians are prescribing for the treatment of COVID-19 patients. This drug has been shown to have a broad-spectrum antiviral characteristics. It can inhibit the infection by several mechanisms, such as inhibiting viral receptors glycosylation and preventing the fusion of the virus with host cells by increasing the endosomal pH (20). Moreover, as this medication can act as an immunomodulator, its antiviral activity may be synergistically enhanced (21). Hydroxychloroquine, a more tolerable form of chloroquine, is also being tested because of its low price and better safety profile. Recently, the FDA strongly prohibited chloroquine and hydroxychloroquine use without strict medical supervision in a hospital or as part of a clinical trial. The agency said that without close monitoring for side effects of these drugs on COVID-19 patients, they might lead to life-threatening complications. Emodin, an anthraquinone compound, has been shown to have a virucidal effect through halting the SARS-CoV-2 S protein and angiotensin-converting enzyme 2 gene (ACE2) interactions (22). Nevertheless, some recent trials have suggested that hydroxychloroquine could not reduce the overall mortality rate in the inpatient setting. Thus, its use is no longer recommended (23, 24).

Promazine, an antipsychotic of phenothiazine class, can also inhibit SARS-CoV-2 replication (25). Hence, it may be a valuable option against COVID-19. Chlorpromazine and loperamide are other repurposed drugs against human coronaviruses, although no trial to date has suggested its effectiveness (26).

OTHER MEDICATIONS USED FOR COVID-19

Remdesivir (RDV), a new nucleoside analog prodrug developed initially for Ebola virus disease (EVD) treatment, was proven to inhibit MERS-CoV and SARS-CoV replication *in-vitro* and *in-vivo* by halting RNA-dependent RNA polymerase activity (20). So far, Remdesivir provided hopes of a significant breakthrough in finding cures for COVID-19. Remdesivir was confirmed to lower pulmonary viral loads, promote pulmonary function, and pre-

vent severe lung injury. Interestingly, *in-vitro* data illustrate that RDV and interferon-beta (IFN- β) were better antiviral agents against LPV and RTV (22, 27). Remdesivir is currently being investigated in multiple clinical trials and used for patients admitted in the intensive care unit (ICU) in the USA. Thus far, Remdesivir has been the sole FDA-approved anti-SARS-CoV-2 medication (28).

EK1 peptide, a CoV fusion inhibitor, can inhibit several coronaviruses infection, such as three bat-SL-CoVs, MERS-CoV, and SARS-CoV. When administered intranasally, this peptide is thought to exert a potential anti-SARS-CoV-2 prophylactic and therapeutic effect (29).

Favipiravir is effective against several viruses, such as respiratory syncytial virus (RSV), SARS-CoV, MERS-CoV, COVID-19, and HCV, through halting the RNA-dependent RNA polymerase (RdRp) activity (30).

Umifenovir, sold under the brand name Arbidol (ARB), is an approved and utilized medication in Russia and China for influenza and several other respiratory viral infections prophylaxis and treatment (31). Arbidol inhibited viral entry and replication in host cells and was effective against HCV, influenza A and B viruses, MERS-CoV, SARS-CoV, and COVID-19 (32).

Nitric oxide (NO) can directly interact with superoxide, mediate bactericidal or cytotoxic reactions, and inhibit SARS-CoV replication (33). Hence, NO inhalation could be effective in patients with severe COVID-19.

Ribavirin is FDA approved for treating HCV and RSV infections which acts through viral RNA synthesis and capping inhibition (34). It has been proved to be active against COVID-19 in randomized trials (35). The FDA-approved penciclovir was originally prescribed for treating recurrent HSV, but it may act against SARS-CoV, MERS-CoV, and SARS-CoV-2 through RdRp inhibition (20, 36). Nafamostat mesylate, a synthetic serine protease inhibitor, is a potent S protein-mediated membrane fusion inhibitor of MERS-CoV and approved anti-coagulant therapy in Asian countries, which may be effective against COVID-19 (37).

