

Special Article



Interim Guidelines on Antiviral Therapy for COVID-19

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► See the letter “Vitamin C as a Possible Therapy for COVID-19” in volume 52 on page 222.

ABSTRACT

Since the first case was reported in Wuhan, Hubei Province, China on December 12, 2019, Coronavirus disease 2019 (COVID-19) has spread widely to other countries since January 2020. As of April 16, 2020, 10635 confirmed cases have been reported, with 230 deaths in Korea. COVID-19 patients may be asymptomatic or show various clinical manifestations, including acute symptoms such as fever, fatigue, sore throat; pneumonia presenting as acute respiratory distress syndrome; and multiple organ failure. As COVID-19 has such varied clinical manifestations and case fatality rates, no standard antiviral therapy regimen has been established other than supportive therapy. In the present guideline, we aim to introduce potentially helpful antiviral and other drug therapies based on *in vivo* and *in vitro* research and clinical experiences from many countries.

Keywords: COVID-19; SARS-CoV-2; Antiviral; Treatment

1. BACKGROUND AND OBJECTIVES

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel Betacoronavirus [1]. Since the first case was reported in Wuhan, Hubei Province, China on December 12, 2019, COVID-19 has spread widely to other countries since January 2020. In Korea, the first case was confirmed

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Conflict of Interest

No conflicts of interest.

Author Contributions

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in a Chinese individual who entered the country from Wuhan on January 20, 2019 [2]. As of April 16, 2020, 10635 confirmed cases with 230 deaths have been reported [3]. Compared to other coronaviruses, SARS-CoV-2 is closest to two strains of SARS virus (bat-SL-CoVZC45 and bat-SL-CoVZXC21) found among bats in Zhoushan, Zhejiang Province, China in 2018 and is 79% homologous to SARS-CoV and 50% homologous to Middle East respiratory syndrome coronavirus (MERS-CoV) [4]. Two-thirds of the first 41 confirmed cases of COVID-19 in China were found to be related to the Wuhan Huanan Seafood Wholesale Market where live animals were sold, and person-to-person transmission has subsequently led to a high number of cases worldwide [5].

COVID-19 patients may be asymptomatic or show various clinical manifestations, including acute symptoms such as fever, fatigue, sore throat, dry cough, dyspnea, and diarrhea; pneumonia presenting as acute respiratory distress syndrome (ARDS); and multiple organ failure [1, 6, 7]. According to data published in China, 80% of patients with COVID-19 showed mild symptoms, 15% showed severe course, and less than 5% showed critical course with accompanying septic shock and multiple organ failure. Although the case fatality rate was found to be 4.3%, it was higher among the elderly, those with underlying conditions, and those with higher Sequential Organ Failure Assessment scores [7, 8].

As COVID-19 has such varied clinical manifestations and case fatality rates, no standard antiviral therapy regimen has been established other than supportive therapy. In the present guideline, we aim to introduce potentially helpful antiviral and other drug therapies based on *in vivo* and *in vitro* research and clinical experiences from many countries.

2. SCOPE AND TARGET

The present guideline addresses antiviral therapy for COVID-19 and some adjuvant therapies to aid the treatment of COVID-19. Since guidelines on the diagnosis and infection control of COVID-19 will be published separately, the present guideline will not address these topics. The guidelines target adults, including pregnant women and the elderly, and pediatric patients, and may be used by all general practitioners and specialists treating COVID-19 patients.

3. ORGANIZATION OF THE COMMITTEE FOR GUIDELINE DEVELOPMENT

In January 2020, the Korean Society of Infectious Diseases, the Korean Society for Antimicrobial Therapy, and the Korean Society of Pediatric Infectious Diseases recommended specialists to form a committee to develop a guideline on antiviral therapy for COVID-19.

The committee consisted of 14 infectious diseases specialists.

4. IDENTIFICATION OF KEY QUESTIONS

Evidence on treatment of SARS-CoV and MERS-CoV, which are similar to COVID-19, were collected and evaluated, and therapy guidelines on COVID-19 from other countries were reviewed to select 7 key questions on antiviral and adjuvant therapy.

5. LITERATURE SEARCH

Therapeutic guidelines regarding MERS-CoV and SARS-CoV published since 2002 and literature on COVID-19 published since December 2019 were searched. The recent literature published in the past 20 years was searched regarding the dosages and adverse effects of antiviral agents, including lopinavir/ritonavir (LPV/r), chloroquine (CQ), hydroxychloroquine (HCQ), remdesivir, favipiravir, interferon (IFN), and ribavirin. PubMed (www.pubmed.gov) was searched using terms constructed by combining 'coronavirus', 'novel coronavirus', 'novel coronavirus 2019', '2019 nCoV', 'COVID-19', 'Wuhan coronavirus', 'Wuhan pneumonia', 'SARS-CoV-2', 'severe acute respiratory syndrome', 'treatment', 'therapy', and 'antiviral'. Since very limited literature on antiviral treatment of COVID-19 was available, all types of literature, including case reports, were reviewed.

6. DETERMINATION OF THE STRENGTH OF RECOMMENDATION AND LEVEL OF EVIDENCE

The strength of recommendation and level of evidence were determined using the criteria put forth by the Infectious Diseases Society of America with some modification (**Table 1**). The recommendations for each key question were determined at expert panel meetings of 14 specialists. The key recommendations chosen were emailed to members of the guideline development committee and external infectious diseases specialists to evaluate the adequacy of each recommendation on a scale of 1 to 9. The results and issues raised were reviewed, and the recommendations and their strengths were revised.

7. EVALUATION BY EXTERNAL EXPERTS

The initial draft of the antiviral therapy guideline for COVID-19 was reviewed by a group of experts on COVID-19. Their reviews were reflected in the final draft of this guidelines.

