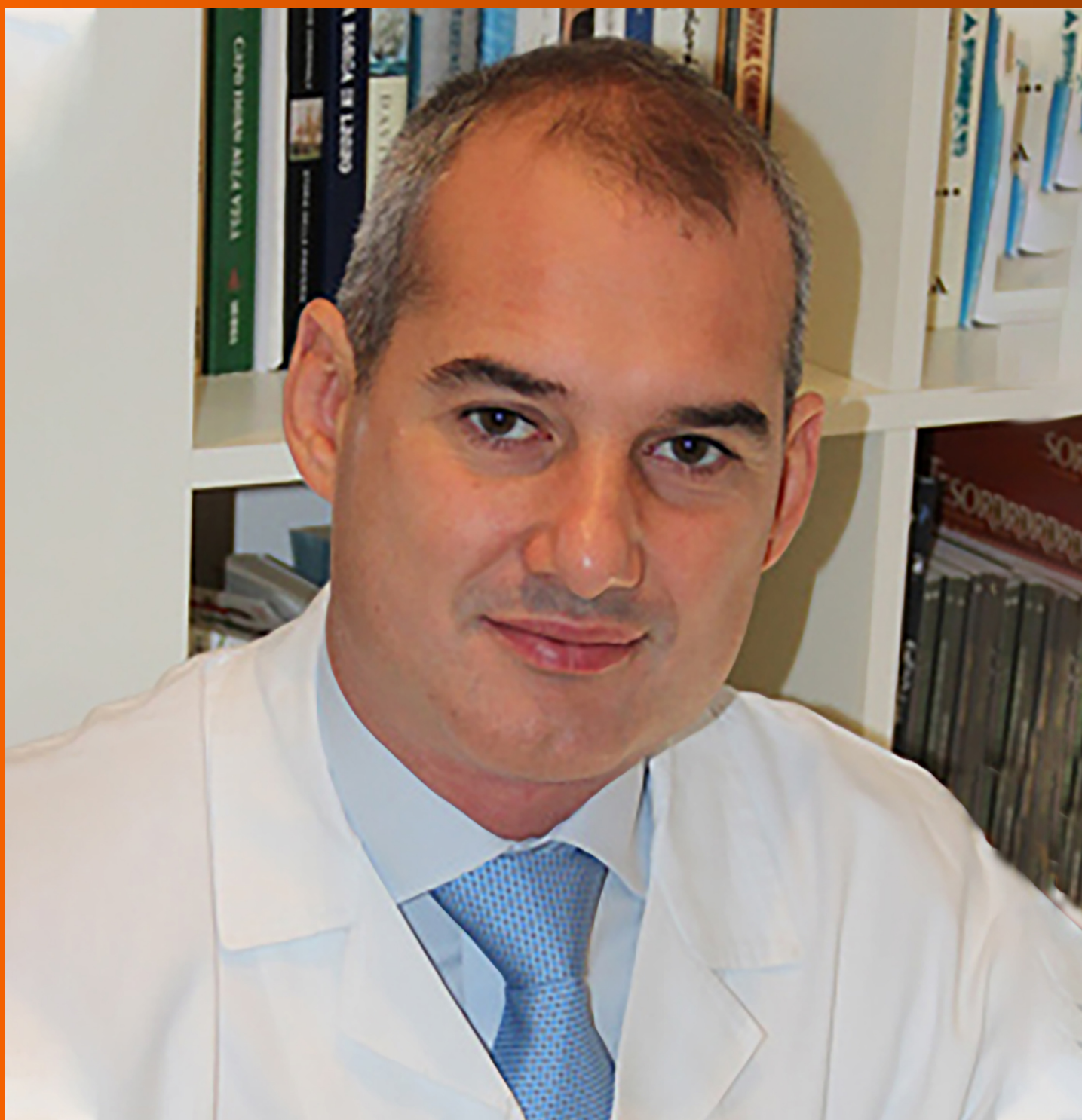


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Theory and reality of antivirals against SARS-CoV-2

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Abstract

At present, over 180 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide and there have been more than 3.8 million deaths due to the virus. However, specific effective antiviral treatment for this infectious disease is absent. At the beginning of the epidemic, relevant cellular and animal experiments of antiviral treatment for SARS-CoV-2 were conducted based on the prior studies of SARS-CoV and Middle East respiratory syndrome coronavirus. Some antivirals were preliminarily validated to be potentially effective in the clinical settings. But as the epidemic continued and more studies were carried out, the efficacy of these antiviral drugs became controversial. This paper reviews the pharmacology and application of interferon, lopinavir/ritonavir, ribavirin, chloroquine, arbidol, favipiravir, remdesivir, and thymosin $\alpha 1$ in coronavirus disease 2019. The actual effect of these drugs remains controversial. Meanwhile, the efficacy and safety of these drugs for patients with coronavirus disease 2019 still need to be explored.