Oseltamivir, also known as Tamiflu, is a well-known influenza neuraminidase inhibitor (NAI) being used for COVID-19 treatment. However, no evidence supports its application (38). Also, its usage is not recommended as it may cause significant drug resistance.

Recently, several reports of successful results of using anti-HIV and -HCV therapies against COVID-19 have been reported. For instance, protease inhibitors, such as simeprevir, and polymerase inhibitors, such as sofosbuvir (GS-7977), are among the most promising anti-SARS-CoV-2 drug candidates (39, 40).

Tocilizumab, sold under the brand name Actemra, is an immunosuppressive medication mainly used for rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (SJIA) treatment. Tocilizumab effectively treated some patients with severe COVID-19 in China, which suggested a novel therapeutic strategy for this fatal infectious disease (41, 42). Tocilizumab exerts its therapeutic effects via competitively inhibiting the interleukin-6 (IL-6) and its receptor (IL-6R) binding (41). Therefore, some guidelines suggest using this medication in COVID-19 patients admitted to the ICU within the first 24 hours of admission who require invasive or non-invasive mechanical ventilation or high-flow oxygen ($>0.4 \text{ FiO}_2/30 \text{ L/min}$ oxygen flow). Nevertheless, not enough data are presented yet to propose tocilizumab or sarilumab use as the standard treatment plan of COVID-19 patients (43).

Ivermectin is an antiparasitic drug used in limited parasitic diseases, such as onchocerciasis. However, its antiviral characteristics have not been approved by the FDA. *In-vitro* studies suggest that this drug exerts its effects by inhibiting intracellular transport processes, such as host importin alpha/beta-1 nuclear transport proteins. Moreover, ivermectin, by suppressing the host's response to the virus, may enhance infection. Besides, it may interfere with SARS-CoV-2 S protein and human cell membrane attachment (44). In addition to its potential general antiviral effect, this medication also has anti-inflammatory effects, which may help treat patients with COVID-19 (45). Some local guidance suggests its use in COVID-19 patients, but there is not enough data for global guidelines to advise for or against its use for COVID-19 treatment.

Some of the herbal formulations which have been proposed to have antiviral activity include Praneem (an herbal extract of neem tree), Gelyoy (*Tinospora cordifolia*) extract, Lianhuaqingwen and ShuFengJieDu Capsules, and Hing (having antimicrobial properties) (46). It is speculated that these herbals are suitable as supplements in symptomatic therapy but not for acute disease treatment.

Studies have shown that convalescent plasma treatment can significantly reduce the mortality rate of severe COVID-19 cases. A randomized, double-blind, placebo-controlled trial concluded that early administration of high-titer convalescent plasma for SARS-CoV-2 to the elderly with the mild form of the disease reduced the progression of COVID-19 (47).

Some studies report the beneficial effect of combining corticosteroid therapy with thalidomide as an immunomodulatory and anti-inflammatory drug for the disease as the effects of thalidomide might be associated with alleviating anxiety to decrease oxygen consumption and improving nausea and vomiting (48).

Angiotensin receptor blockers (ARBs) are another newly discussed therapeutic option for treating COVID-19 patients (49). When bound to the ACE2 receptors, SARS-CoV-2 can lead to exacerbation of pneumonia through dysregulating the renin-angiotensin system (RAS). Following administration of ACE1 inhibitors (ACEIs) and angiotensin type-1 receptor blockers (ARBs), an amelioration of pulmonary inflammatory responses were observed. Since ACE2 acts as receptors for the SARS-CoV and MERS-CoV S glycoprotein, it was proposed that ARBs, such as losartan or telmisartan, would be potentially effective in controlling the spread of SARS-CoV-2 (50). It was observed that people who received these antihypertensive got lesser attacks of colds and flu-like illnesses (51). Therefore, it is speculated that ACEIs and ARBs could be COVID-19 infected patients.