Antiviral therapy guideline

Key question 1. Is antiviral therapy recommended for patients with COVID-19?

- Other than supportive therapy, there is no antiviral agent proven effective for COVID-19.
- Based on limited data, antiviral therapy may be attempted at the discretion of healthcare providers (CIII).

No drug has been proven to be effective for COVID-19 in well-designed clinical trials. Although drugs that have been reported to inhibit SARS-CoV-2 in cell and animal studies are being used in clinical settings, data on the clinical effects among COVID-19 patients are

Table 1. Recommendation of evidentiary strength and quality

Strength of recommendation	Quality of evidence for recommendation
A: Should always be offered	I: One or more properly designed randomized, controlled trials
B: Should generally be offered	II: One or more well-designed, nonrandomized trial, cohort, or case-controlled analytical studies (preferably from more than one center), or dramatic results from uncontrolled experiments
C: Optional	III: Expert opinion or descriptive studies

lacking. Most COVID-19 patients show mild symptoms, but many other patients require hospitalization or intensive care, and the mortality rate also ranges from 1% to 3% [9-11]. Therefore, drugs that have been reported effective in laboratory settings and are known to cause adverse effects infrequently when used for other indications may be considered for COVID-19 patients. However, since the benefit of drug use remains unclear, the decision to administer antivirals to individual patients should be determined by healthcare providers upon consideration of factors that may influence the effects and adverse effects of drugs, including patients' statuses and underlying diseases.

It is important and urgent to identify antiviral agents that are effective for COVID-19 through well-designed randomized clinical trials.

Key question 2. For which patients is antiviral therapy considered?

- Antiviral therapy may be considered for patients with confirmed COVID-19 (CIII).
- The use of antiviral therapy can be considered for patients with confirmed COVID-19 with moderate to severe course including pneumonia, those with worsening clinical findings, and those who are likely to progress to severe COVID-19 disease (the elderly, those with chronic diseases, and immunocompromised patients) (CIII).

Patients with confirmed COVID-19 refer to those with confirmed infection according to the testing criteria regardless of clinical manifestations [12], and antiviral therapy may be considered for these patients.

Since most mildly symptomatic patients clear the infection spontaneously without active pharmacological intervention, antiviral therapy is not recommended for mildly symptomatic patients. Among 44,672 cases of confirmed COVID-19 reported by the Chinese Centers for Disease Control and Prevention (accessed on February 11, 2020), the case fatality rate was less than 1% among those aged 0 – 49 years, slightly increased to 1.3% among those in their fifties, and significantly increased to 3% among those older than 60 years [13].

In addition among 4,212 cases confirmed in Korea (accessed on March 2, 2020), only 2 deaths have been reported in patients younger than 50 years (case fatality rate 0.2%), and the case fatality rate increased to 0.5% among those in their fifties and to 1% among elderly patients older than 60 years [10]. Therefore, the evidence suggesting antiviral therapy for mildly symptomatic patients younger than 50 – 60 years remains controversial. A clinical trial comparing an antiviral therapy group and a control group among Korean patients with mildly symptomatic COVID-19 is underway (NCT04307693), and is expected to produce scientific evidence of the effects of antiviral therapy in mildly symptomatic patients.

The elderly, patients with chronic diseases, and those with severe pneumonia are known to be groups at high risk of death and requiring intensive care due to COVID-19. According to data obtained from 138 Chinese patients in Wuhan diagnosed with COVID-19 pneumonia [7], the elderly, patients with chronic diseases, and those with severe pneumonia were likely to require intensive care. According to an analysis of 54 deaths in Korea, the elderly, patients with chronic diseases, and immunocompromised patients were more likely to die, suggesting the need for active pharmacological intervention in high-risk patients and those with severe

pneumonia [14]. Therefore, among patients with confirmed COVID-19, antiviral therapy can be considered more among those with high-risk factors, including moderate to severe pneumonia, the elderly, those with chronic diseases, and immunocompromised patients.

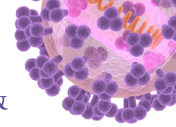
Key question 3. What is the most appropriate time to initiate antiviral therapy?

- Antiviral agents should be administered soon after the diagnosis or as early as possible (BIII).
- For patients with severe symptoms who are strongly suspected to have COVID-19 but are yet to receive the results of confirmatory tests, antiviral therapy can be initiated before the test results are confirmed (BIII).

In many observational studies on antiviral therapy for SARS-CoV, treatment was reported to be effective when antiviral agents were administered within 48 hours of admission or diagnosis [15, 16]. In influenza, for which antiviral agents are most commonly used, the use of antiviral agents within 48 hours of symptom, onset is known to slow the disease progression and decrease the nasopharyngeal viral load [16, 17]. In viral respiratory infections, including influenza, the nasopharyngeal viral load is known to be an index of disease severity, and high nasopharyngeal SARS-CoV-2 loads have also been reported to be associated with severe COVID-19 [18-20]. Therefore, when antiviral therapy is considered for COVID-19 patients, antiviral agents should be administered as early as possible. Moreover, for patients with severe clinical symptoms suggestive of COVID-19, antiviral therapy can be initiated based on clinical judgment even before laboratory test results are obtained.

Key question 4. Which antiviral agents can be used?