Key Words: SARS-CoV-2; Antivirals; Efficacy; Safety; Middle East respiratory syndrome coronavirus

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Core Tip: This paper reviews the pharmacology and application of interferon, lopinavir/ritonavir, ribavirin, chloroquine, arbidol, favipiravir, remdesivir, and thymosin $\alpha 1$ in coronavirus disease 2019 (COVID-19). The actual effect of these drugs remains controversial. Meanwhile, the efficacy and safety of these drugs for patients with COVID-19 still need to be explored.

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INTRODUCTION

Similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), the SARS-CoV-2 belongs to the genus *Betacoronavirus* and is genetically close to a novel type of bat-derived coronavirus. The SARS-CoV-2 genome shares 79.5% homology with the SARS-CoV genome. Further, SARS-CoV-2 shares a common cell entry receptor with SARS-CoV [1]. Currently, SARS-CoV-2 has had a higher infectivity but a lower fatality rate than severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[1]. At the beginning of the epidemic, researchers across the globe have examined prior reports of SARS-CoV and MERS-CoV and conducted relevant cellular and animal experiments, and several antivirals were preliminarily validated to be potentially effective in the clinical settings. However, in the actual treatment process, effective antivirals are still absent. In the present paper, we seek to summary the potential antivirals against SARS-CoV-2.

INTERFERONS

Interferons (IFNs) are a class of proteins that exhibit broad-spectrum antiviral, antitumoral, and immunomodulatory effects. IFNs can be classified into type I (such as α and β), type II (γ), and type III (λ) based on the cell surface receptors, acid stability, initiation sequence, and chromosomal location[2]. The interaction between IFN and the target cells leads to the production of antiviral proteins that interfere with mRNA transcription. This hinders viral nucleic acid synthesis and inhibits viral replication[3]. Previous studies have demonstrated that high-dose IFN (types I and III) administration exhibits significant inhibitory effects on SARS-CoV and MERS-CoV in cell culture, animal studies, and patients. In particular, MERS-CoV was found to be more sensitive to IFNs than SARS-CoV in cell culture experiments[4]. The study by Omrani *et al*[5] showed that treating MERS with IFNs prolonged the survival by 14 d in 70% of patients. Conversely, in the report by Al-Tawfiq *et al*[6], all five patients eventually died. However, the authors of both the studies agreed that severe infections and comorbidities were the main reasons for poor efficacy. Al-Tawfiq *et al*[6] suggested that delayed treatment was a prognostic factor, and initiating treatment within 48 h of hospitalization or immediately after diagnosis could lead to better outcomes. Three types of IFN have been used to treat coronavirus infections. A study has suggested that IFN- β displays the most prominent therapeutic effect[7]. The recommended route of administration for IFN- α is inhalation of nebulized solution in novel coronavirus pneumonia diagnosis and treatment plan of China[8]. According to the autopsy report of the first patient who died from pneumonia caused by SARS-CoV-2, the lesions were found to be concentrated in the lungs, whereas evidence of damage in other organs was insufficient[9]. Nebulizer inhalation therapy can thus be directly delivered to the target organs, namely, the respiratory tract and the lungs, resulting in rapid onset of drug action and high local drug concentrations. Other advantages of inhalation therapy include low dosage, convenient administration, and few systemic adverse reactions[10]. However, all IFNs currently available in the market are injectable formulations. Intravenous formulations often contain preservatives such as phenol and nitrite, which can induce asthma attacks upon inhalation. Non-nebulized inhalation formulations do not meet the requirements for effective nebulization of particles. Further, they cannot be eliminated by the respiratory tract and may deposit in the lungs, increasing the incidence of lung infections[9]. Previous clinical studies on SARS and MERS mainly utilized subcutaneous or intramuscular injections. Further, the efficacy of the inhaled nebulizer lacks supportive evidence. If the nebulizer is used in a relatively closed environment, patients will be at risk of contracting the infection through aerosol transmission[8]. Therefore, the optimal IFN subtype and drug delivery route have not been confirmed through large-scale, standardized clinical studies. Early administration may lead to better outcomes in patients with mild-to-

moderate disease.