Some nutrients and all immune enhancers can enhance host immunity against viruses. Vitamins are proved to have beneficial effects in preventing or lessening the damage imposed by microorganisms such as viruses. Vitamin A, an "anti-infective" vitamin, can affect viral replication inhibition (22). Therefore, this nutrient might be a promising choice for the treatment of COVID-19 patients.

Not much is known about the preventive and therapeutic effects of B vitamins against this disease. Several studies have been conducted in this regard. For example, vitamin B2 (Riboflavin) effectively reduced MERS-CoV titer in humans (52). Vitamin B3 inhibited the infiltration of neutrophils into the lungs by inducing a solid anti-inflammatory response against lung injury (22). Vitamin B6 also plays a vital role in body immune function (53). Therefore, B vitamins might be fundamental options for treating

these patients.

Vitamin C (Ascorbic acid) can alleviate immune defense by supporting immune system function. Therefore it may be helpful in the prevention and treatment of COVID-19 (54).

Vitamin D is being considered as another therapeutic option for COVID-19 (55). Its mechanism contributes to increased activation and stimulation of the maturation of immune cells.

Vitamin E and selenium have been suggested to be effective by their antioxidant activity. Zinc as a dietary mineral enhances innate and adaptive immunity. Besides, it may decrease COVID-19-related symptoms like diarrhea (56). Iron deficiency has been shown to predispose humans to the development of recurrent respiratory tract infections. Therefore, iron supplements could do a favor in this entity.

Novel therapeutic approaches such as allogeneic mesenchymal stem cells are being investigated for patients with acute COVID-19 infections.

It should be considered that inappropriate antibiotic application should be avoided unless there is some evidence of secondary bacterial infection. The most common empirical antimicrobial recommended are respiratory fluoroquinolones such as moxifloxacin or levofloxacin (19). Interestingly, teicoplanin, an anti-staphylococcal antibiotic, showed efficacy in inhibiting the first stage of the MERS-CoV cycle in host cells, thus being tested further for its antiviral activity (57).

Other adjunctive medications and recommendations for COVID-19 treatment include antipyretics such as ibuprofen, carbohydrate-containing regimens, protein-rich foods, H₂ receptor antagonist, and proton pump inhibitors.

As a result of COVID-19, inflammation and a prothrombotic state have been associated with fibrin, fibrin degradation products, fibrinogen, and D-dimers elevated levels. Some studies noted worse clinical outcomes in patients with elevations in these markers and evidence of COVID-19 patients with acute respiratory failure present with a severe hypercoagulability state rather than consumptive coagulopathy with a subsequent worse outcome. The guidelines recommend a prophylactic dose of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) to reduce deep vein thrombosis (DVT) incidence in hospitalized patients with COVID-19 (58). Therefore, these patients should not

be discharged during DVT prophylaxis (59). In the outpatient setting, no data are available to support the measurement of coagulation markers, such as D-dimers, prothrombin time, platelet count, and fibrinogen. Thus, anticoagulants and antiplatelet therapies should not be initiated in these patients.

Other supportive therapies, such as oxygen therapy, bilevel positive airway pressure (BiPAP), or continuous positive airway pressure (CPAP), are beneficial and may delay or inhibit the need to undergo invasive mechanical ventilation.

IMMUNE ENHancers IN COVID-19

Interferon- α and - β can trigger innate antiviral responses. Thus, they are effective in replication inhibition of MERS-CoV and SARS-CoV. Administration of interferon- α 2A (IFN- α 2A) was introduced by the Chinese National Health Association (NHC) and included in the clinical guidelines of COVID-19. Ribavirin, a nucleoside analog with broad-spectrum antiviral effects, had raised the survival of these patients and is recommended to use in monotherapy or combination with either interferon α 2A (IFN- α 2A) or lopinavir/ ritonavir (35).

Previous experiences during the SARS-CoV outbreak suggested a potential benefit in administering high-dose intravenous immunoglobulins (IVIg) (60). Observations in Wuhan and other parts of China during the current pandemic indicated that IVIg administration before the emergence of respiratory distress and early clinical deterioration could successfully halt the disease progression and improve the clinical outcomes in these patients.