1. CQ has been reported to inhibit viral reproduction in *in vivo* and *in vitro* studies of existing coronavirus strains. It was also reported to effectively inhibit viral replication in an *in vitro* study of COVID-19. Since CQ phosphate is not available in Korea, HCQ can be administered instead at an 800 mg qd loading dose for the first day, followed by 400 mg qd (CIII).
2. LPV/r (Kaletra®) 400 mg/100 mg can be used up to twice a day, when used alone. Syrup formulations can be used for pediatric patients (refer to pediatric doses and uses) (CIII) [21-24].
3. Monotherapy with type I interferon (IFN) is not recommended for COVID-19 patients (IIIA). If type I IFN is considered, a combination therapy with type I IFN and LPV/r (Kaletra®) is recommended (CIII). However, since the expected effects of type I IFN may vary depending on the stage of the disease (early or late stage), this aspect should be taken into additional consideration. Of various forms of type I IFN, IFN-β1b is recommended as the preferred agent in COVID-19 (CIII) [25].
4. As of March 2020, remdesivir is under clinical trial for COVID-19 in other countries and can only be used in clinical trials (CIII) [26].
5. Favipiravir has been reported to inhibit viral infections of SARS-CoV-2 at relatively high concentrations. In Korea, it may be used in clinical trials after obtaining approval from the Ministry of Food and Drug Safety (CIII) [27].



6. Ribavirin is not recommended as first-line therapy due to common adverse reactions (IIB). However, if first-line medications cannot be used or found to be ineffective, combined therapy with LPV/r or IFN may be considered (CIII). However, monotherapy with ribavirin is not recommended.

● Chloroquine, hydroxychloroquine

CQ, which has long been used to treat malaria and intracellular bacterial infections such as those of *Coxiella burnetii* and *Tropheryma whipplei*, is a heme polymerase inhibitor. In *in vitro* studies, it was found to increase the pH of polyphagosomes and inhibit the glycosylation of cellular receptors of SARS-CoV, thereby interfering with cell-virus binding [28-30]. *In vitro* studies of SARS-CoV and MERS-CoV revealed findings of low half maximal effective concentration (EC₅₀) (range, 5.76 – 12.9 μM) [31, 32]. The EC₅₀ was also found to be low (0.306 ± 0.0091) in *in vitro* studies of SARS-CoV [33]. Moreover, CQ is known to inhibit viruses with little toxicity and to modulate immune responses through various host proteins and cellular processes [34, 35].

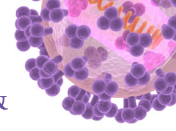
In vitro research regarding SARS-CoV-2 showed that CQ inhibited viral growth [36]. A clinical trial conducted in China showed that the CQ group had significant improvement in viral clearance or clinical symptoms compared to the control group [37]. Therefore, Chinese infectious diseases specialist groups recommend 10 days of CQ at 500 mg bid in patients with mild, moderate, and severe COVID-19 pneumonia without any contraindications to CQ [38].

HCQ, an analog of CQ, was also found to have anti-SARS-CoV activity in *in vitro* studies [39]. Given that HCQ can be taken for a longer duration than CQ, can be used at higher doses than CQ, has less drug interactions, and has higher tissue concentrations in lungs, liver, kidneys, and spleen than in the plasma, it may be relatively safer [40, 41]. Recent reports have also suggested that HCQ has superior anti-SARS-CoV-2 effects to CQ [42]; thus, research findings on this will require further attention.

Among the 62 COVID-19 patients, time to clinical recovery was significantly shortened in the HCQ treatment group. Compared with the control group [3.2 ± 1.3 days], the time to defervescence was significantly shorter in the HCQ treatment group [2.2 ± 0.4 days]. Also, a higher rate of clinical improvement of pneumonia in the HCQ treatment group (80.6%, 25 of 31) when compared with the control group (54.8%, 17 of 31) was reported [43]. However, a recent study from China showed that there was no difference in terms of virologic clearance and clinical outcomes including duration of hospitalization, temperature normalization, and radiological progression between the groups of COVID-19 patients treated with and without HCQ [44].

A recent multicenter, parallel, open-label randomized trial conducted in China among 150 hospitalized adult patients with COVID-19 showed that there was no difference in the overall 28-day negative virologic conversion rate between the two groups treated with HCQ and standard of care (85.4% vs. 81.3%, *P* = 0.341). Also, negative virologic conversion rates at day day 4, 7, 10, 14 and 21 did not differ between the two groups. Furthermore, the rate of alleviation of symptoms by day 28 was similar in the two groups [45].

In an open label non-randomized clinical trial conducted among 42 COVID-19 patients in France, the HCQ + azithromycin combination therapy (n = 6) group, HCQ monotherapy (n = 20) group, and control group (n = 16) were compared for virologic cure rate on day 6. The cure rates were



100%, 57.1%, and 12.5% in each group, respectively. These results suggested that the anti-viral effects were greater in the HCQ + azithromycin combination group [46]. However, a conflicting result from another study conducted in France among patients with COVID-19 has been reported [47]. Repeated nasopharyngeal swabs in 10 patients using a qualitative PCR assay were still positive for SARS-CoV2 RNA in 8/10 patients (80%, 95% confidence interval: 49-94) at days 5 to 6 following the initiation of treatment. Thus, this study may imply no significant evidence of antiviral activity from the combination of HCQ and azithromycin for the treatment of the hospitalized patients with severe COVID-19 [47]. Clinicians should be advised that clinical efficacy was not rigorously evaluated in these studies and combined use of these medications may cause adverse reactions such as severe QT prolongation, which warrants close monitoring via electrocardiogram during the treatment [46].

High cytokine concentrations have been confirmed in the plasma of patients with severe COVID-19 disease, and cytokine storm was found to be associated with disease severity [1]. In contrast to other antiviral agents, HCQ is a safe anti-inflammatory agent that has shown success in various autoimmune diseases. It is expected to significantly decrease the production of various cytokines, particularly pro-inflammatory factors; thus, the effects stemming from this characteristic may be expected [41].

Among clinical trials and guidelines, slightly different doses of HCQ are recommended for COVID-19 [38, 42, 46]. Considering the long half-life of HCQ, the present guideline recommends an 800 mg qd loading dose of HCQ on the first day, followed by 400 mg qd on subsequent days.