LOPINAVIR/RITONAVIR

Lopinavir/ritonavir tablet is a compound formulation consisting of lopinavir and ritonavir that is used as a second-line treatment for HIV[11]. In particular, lopinavir is an HIV-1 protease inhibitor that blocks the cleavage of the Gag-Pol polyprotein, leading to the production of immature, non-infectious viral particles while ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, resulting in increased lopinavir concentrations[12,13]. During the SARS outbreak, researchers from Hong Kong, China conducted *in vitro* and *in vivo* studies[14]. The *in vitro* studies showed that lopinavir and ribavirin at concentrations of 4 mg/mL and 50 mg/mL, respectively, exhibited antiviral activity against SARS-CoV after 48 h[14]. A controlled clinical study revealed that the addition of lopinavir/ritonavir to the previously used ribavirin and hormonal regimens lowered the incidence of acute respiratory distress syndrome or death and reduced hormonal use and nosocomial infections. Additionally, reduced viral loads and increased peripheral lymphocyte counts were observed in patients[14]. *In vitro* cellular experiments on MERS demonstrated that lopinavir/ritonavir exhibited anti-MERS-CoV activity[15]. Through animal models, the combination was demonstrated to exhibit a significant therapeutic effect relative to the control[16]. Lopinavir/ritonavir has been reported to display considerable efficacy when used as a combination therapy in the clinical setting[17]. Based on research on SARS and MERS to date, lopinavir/ritonavir has been often used in the SARS-CoV-2 treatment across the globe. A study from South Korea reported that in a patient with severe coronavirus disease 2019 (COVID-19) administered with lopinavir/ritonavir on the 10th day of disease onset, the β -coronavirus load began to decrease on the following day[18]. Certainly, the potential of natural disease outcome could not be ruled out. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with COVID-19 was held by Cao *et al*[19]. The results showed that there was no significant benefit of lopinavir/ritonavir compared with conventional treatment in the hospitalized severe patients with COVID-19. Although it was a negative conclusion, we can still explore the effect of lopinavir/ritonavir in the treatment of mild-to-moderate disease, and observe its reduction in the occurrence of severe disease. With the wider adoption of lopinavir/ritonavir in clinics, adverse reactions such as diarrhea, nausea, vomiting, and liver damage are common, which need to be constantly vigilant.

RIBAVIRIN

Ribavirin is a synthetic nucleoside analog that can inhibit a multitude of RNA and DNA viruses. Upon entry into cells, ribavirin is phosphorylated. Thereafter, it competitively inhibits the biosynthesis of guanosine triphosphate, which is required by the virus. This interferes with the synthesis of viral RNAs and proteins, thereby inhibiting viral replication and transmission[20]. Owing to the lack of other effective treatments in 2003, ribavirin was widely used to treat SARS[21]. However, during the course of application, the efficacy of ribavirin in patients with SARS was not definitive. Retrospective studies suggested that SARS-CoV was resistant to ribavirin[22]. Further, cohort studies failed to draw definitive conclusions regarding its efficacy owing to the study designs or the inability to distinguish its therapeutic effects from those of other drugs[23]. *In vitro* studies revealed that ribavirin exhibits detectable antiviral activity. However, this activity was low or decreased in cell lines after 48 h of incubation. The combination of ribavirin and IFN has been demonstrated to display a synergistic antiviral effect[24]. In the MERS epidemic, ribavirin was administered as a treatment regimen. Many studies have adopted the combined regimen of ribavirin and IFN and attained success in *in vitro* models[25]. However, the efficacy of the combined regimen in clinical practice remains inconclusive owing to the occurrence of sporadic cases and the heterogeneity of studies in different regions[6]. Based on the SARS or MERS studies, an effective concentration cannot be attained with the conventional dosage of ribavirin; however, the increased dosage will lead to a multitude of adverse reactions, primarily hemolytic anemia and abnormal liver function. Ribavirin alone might not exert a significant clinical effect; however, its early use in combination with IFN or lopinavir/ritonavir may result in a certain degree of clinical effect. The eighth version of the diagnosis and treatment plan of China specified the usage and dosage of ribavirin, and recommended "500 mg/administration, 2 to 3 intravenous drips per day

in adults" and "the duration of treatment should not exceed 10 d" was specified[8]. It still requires confirmation in larger studies to prove the therapeutic effect on mild-to-moderate and severe patients with COVID-19.