Thymosin α 1 stimulates precursor T cell development in the thymus and increases the glucocorticoid-induced death resistance of the thymocyte. Some recent studies showed that thymosin α 1 might be an immune enhancer to coronaviruses (22).

Levamisole can promote cellular immunity functions, and in combination with ascorbic acid, could improve the number and function of lymphocytes, the most vital immune cells in defending the body against SARS-CoV-2 (25).

Cyclosporine (CsA) is frequently identified for its ability to prevent allograft rejection effectively and is extensively administered following liver, kidney, and heart transplantation. It can be applied as an inhibitor of the respiratory virus such as COVID-19 (61, 62).

CORTICOSTEROIDS USE IN COVID-19 TREATMENT

As the leading cause of deaths in COVID-19 patients, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are caused in part by host immune responses. Corticosteroids have the advantage of suppressing lung inflammation and therefore prevent diffuse alveolar damage, but their harmful effect may be due to inhibition of immune responses and virus clearance (63). In other words, glucocorticoids should not be a routine mediation in the management of COVID-19 as they impair antibody responses.

However, dexamethasone with a dosage of 5–10 mg or methylprednisolone with a dosage of 40–80 mg is recommended for intravenous administration in severely ill patients with O₂ saturation (SpO₂) < 90% (64). Also, several applications of glucocorticoids have been reported in a significant number of severe cases with severe sepsis and septic shock.

Despite all of the mentioned indications, no exact clinical data exists to indicate the benefits of corticosteroids in treating respiratory infections due to RSV, influenza, MERS-CoV, SARS-CoV, and COVID-19. Some reports suggested increased mortality, secondary infection rates, and complications due to corticosteroid therapy in survivors.

In children with suspected or confirmed COVID-19 cases, corticosteroids can be considered in the following scenarios (65, 66):

1. Rapidly deteriorating pulmonary function and the occurrence of ARDS;

2. Obvious toxic symptoms, encephalitis or encephalopathy, and hemophagocytic syndrome (HPS);

3. Septic shock;

4. Auscultation of prominent wheezing in which a short-term corticosteroid therapy may be indicated.

A recent large open-label, placebo-controlled trial has shown that dexamethasone administration caused lower mortality in patients receiving either sole oxygen therapy or invasive mechanical ventilation at randomization. Nevertheless, such promising results were not observed in patients not receiving any respiratory support (67, 68).

CONCLUSION

In the current review, we presented the latest advancements in the treatment of COVID-19 patients. Along with supportive therapies, no specific treatment has been introduced for COVID-19. The efficacy of some antivirals, convalescent plasma transfusion, and many similar cases need to be studied in more clinical trials.

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Conflict of interest

All authors declare no conflict of interest.

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Opsežan pregled lečenja COVID-19

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SAŽETAK

Ozbiljan akutni respiratorni sindrom korona virusa 2 (SARS-CoV-2) je oboljenje virusa koje je 2019. godine izazvao virus COVID-19. Ovaj novi korona virus postaje sve veća globalna pretnja po javno zdravlje. Do 18. aprila 2021. godine, potvrđeno je 140 miliona inficiranih slučajeva i 3 miliona smrtnih slučajeva. Premda su dva leka odobrena za lečenje ove bolesti, remdesivir i deksametazon, brojne studije su u toku kako bi se ispitale nove terapijske opcije. Međutim, do sada, mnoge terapije bile su pomoćne i klinička efikasnost tih lekova još uvek se ispituje. Cilj ovog preglednog rada je sumiranje trenutnih načina lečenja, poput primene nekoliko antivirusnih lekova, transfuzije plazme rekonvalescenata, pomoćnih lekova sa namerom formiranja kliničkog vodiča za lekare i resursa za buduće evaluacije u različitim kliničkim ispitivanjima.

Ključne reči: COVID-19, SARS-CoV-2, terapeutici, antivirusni lekovi, COVID-19 seroterapija