However, since combined use of CQ and HCQ can cause cardiotoxicity with QT prolongation, renal dysfunction, and hepatic dysfunction, caution is required when patients have existing conditions. In addition, interaction with other drugs being used concurrently should be confirmed carefully prior to administration [48].

● Lopinavir/ritonavir

The combination of LPV and ritonavir, which are protease inhibitors that inhibit major enzymes that promote viral replication, has been found to have anti-MERS-CoV activities in studies using Vero cells [49]. The EC_{50} was found to be 8 μ M [32]. The therapeutic serum LPV concentration for HIV patients is 8–24 μ M, which suggests that it may be used for the treatment of COVID-19 [50]. It was suggested that LPV exerts its antiviral effects through the inhibition of a major protease (M^{pro}) of SARS-CoV. Since SARS-CoV and SARS-CoV-2 M^{pro} have 96% homology in protein-coding gene sequences, LPV is expected to have antiviral effects on SARS-CoV-2 M^{pro} as well [51, 52]. The only *in vivo* study on marmosets that evaluated the therapeutic efficacy of LPV/r or IFN- β in MERS-CoV used a model of infection and showed slightly improved treatment outcomes in the treatment group compared to those in the control group [53]. Subjects in the treatment group showed less weight loss, relatively mild lung infiltration on imaging and tissue biopsy, and a relatively lower viral load in pulmonary lesions. At 36 hours after viral inoculation, the mortality rate was 0–33% in the treatment group and 67% in the control or mycophenolate mofetil treatment groups.

LPV/r has been used in SARS-CoV patients, and a retrospective analysis revealed that patients who received LPV/r early had lower mortality and received less endotracheal intubation compared to other patients [54]. Moreover, patients who received LPV/r showed early decreases in nasopharyngeal viral load [55]. No study has confirmed the efficacy of LPV/r in MERS, and only a small number of case reports [56, 57] and Korean case series of 139

patients are available [58]. In a study conducted among healthcare professionals exposed to MERS patients, those that received ribavirin and LPV/r had 40% lower risks of contracting the disease, suggesting that LPV/r may have actual therapeutic effects and could potentially be used as chemoprophylaxis for those exposed to the pathogen. However, since LPV/r was generally used in conjunction with ribavirin, IFN, or steroid, the efficacy of LPV/r monotherapy has not been evaluated. The results of an RCT on LPV/r in patients with severe COVID-19 have been reported recently in China [59]. In this study, severe COVID-19 patients treated with LPV/r did not show a difference with patients who received only conservative treatment in terms of time to clinical improvement and 28-day mortality.

However, the time when severe COVID-19 patients participated in the study was 13 days after symptom onset on average, and it was the point they had already progressed to very severe status. Therefore, participants might not have enough anti-viral effect due to the late administration of LPV/r. However, since monotherapy of LPV/r was found to be ineffective in COVID-19 patients that have already progressed to severe stages, other antivirals or the combination of multiple agents can be considered for severe patients rather than LPV/r monotherapy, in considering of the study's findings. Furthermore, additional studies are needed on the effects of early use of LPV/r among COVID-19 patients.

● Interferon

Both IFN- α and IFN- β have *in vitro* inhibitory effects on SARS-CoV and MERS-CoV [52, 60, 61]. Thus, some *in vitro* inhibitory effects of type I IFN on SARS-CoV-2 are expected, although there is no available data on this subject. It is worth noting that MERS-CoV is more sensitive to type I IFN than SARS-CoV *in vitro* [62]. Many previous clinical studies have been performed, particularly on MERS-CoV, regarding the use of type I IFN as part of a combination regimen with ribavirin or LPV/r [22]. Therefore, a monotherapy of type I IFN such as IFN- α or IFN- β is not recommended in patients with COVID-19 (IIIA). Among the various combination regimens, the LPV/r-containing regimen was considered the most promising for MERS and has been assessed in a randomized trial conducted in Saudi Arabia [25, 53]. If the use of IFN- α or IFN- β is considered, the combination regimen of type I IFN + LPV/r should be considered (IIIC). Although *in vitro* and *in vivo* studies on type I IFN have shown a mild to moderate inhibitory effect on SARS-CoV and MERS-CoV, theoretical concern for the use of type I IFN regarding the appropriate timing and dose during the disease course should be considered. Type I IFN plays a critical role in regulating the antiviral innate immune response [63]. However, previous studies revealed a paradoxical inhibitory effect by suppressing natural killer (NK) cell antiviral function [64] and IFN- γ release from NK cells [65] due to the shift in balance between STAT1 and IFNAR [63]. Most challenging animal studies have involved the administration of type I IFN during the early course of SARS-CoV or MERS-CoV infections. Thus, these models do not recapitulate the mid- to late-course of human SARS-CoV or MERS-CoV infections. In this context, it is difficult to extrapolate that the use of type I IFN might be beneficial or harmful in clinical settings including patients with various stages of COVID-19. Among IFN subtypes, IFN- β 1b causes the greatest *in vitro* inhibition of MERS-CoV [52, 65]. Thus, until further studies on COVID-19 are available, IFN- β 1b is recommended as the preferable one among various types of IFN for patients with COVID-19. IFN- β 1b (Befaferon[®]; Bayer, 0.25 mg (8 million units [1 mL])) is administered subcutaneously on alternative days for 14 days.

● Remdesivir

Remdesivir (GS-5734) is a monophosphoramidate prodrug of an adenosine analog with a broad spectrum of antiviral activity against various RNA virus families, including the *Filoviridae*,

Paramyxoviridae, *Pneumoviridae*, and *Orthocoronavirinae*. Its antiviral activity occurs by interfering with the function of viral RNA-dependent RNA polymerase (RdRp). It incorporates into the nascent viral RNA chains and causes their premature termination [66-68].