CHLOROQUINE

Chloroquine is an antimalarial drug that has been on the market for many years. Chloroquine is also used to treat autoimmune rheumatic diseases. *In vitro* cellular experiments showed that chloroquine effectively blocked infections owing to SARS-CoV-2 at low concentrations and exhibited a high selectivity[26]. Further, the outcomes of more than 100 patients administered with chloroquine phosphate were superior to those administered with the control drug[27]. Chloroquine was found to improve the lung imaging findings, promote a virus-negative conversion, and shorten the disease course[27]. Chloroquine was studied during the SARS epidemic. Further, it was demonstrated to effectively prevent the spread of SARS-CoV in the cell culture. Treatment of cells with chloroquine prior to or after SARS-CoV infection effectively inhibited the spread of the virus[28]. Chloroquine is a weakly basic drug that can alter the pH of endosomes, thereby blocking pH-dependent viral replication. Meanwhile, chloroquine can interfere with the glycosylation of viral cell receptors and inhibit viral replication. Chloroquine also acts as a potent autophagy inhibitor and interferes with viral infection and replication *via* affecting autophagy[29]. The replacement of an ethyl group by hydroxyethyl in chloroquine will result in the formation of hydroxychloroquine. Hydroxychloroquine and chloroquine have similar pharmacokinetics, indications, and associated adverse reactions. However, compared to chloroquine, the overall incidence of adverse reactions associated with hydroxychloroquine is lower and is mainly reflected in the lower incidence of ocular adverse reactions[30]. Conceptually, hydroxychloroquine should be effective and might serve as a better option from the perspective of drug safety. The study by Gautret *et al*[31] showed that 20 cases treated with hydroxychloroquine had a significant reduction of the viral carriage and much lower average carrying duration compared to the 16 controls. Especially, six patients who used hydroxychloroquine in combination with azithromycin had a 100% negative rate of nasopharynx swab virus on the sixth day. Despite its small sample size, the study brings great hope that hydroxychloroquine treatment is significantly associated with a viral load reduction in COVID-19 patients and its effect is reinforced by azithromycin. Owing to the above antiviral mechanisms and previous research and application outcomes, chloroquine and hydroxychloroquine, with or without azithromycin, have been studied in multiple clinical trials for the treatment of COVID-19. Subsequent analyses confirmed that hydroxychloroquine alone was not effective in the treatment of SARS-CoV-2, and it increased the risk of death when combined with azithromycin[32]. Hydroxychloroquine did not show any new coronavirus clearance or clinical benefit. On the other hand, it brought additional side effects[33]. The use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 was not recommended. However, many clinical trials are still in progress. An editorial suggested that hydroxychloroquine might have a preventive effect, and its potential preventive benefit remains to be determined[34].

ARBIDOL

Arbidol is a small indole-derivative molecule developed by the former Soviet Union. It is primarily indicated in flu caused by influenza A and B viruses. Arbidol has been used in Russia for more than 20 years and has exhibited good safety and tolerability [35]. Further, it was approved for marketing in China in 2006[35]. As a hemagglutinin inhibitor, an IFN inducer, and an immunostimulating agent, arbidol can bind to lipid and protein residues of the viruses and prevent cell entry and fusion by locally impairing viral attachment to the cell plasma membrane. In addition, it inhibits viral replication, assembly, and budding[35,36]. Thus, arbidol demonstrates remarkable potential as a broad-spectrum antiviral agent. *In vivo* and *in vitro* experiments have confirmed that it exerts antiviral activity against many RNA or DNA viruses, such as adenovirus, respiratory syncytial virus, hantaan virus, hepatitis B virus, hepatitis C viruses, SARS-CoV, and MERS-CoV[35,37]. However, it is a relatively new drug for the treatment of influenza A and B viruses. Accordingly, earlier work had mainly focused on *in vitro* experiments, and clinical data supporting its use for SARS-CoV and MERS-CoV are lacking. For the current SARS-CoV-2 epidemic, arbidol was mentioned