In vitro experiments have revealed an antiviral activity against MERS-CoV, SARS-CoV, and various human and zoonotic coronaviruses [69]. Very recently, after the identification of SARS-CoV-2, Chinese researchers reported that it has antiviral activity against SARS-CoV-2 in an *in vitro* study using Vero E6 cells with an EC₉₀ value of 1.76 μ M [36]. It was observed that remdesivir also inhibited viral infection in a human cell line [36].

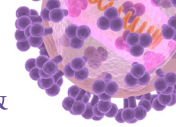
In a mouse model of SARS-CoV infection, prophylactic and early therapeutic administration of remdesivir significantly reduced the viral load in the lung and improved clinical signs and respiratory function [69]. In a rhesus macaque model of MERS-CoV infection, prophylactic (24 hours before infection) and therapeutic (12 hours after infection) administration of remdesivir decreased the disease severity, viral replication, and damage to the lungs [70].

In humans, data regarding safety and pharmacokinetics were obtained in clinical trials. It was also administered to a 19-day-old newborn with Ebola virus disease and the baby recovered without significant adverse events during the therapy [71]. In a recent study of Ebola virus disease, remdesivir was administered to 175 participants without significant adverse events [72]. Although this study failed to show an antiviral efficacy of remdesivir against Ebola virus disease in humans, valuable safety data from 175 individuals were obtained. Remdesivir was administered compassionately to the first patient diagnosed with COVID-19 in the United States for the first time to treat SARS-CoV-2 infection on January 26, 2020. The patient tolerated the drug without significant adverse events and recovered well from SARS-CoV-2 infection [73]. The treatment effect of remdesivir needs to be assessed further because this patient had relatively mild disease, and the drug was administered on hospital day 7 (illness day 11). It appeared somewhat promising because the fever resolved within a day and the results of reverse transcription polymerase chain reaction assay showed viral load reduction in the nasopharyngeal swab and negative results in the oropharyngeal swab the next day. In a most recent report from April 2020, 61 patients with severe COVID-19 from nine countries were treated with compassionate-use remdesivir. Among 53 patients whose data were available for analysis, 36 patients (68%) showed clinical improvement [74].

Based on *in vitro* and *in vivo* data, and safety data in humans from previous studies, several randomized, placebo-controlled clinical trials of remdesivir in SARS-CoV-2 infection have been initiated and patients have actively been enrolled in China, Korea, the United States, and other countries [75]. The results of these trials will provide some important answers for the treatment of SARS-CoV-2 infection.

● Favipiravir

Favipiravir (Avigan[®], T-705) is a drug known to be effective against various RNA viruses. Although its mechanism of action remains unclear, it is thought to act as a purine analog and inhibit the action of the RdRp of the virus [76, 77]. It was studied in an RCT among patients with uncomplicated influenza, and it was approved for use in new or reemerging influenza in Japan in 2014. Moreover, it has been reported to be effective in animal studies of severe fever with thrombocytopenia syndrome virus, *Bunyaviridae* [78], West Nile virus [79], and Chikungunya virus [80]. Although it was used in the 2014 Western African epidemic of Ebola virus infection, the effects were inconsistent [81, 82]. Regarding SARS-CoV-2, it was



reported to inhibit viral infections at a relatively high half maximal effective concentration ($EC_{50} = 61.88 \mu\text{M}$, selectivity index >6.46) [36]. In a Chinese study that compared the effects of favipiravir and LPV/r in combination with IFN- α in 80 patients, the favipiravir group had shorter time to viral clearance, which was around half of that of the LPV/r group, and showed improvements more frequently on imaging. However, no randomization or blinding was employed in this study, and clinical improvement was not evaluated [27]. In a double-blind RCT (preprint) in which favipiravir and umifenovir (Arbidol[®]) was administered to each of 120 patients, the proportion of patients who experienced improvements in fever, had oxygen therapy withdrawn, and had improvements in cough on day 7 was higher in the favipiravir group. Nevertheless, the difference was only 10%, and no significant difference was noted in patients classified as having severe disease [83]. Both of these studies reported gastrointestinal symptoms (5.7% and 13.8%, respectively), increases in serum liver enzyme levels (2.9% and 7.8%, respectively), and uricemia (unreported and 13.8%, respectively) as adverse effects; however, no discontinuation due to the adverse effects were reported. In addition, a study conducted to determine the dose for patients with influenza (NCT01068912) showed a similar pattern regarding the type and frequency of major adverse events. Favipiravir, available in oral formulations, is administered at 1,600 mg bid on day 1, followed by 600 mg bid starting from the next day [27]. A previous study in which favipiravir was administered to critically ill patients with influenza reported that serum drug concentrations were lower than the effective concentration, which merits consideration when favipiravir is used in patients with severe diseases [77]. At present, favipiravir is not approved in Korea.

● Ribavirin

Several *in vitro* studies showed that high concentrations of ribavirin can inhibit the growth of SARS-CoV or MERS-CoV [52, 55, 61, 84]. However, the usual dose of ribavirin used at the clinic does not reach the concentration required to inhibit SARS-CoV or MERS-CoV, and inhibition was achieved instead at doses toxic to the human body. Most studies on ribavirin among patients with SARS-CoV yielded inconclusive results about treatment effects [85-92]. This is because most studies, which were descriptive or retrospective, were not designed well and assessed ribavirin used in combination with other drugs, making it difficult to evaluate the effects of ribavirin alone. Therefore, it is difficult to recommend monotherapy of ribavirin.

Regarding the combined use of ribavirin and IFN, several *in vitro* studies on SARS-CoV found that the combination therapy decreases the required dose of ribavirin and results in a synergistic effect [16, 93, 94]. Also for MERS-CoV, monotherapy of IFN- α 2b and ribavirin was effective only at high doses in Vero cells and LLC-MK2 cells but was effective at lower concentrations when used together [93]. In addition, an animal study of MERS-CoV in rhesus macaques confirmed that combination therapy of IFN α 2b and ribavirin improved clinical findings and reduced the disease severity [95]. Clinical studies on combination therapy of ribavirin and IFN have mostly been conducted on MERS-CoV, and no clinical effects have been observed in most cases, in contrast to *in vitro* findings. In a study that retrospectively compared cases for which IFN- α 2a or IFN- β 1a was combined with ribavirin, neither combination therapy was effective [95]. In a large retrospective study conducted on 349 MERS-CoV patients, combination therapy of ribavirin with IFN (IFN- α 2a, IFN- α 2b, or IFN- β 1a) did not decrease the mortality rate on day 90 or reduce MERS-CoV RNA rapidly [95]. Therefore, the use of combination therapy of ribavirin and IFN may be considered when first-line medications cannot be used or are found to be ineffective.

Two clinical trials of combination therapy of ribavirin and LPV/r in SARS-CoV have been conducted. Significant clinical improvement was observed in combination therapy with ribavirin and LPV/r in both studies. In the study conducted by Chu et al., combination therapy of ribavirin and LPV/r (n = 41) resulted in a significantly lower mortality rate and incidence of ARDS compared to ribavirin monotherapy (n = 111) in SARS-CoV infection ($P < 0.001$) [55]. Moreover, in the study conducted by Chan et al., ribavirin and LPV/r combination therapy (n = 44) resulted in significantly lower rates of endotracheal intubation and mortality when compared to ribavirin monotherapy (n = 31) in SARS-CoV ($P < 0.05$) [21]. Therefore, the use of ribavirin and LPV/r combination therapy may be considered when first-line medications cannot be used or are found to be ineffective.

Ribavirin has been reported to cause adverse reactions, such as hemolytic anemia, bradycardia, liver dysfunction, pancreatitis, hypomagnesemia, and metabolic derangement [96, 97]. These reactions are more common when high-dose ribavirin is used [88, 91, 96, 97]. When ribavirin is used, particularly at high doses, close monitoring for adverse reactions is required.

- For dosage and administration, refer to **Table 2**.
- For mechanism of action, refer to **Figure 1**.
- For patients with dysphagia (swallowing problem), please refer to <http://www.covid19-druginteractions.org/> for updates.

Key question 5. For how long should antiviral agents be used?

- Generally, antiviral agents are recommended for 7 – 10 days; however, the duration may be shortened or prolonged depending on the patient's status.
- The duration may differ for different agents and may be changed depending on recent updates.

Table 2. Doses of antiviral agents for COVID-19

Drug	Normal renal function (CrCl >50 ml/min)	Impaired renal function (CrCl 25 – 50 ml/min)	Hemodialysis or CrCl <20 ml/min
Lopinavir/ritonavir [21-24]	Lopinavir/ritonavir 400 mg/100 mg po q12h	Same dose	Same dose
Hydroxychloroquine ^a	800 mg loading dose on day 1, followed by 400 mg po once-daily maintenance doses	Data not available	Data not available
Interferon-β1b [25]	0.25 mg/mL subcutaneous injection every other day	Data not available	Data not available
Remdesivir [26]	200 mg loading dose on day 1, followed by 100 mg IV once-daily maintenance doses	Same dose	Same dose
Favipiravir [27]	1,600 mg po q12hr loading dose on day 1, followed by 600 mg po q12hr maintenance doses	Data not available	Data not available

CrCl, creatinine clearance

- The doses are for adults and should be adjusted based on body weight and age for pediatric patients.

^aHCQ: Although the present guideline recommends the use of HCQ at 400 mg po 24hr, the results of various clinical trials currently underway in China that apply various doses may lead to a change in the recommendation. Studies that are currently underway use the following doses of HCQ (listed in the order of research date):

- (1) HCQ 100 mg PO q12hr vs. 200 mg q12hr PO (ChiCTR2000029559, 2020.2.4-): Wuhan, (<http://www.chictr.org.cn/showprojen.aspx?proj=48880>)
- (2) HCQ 400 mg PO q24hr for 5 days (2020.2.8-): Shanghai, (<https://clinicaltrials.gov/ct2/show/NCT04261517>)
- (3) HCQ 200 mg PO q12hr (unspecified duration) (ChiCTR2000029740, 2020.2.11-): Beijing, (<http://www.chictr.org.cn/showprojen.aspx?proj=49317>)
- (4) Days 1-3: HCQ 400 mg PO q8hr. Days 4-14: HCQ 400 mg PO q12hr (Hydroxychloroquine treating novel coronavirus pneumonia (COVID-19): a multicenter, randomized controlled trial. 2020.2.15-): Shanghai, (<http://www.chictr.org.cn/showproj.aspx?proj=49524>)
- (5) Day 1: first dose: 600 mg PO, second dose: 600 mg PO after 6 h; Days 2-10: 200 mg PO q24hr. Treating course: 10 days (ChiCTR2000029899, 2020.2.16-): Beijing (<http://www.chictr.org.cn/showprojen.aspx?proj=49536>)
- (6) HCQ 200 mg PO q12hr for 14 days (ChiCTR2000029992, 2020.2.18-): Xiamen <http://www.chictr.org.cn/historyversionpuben.aspx?regno=ChiCTR2000029992>
- (7) HCQ 400 mg PO q12hr for 10 days for patients diagnosed with mild, moderate, and severe cases of novel coronavirus pneumonia and without contraindications to CQ. (Expert consensus on CQ phosphate for the treatment of novel coronavirus pneumonia, 2020 Feb 20;43(0))
- (8) HCQ 200 mg PO for 14 days (ChiCTR2000030054, 2020.2.22-): Wuhan <http://www.chictr.org.cn/showprojen.aspx?proj=49869>
- (9) Day 1: HCQ 400 mg bid; Days 2-5: HCQ 200 mg bid (*In Vitro* Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. pii: ciaa237).