in the novel coronavirus pneumonia diagnosis and treatment plan of China[8]. According to media reports, *in vitro* cellular experiments showed that arbidol at 10-30 μm was 60 times more efficacious at inhibiting coronavirus than the control drug. Further, it significantly inhibited the cytopathic effect of the virus[38]. Although *in vitro* experiments have demonstrated its efficacy, whether the standard dosage can result in an effective concentration *in vivo* remains unknown. Clinical studies with arbidol have been reported; however, patients with favorable outcomes often received a combination with other drugs instead of arbidol alone. In addition, the sample sizes of the studies were small[39]. The early epidemic was identified to coincide with the flu season. The use of arbidol might be beneficial to flu patients who cannot be screened in time.

FAVIPIRAVIR

Favipiravir is a novel type of RNA polymerase inhibitor that has obtained marketing approval for the treatment of novel and re-emerging influenza. A study has shown that in addition to those on influenza viruses, favipiravir exhibits robust antiviral effects on different RNA viruses, such as the Ebola virus, arenavirus, bunyavirus, and rabies virus[40]. Favipiravir is converted intracellularly into favipiravir ribofuranosyl-5'-triphosphate, which is structurally similar to purine and can compete with purine for viral RNA polymerase. This hinders the replication and transcription of viral RNA strands and increases the rate of mutation during viral genome replication, leading to a significant reduction in virus-specific infectivity and to virus elimination[41]. As SARS-CoV-2 is an RNA virus, favipiravir should, in principle, be effective against the virus. However, since its launch in 2014, only few clinical studies with favipiravir have been conducted on coronavirus. A study in Vero E6 cells infected with SARS-CoV-2 showed that favipiravir was not an ideal drug, with a half maximal effective concentration (EC₅₀) of 61.88 $\mu\text{mol/L}$, 50% cytotoxic concentration of > 400 $\mu\text{mol/L}$, and selectivity index of > 6.46. Although its EC₅₀ value in the Ebola-infected Vero E6 cells reached 67 $\mu\text{mol/L}$, it was demonstrated to exert 100% protection against Ebola infection in mice. Thus, different conclusions could be derived from the *in vitro* experiments and *in vivo* studies[26]. Further, the clinical trial is currently underway in Shenzhen. Preliminary results of this trial have shown promising efficacy and a low incidence of adverse reactions. After 3 to 4 d of treatment, the negative conversion rate of the viral nucleic acids was significantly higher in the treatment group than the control group[42]. Media reports generally assert optimism; however, they are not based on rigorous scientific evidence. In a small trial of SARS-CoV-2, 120 patients were treated with favipiravir. Although favipiravir improved the latency to relief for pyrexia and cough, it did not significantly improve the clinical recovery rate on day 7 [43]. Therefore, conclusions from authentic and validated studies are still needed to further delineate the efficacy and tolerability of the drug.

REMDESIVIR

Remdesivir is a novel nucleoside analog and a broad-spectrum antiviral agent. It binds to the nascent viral RNA strands, leading to the premature termination of viral replication[44]. The results of *in vitro* cellular experiments and animal studies have demonstrated that it exerts extremely potent *in vitro* antiviral activities against coronaviruses that infect human and different bat-derived coronaviruses[45]. In a mouse model of SARS-CoV, prophylactic and early treatment with remdesivir significantly reduced the viral load in the lungs of mice and improved the clinical symptoms and respiratory functions[46]. Additionally, remdesivir effectively reduced the viral titer in the lung tissue of mice infected with MERS-CoV and improved lung tissue injury. Its efficacy was superior to that of the combination of lopinavir/ritonavir and IFN- β [17]. In Vero E6 cells, the EC₅₀ and EC₉₀ of remdesivir for SARS-CoV-2 are 0.77 μM and 1.76 μM , respectively[26]. Remdesivir has been studied in several clinical trials for the treatment of SARS-CoV-2, and it has been approved by the Food and Drug Administration for the treatment of COVID-19 in hospitalized patients[47]. Wang *et al*[48] had published a randomised, double-blind, placebo-controlled, multicentre trial about remdesivir in adults with severe COVID-19. Compared with the placebo group, the clinical improvement time of the remdesivir group was shortened by an average of 2 d and the invasive mechanical ventilation time was shortened by an average of 4 d, but the above differences were not statistically