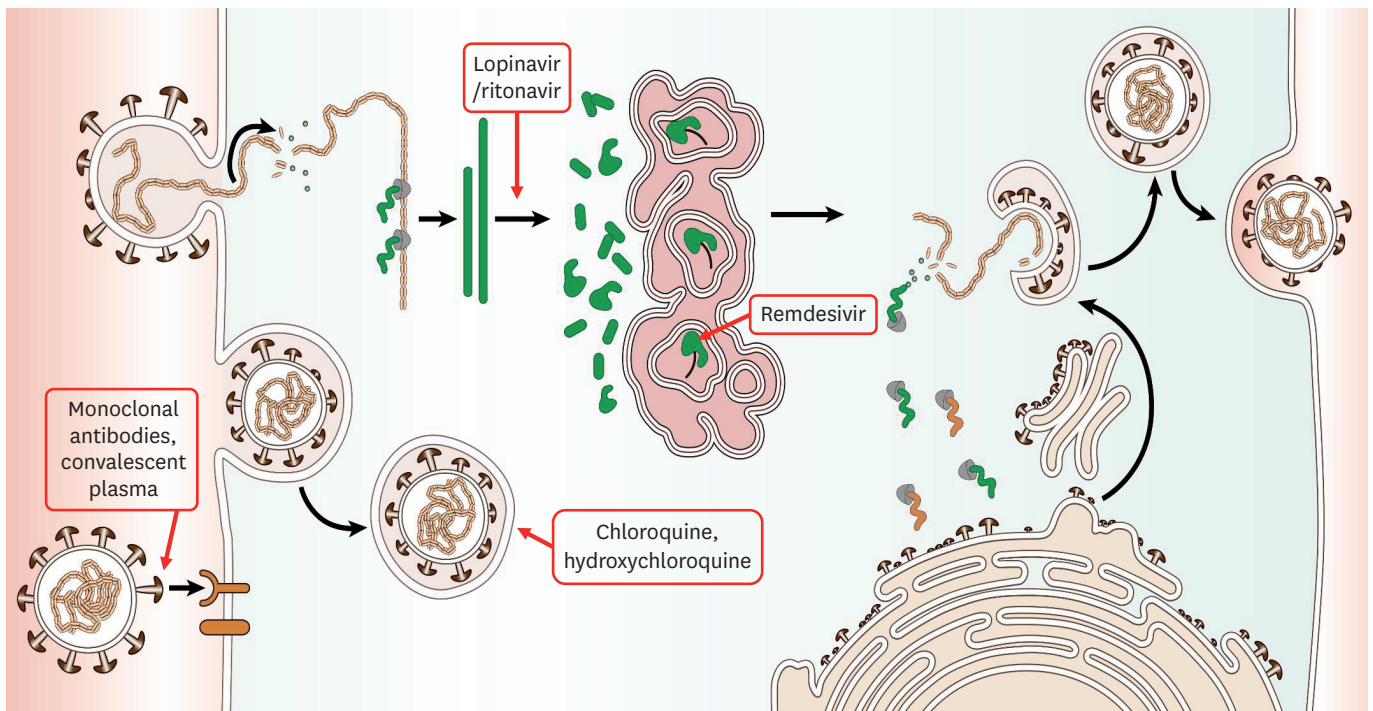


Figure 1. Mechanisms of action revealed for various COVID-19 drugs

In the past, for SARS-CoV and MERS-CoV patients, antiviral therapy was administered for 10–14 days [98-101]. The duration of antiviral therapy for COVID-19 varies depending on the drug, the clinical guideline of each country, and clinical trial protocols. A minimum of 10 days and maximum of 21 days of LPV/r treatment is recommended [59, 102-104], and HCQ is recommended for a minimum of 5 days and maximum of 14 days [42, 46, 104, 105]. For remdesivir, which can be used in Korea only in clinical trials, a minimum of 5 days to maximum 10 days of treatment is recommended according to various clinical trial protocols [106].

The clinical significance of different treatment durations on clinical outcome remains unclear, warranting further research on the appropriate duration of antiviral therapy. In cases where viral clearance is delayed due to immunosuppression, prolongation of treatment can be considered. In contrast, when patients show rapid recovery or when drug adverse effects are a concern, the duration of antiviral therapy may be shortened. Although the present guideline recommends 7 – 10 days of antiviral therapy for COVID-19 patients, individual decisions should be made upon consideration of patient status.

Key question 6. Are there other pharmacological treatments other than antiviral therapy?

1. Steroid

No study has established the benefit of steroid, and routine use of steroids is not recommended as long-term exposure is associated with various adverse effects. However, when other indications for steroids are present, including worsening asthma and severe septic shock requiring vasopressors, and ARDS, the use of steroids may be considered (CIII).

2. Intravenous immunoglobulin (IVIG)

The use of IVIG is not recommended routinely for COVID-19 as no evidence supporting its use for COVID-19 exist. However, IVIG may be considered in cases of sepsis depending on the clinical judgment (CIII).

3. Neuraminidase inhibitors

The routine use of neuraminidase inhibitors, anti-influenza agents, is not recommended for treatment of COVID-19 (BI). Anti-influenza agents may be used when there is coinfection with influenza or when there is a strong suspicion of co-infection (AI).

4. Antibiotics

The routine use of antibiotics is not recommended for the treatment of COVID-19 (AI). However, antibiotics may be used when bacterial co-infection is present or suspected (AI). An appropriate antibiotic should be chosen by healthcare providers depending on the patient's clinical symptoms and status.

● Steroids

No study has established that steroid use improves outcome. In an observation study of SARS patients, the use of steroids did not improve the mortality, and adverse effects such as avascular necrosis, psychosis, diabetes, and delayed viral clearance were reported [107]. In addition in a study of MERS patients, the use of steroids was not effective and instead led to delayed clearance of MERS-CoV in the lower respiratory tract [108]. Therefore, the routine use of steroids is not recommended for patients with COVID-19. Patients with severe sepsis and septic shock who received steroids recovered faster from the shock and had improved mortality when compared to those who did not receive steroids [109, 110]. Moreover, among patients admitted for community-acquired pneumonia, the use of steroids decreased the use of mechanical ventilation, progression to ARDS, and the length of hospital stay, but increased the risk of hyperglycemia [111]. Among patients with ARDS, the use of steroids has been reported to reduce the mortality rate and the length of mechanical ventilation [112, 113]. The use of methylprednisolone in patients with severe COVID-19 at 1 – 2 mg/kg/day for 5 – 7 days has been reported to be associated with the decrease in the length of oxygen treatment and the improvement of chest radiograph findings [114]. Among 201 COVID-19 patients with ARDS, the use of steroids was shown to be associated with lower mortality. However, confounding variables could not be adjusted for in the said retrospective cohort study [115]. Therefore, the findings cannot be generalized to other COVID-19 patients. Currently, there are several studies in progress to examine the efficacy of steroids for the treatment of the COVID-19 and the results should be carefully interpreted in the clinical context.

Accordingly, the administration of steroids may be considered in patients with severe COVID-19 who have worsening asthma or chronic obstructive pulmonary disease, severe septic shock requiring vasopressors, and ARDS [116-118]. If steroids are used, the occurrence of hyperglycemia, hypernatremia, and hypokalemia should be monitored closely and corrected [116, 119].

● Intravenous immunoglobulin (IVIG)

IVIG are immunomodulators that regulate cytokines and have anti-inflammatory effects. Whether IVIG have direct effects on coronavirus has not been elucidated, and no RCT has

been conducted on this matter. However, in a retrospective study of 12 SARS patients who deteriorated despite the administration of pentaglobulin (5 mg/kg, 3 days), steroids, and ribavirin, only one patient died with the rest of the patients showing good prognosis without any adverse effects [120]. In a case report, antiviral agents and IVIG were administered to a patient with SARS-CoV-2 infection; however, the effects have not been proven, and whether IVIG contains SARS-CoV-2-specific antibodies remains unknown. IVIG, which may induce hypercoagulation, have been reported to increase the risk of venous embolism, including pulmonary embolism, in SARS patients, thus warranting extra caution [121]. Therefore, IVIG is not routinely recommended for the treatment of SARS-CoV-2 infection. Nevertheless, the use of IVIG may be considered in sepsis or ARDS depending on the clinical judgment.

● Neuraminidase inhibitors

Neuraminidase inhibitors have not been found to inhibit the cytopathic effects of SARS-CoV in *in vitro* cell culture [61]. Thus, the routine use of neuraminidase inhibitors, which are anti-influenza agents, is not recommended for COVID-19. Based on experiences with the use of oseltamivir (a neuraminidase inhibitor) among 99 COVID-19 patients at a hospital in Wuhan [6], oseltamivir is being administered to patients with suspected or confirmed COVID-19 at many Chinese hospitals despite a clear lack of evidence [122]. It is thus necessary to confirm the results of clinical trials currently underway (NCT04303299, NCT04261270, and NCT04255017). However, anti-influenza agents may be used when there is coinfection with influenza or when there is a strong suspicion of coinfection.

● Antibiotics

According to the data reported in China, relatively small portion of patients (10 – 20%) have concurrent bacterial pneumonia. Therefore, the routine use of antibiotics is not recommended [8, 123]. However, antibiotics may be used when bacterial infection is also present or suspected. The choice of antibiotics should be based on the patient's clinical condition (whether pneumonia is community-acquired or healthcare-associated), local epidemiology, and antibiotic susceptibility [116].

Key question 7. Is convalescent plasma therapy recommended?

- Although large-scale studies are required, convalescent plasma therapy can be mentioned as an option for COVID-19 as it may help with the prognosis and disease progression. However, since the amount of antibodies may vary depending on the severity of the disease and the timing of collection, donors should be selected carefully.

In convalescent plasma therapy, antibodies may inhibit viral proliferation, and plasma components may also supplement coagulating agents in hemorrhagic fevers, such as Ebola. Therefore, it has been used among patients with 2009 seasonal influenza A (H1N1), avian influenza A (H5N1), SARS, and Ebola. No large-scale RCT is available on the use of convalescent plasma therapy in SARS. Case reports on SARS suggested that disease duration was shorter in the group that received convalescent plasma therapy and that the prognosis was particularly good when it was administered within 14 days [124-126]. However, in most studies, the decision to use convalescent plasma therapy depended on individual physicians, and the doses were not consistent. In a meta-analysis including SARS and influenza (H1N1, H5N1, and H1N1), the use of convalescent plasma or serum improved

the mortality [127]. In China, five patients with severe respiratory failure secondary to COVID-19 who were on mechanical ventilators received convalescent plasma therapy on days 20 and 10 of admission. The body temperature normalized 1 week after the administration of convalescent plasma therapy, and the organ failure assessment score, PaO₂/FiO₂ ratio, and clinical findings improved. The neutralizing antibody titer also increased and SARS-CoV-2 tests conducted 1 and 12 days after the administration yielded negative results [128]. In Korea, two cases of severe COVID-19 patients presented ARDS, who showed a favorable outcome after the use of convalescent plasma in addition to antiviral agents and systemic corticosteroid [129].

Although large-scale studies on SARS-CoV-2 are required, convalescent plasma therapy can be mentioned as an option for COVID-19 as it may help with the prognosis and disease progression. However, as reported in MERS patients, the amount of antibodies may vary depending on the severity of the disease and the timing of collection, so donors should be selected carefully [130, 131].

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SUPPLEMENTARY MATERIAL

Guideline Korean version.

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