Table 1 Summary of each drug used in clinical practice[8,51,64-67]

Antiviral	Notes	Usage and dosage (adults)
IFN	(1) Not recommended for the treatment of patients with severe or critical COVID-19, except in a clinical trial; (2) Patients with early (<i>i.e.</i> , < 7 d from symptom onset) mild and moderate disease may benefit; and (3) IFN- α has primarily been used as nebulization and usually as part of a combination regimen	(1) Nebulized IFN- α : 5 million units, add 2 mL of sterile water for injection, twice daily. Preferably less than 10 d; and (2) Subcutaneous IFN- β : 8 million international units every other day. Preferably less than 10 d
LPV/r	(1) Not recommended to treat patients with COVID-19 at any severity; (2) Not recommended to use alone; and (3) The plasma drug concentrations of typical doses are far below the levels that may be needed	Lopinavir 400 mg/ritonavir 100 mg orally twice daily. Preferably less than 10 d
RBV	(1) There is not enough sample size, scientific and objective clinical data to prove effective; and (2) Not recommended to use alone. Usually in combination with IFN and/or LPV/r	500 mg per time, inject 2-3 times per day intravenously. Preferably less than 10 d
CQ	(1) Not recommended to treat patients with COVID-19 at any severity; and (2) Recommendation against CQ with or without azithromycin	(1) CQ 600 mg twice daily for 10 d (high dose, serious side effect). CQ 450 mg twice daily for 1 d, then CQ 450 mg for 4 d (low dose, mild side effect); (2) HCQ 800 to 1600 mg orally on the first day, 1 to 3 divided doses. 200 to 800 mg orally daily for 5 to 21 d, 1 to 2 divided doses; and (3) CQP 500 mg twice daily for 10 d
Arbidol	There is not enough sample size, scientific and objective clinical data to prove effective	100 mg orally twice daily for 5 d. Preferably less than 10 d
Favipiravir	There is not enough sample size, scientific and objective clinical data to prove effective	1600 mg for the first dose, then 600 mg orally twice daily for 5 d
Remdesivir	(1) Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19; and (2) Consider remdesivir for hospitalized patients with COVID-19 who require supplemental oxygen but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation	200 mg on day 1, then 100 mg injected intravenously once daily for 5-7 d
Thymosin $\alpha 1$	There is not enough sample size, scientific and objective clinical data to prove effective	1.6 mg subcutaneous injection, twice a week, each time 3-4 d apart. Preferably more than 4 wk

IFN: Interferon; LPV/r: Lopinavir/litonavir; RBV: Ribavirin; CQ: Chloroquine; HCQ: Hydroxychloroquine; CQP: Chloroquine phosphate; COVID-19: Coronavirus disease 2019.

significant. Positive data was published by the American Institute of Allergy and Infectious Diseases at almost the same time. Preliminary data analysis from a randomized controlled trial of 1063 patients showed that COVID-19 patients who had progression had lung involvement recovered faster than similar patients who had received placebo[49]. The median time to recovery was 11 d in patients receiving remdesivir and 15 d in patients receiving placebo, but the fatality rate did not improve. Two studies showed that remdesivir did not reduce the mortality, but can shorten the course of disease. In another cohort of patients hospitalized for severe COVID-19, clinical benefit was observed in 36 (68%) of 53 patients who were treated with remdesivir[50], but there was no control group for this study. There is no sufficient evidence to prove that remdesivir can improve the survival rate, so it is not recommended by the guideline of World Health Organization[51]. It still requires confirmation in larger studies to prove the therapeutic effect on mild-to-moderate and severe patients with COVID-19.

THYMOSIN A1

Thymosin $\alpha 1$ is a group of immunoactive peptides that can induce T-cell differentiation and maturation and regulate T-cell functions. Thymosin $\alpha 1$ is a broad-spectrum antiviral biologic that is clinically used as a primary or adjuvant treatment for chronic hepatitis, acquired immunodeficiency syndrome, other viral infections, and tumors. Most patients with COVID-19 exhibit reduced lymphocyte counts, suggesting that SARS-CoV-2 may primarily affect lymphocytes, particularly T cells[52]. As thymosin $\alpha 1$ can promote T-cell development, differentiation, and maturation, it can be employed as an adjuvant antiviral therapy to enhance the immune response to the virus in immunocompromised patients. A prior case report described the use of thymosin $\alpha 1$ as part of a combination therapy in the treatment of MERS-nCoV infection[53]. The

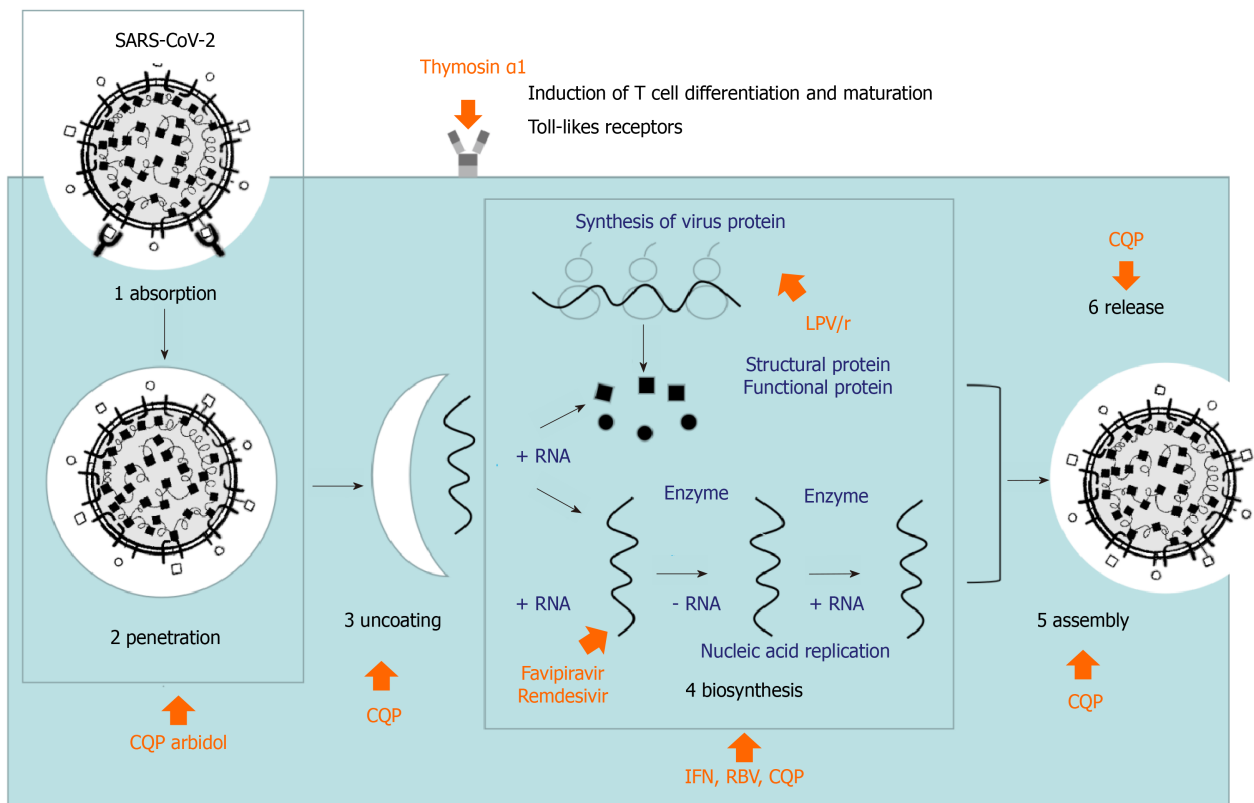


Figure 1 Schematic diagram of main antiviral targets[3,12,13,20,35,36,44,55,56]. IFN: Interferon; RBV: Ribavirin; CQP: Chloroquine phosphate.

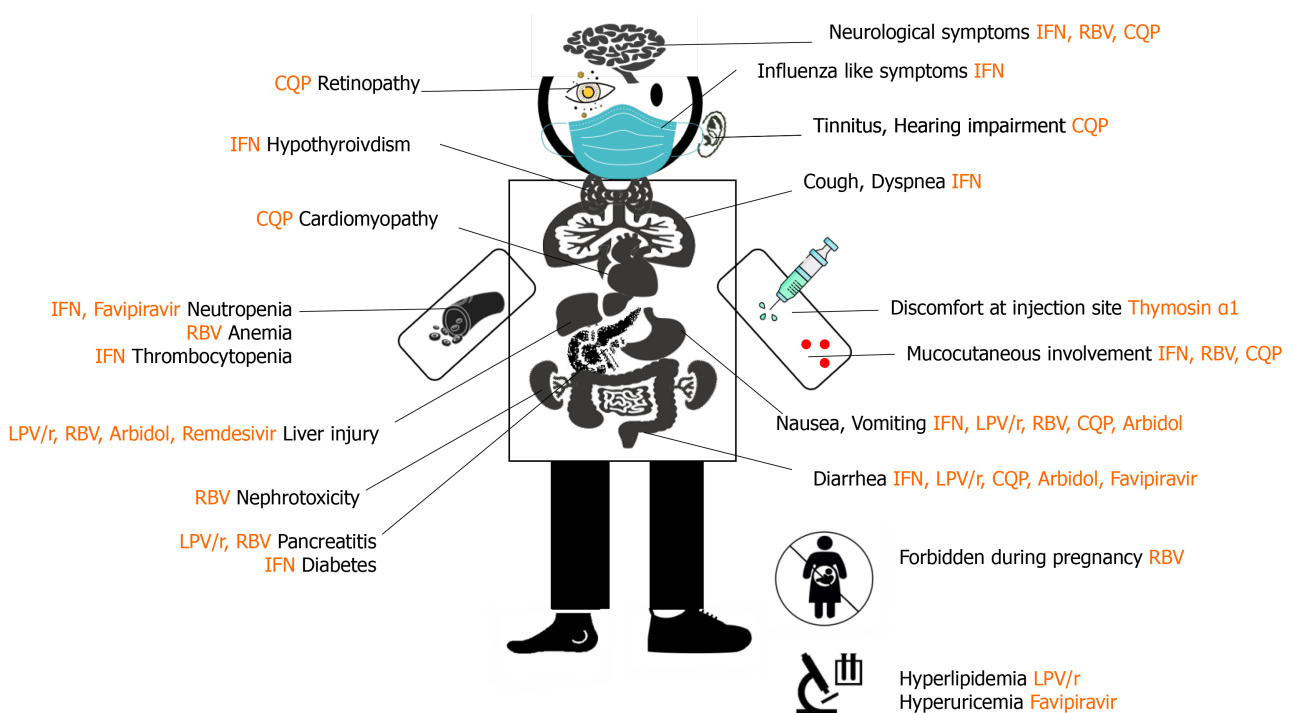


Figure 2 Schematic diagram of main adverse reactions of antiviral drugs[29,46,57-63]. IFN: Interferon; LPV/r: Lopinavir/litonavir; RBV: Ribavirin; CQP: Chloroquine phosphate.

autopsy report of a patient with COVID-19 revealed the occurrence of alveolar septal congestion, edema, and the infiltration of mononuclear cells and lymphocytes[9]. Lymphocyte infiltration is the immune response elicited by the host to eliminate the virus. However, an overactive response may eliminate the virus while concurrently inducing local inflammatory response in the lung tissue or uncontrolled systemic

inflammatory response. Whether the use of thymosin $\alpha 1$ will aggravate the immune response and lead to immune-mediated damage should be elucidated. For healthy individuals with normal immunity, the preventive effect of thymosin remains unclear. Therefore, additional research is required to determine the stage of the infection that is most suited for the use of thymosin[54]. As thymosin can enhance the body's immune response, some hospitals have initiated clinical studies of antiviral agents in combination with thymosin $\alpha 1$. Data from these studies are expected to serve as useful references[54].

CONCLUSION

The drugs mentioned in this paper have certain theoretical basis, but the actual research results are not completely satisfactory, especially for severe patients (Figures 1 and 2, Table 1). There is a distance between theory and practice. The efficacy and safety of these drugs need to be verified in future clinical research. We still have to be optimistic. In the early stage, we did not know about this disease, but now we have enough experience to diagnose it. It will achieve better results if having early diagnosis and early treatment. A clearer picture is expected in the near future to ensure that safe and effective drugs can be utilized and the overuse of ineffective drugs can be avoided.

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