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Review Article

Rational Use of Antiviral Drugs Against SARS-CoV2

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Abstract: *Background:* In December 2019, the outbreak of infectious pneumonia caused by a novel strain of coronavirus was named 'SARS-CoV2', which appeared in Wuhan, China. The said virus is highly contagious and rapidly spread across the world. So far, there is no effective antiviral drug in clinic. *Objective:* To make clinicians standardize the usage of the antiviral therapies against COVID-19, worldwide. *Method:* According to the recommended diagnosis and treatment protocols and relevant literature reports, suggested therapeutics include α-interferon (nebulization), lopinavir/ritonavir, ribavirin (recommended in combination with α-interferon or lopinavir/ritonavir), chloroquine phosphate, and arbidol. Recommendations based on various perspectives, such as timing and duration of medication, usage and dosage, adverse reactions and corresponding monitoring indicators, interactions, combination of antiviral drugs, efficacy evaluation indicators and discharge criteria were listed. *Result:* Pharmacist and clinicians provides knowledge of drug therapeutics for antiviral therapy and pharmaceutical care of clinical COVID-19. *Conclusion:* Recommendations of rational use of antiviral drugs against SARS-CoV2 may provide a timely reference to frontline clinicians in their fight against COVID-19 pneumonia to improve the clinical cure rate.

Keywords: COVID-19, Antiviral Drugs, SARS-CoV2

1. Introduction

At present, COVID-19 is rapidly spreading throughout the world, resulting in a pandemic. No effective antiviral therapy has been identified yet against COVID-19, adding to the complexity of the current scenario. On February 18, 2020, the National Health Commission of China issued the "Diagnosis and Treatment Scheme for New Coronavirus Pneumonia (Trial Version 6)" [1]. The issue suggested a wide range of antiviral medications to treat COVID-19 patients. The suggested therapeutics include α-interferon (nebulization), lopinavir/ritonavir, ribavirin (recommended in combination with α-interferon or lopinavir/ritonavir), chloroquine phosphate, and arbidol. Here, we provide a few recommendations on the timing, duration of the treatment, dosage of the drug, adverse reactions and monitoring indicators, interactions, combined medications and efficacy evaluation indicators based on our practice and available evidence. Authors recommendations will be critical to standardize the usage of the antiviral therapies against COVID-19, worldwide. Moreover, these recommendations may provide a timely reference to frontline clinicians in their fight against COVID-19 pneumonia to improve the clinical cure rate.

2. Medication Timing and Duration of Treatment

The on-time initiation of antiviral therapy is critical to treat COVID-19 patients. A systematic review reported that an early administration of lopinavir/ritonavir reduced patient mortality, and subsequently reduced glucocorticoid dosage.

On the contrary, delayed administration of lopinavir/ritonavir had no significant effect [2]. A previous study reported that the immediate administration of ribavirin post-SARS-CoV-2 diagnosis could ameliorate the disease pathology [3]. However, introducing ribavirin treatment 6-14 days post the development of symptoms had no significant effect [4]. α-interferon, chloroquine phosphate, and arbidol should be administered at the onset of the disease to prevent the virus from invading the human cells. The "New Coronary Virus Pneumonia Diagnosis and Treatment Plan (Trial Version 6)" states that the antiviral drugs lopinavir/ritonavir, ribavirin, and arbidol should not be used for more than ten days [1], and chloroquine phosphate for no more than seven days [5]. The experts came into consensus on the comprehensive treatment of coronavirus held in Shanghai in 2019, and pointed out that antiviral drugs should be discontinued when the viral nucleic acid test becomes negative [6].

3. Usage and Dosage

(1) α-interferon [1]: Five million units or an equivalent dose for adults. Add 2 ml of sterile water for nebulization, twice daily. α-interferon being a recombinant protein product, could be denatured during atomization if over-heated. Hence, ultrasonic atomization is not recommended. Instead, jet atomizers (air compression atomizers), vibrating screen atomizers, or oxygen driven atomization could be used. The atomization process induces aerosol. Therefore, α-interferon cannot be atomized with chymotrypsin, acetylcysteine, and ipratropium bromide, simultaneously [7]. Hence, it is recommended to carry out the atomization process in negative pressure ward [7].

(2) Protease inhibitors: Lopinavir/ritonavir [1]: 400 mg/100 mg twice daily (2 tablets) for adults suffering from COVID-19 associated pneumonia. It should be taken orally after a meal, swallowing the entire tablet without chewing, breaking, or crushing. Lopinavir/ritonavir oral solution (80 mg/20 mg per ml) should be taken twice daily at a dose volume of 5 ml. The oral solution can be taken with food to increase the bioavailability of the drugs. Oral solutions can also be administered through tube feeding. Patients with severe liver dysfunction cannot take lopinavir/ritonavir. In contrast, patients with mild to moderate liver dysfunction, renal dysfunction, and CRRT need not adjust the dose. Besides, pregnant and lactating women can take lopinavir/ritonavir.

(3) Ribavirin [1]: 500 mg/ml twice or thrice a day for adults suffering from COVID-19 associated pneumonia. Slow intravenous injection of 1 mg/ml or 5 mg/ml ribavirin, diluted with saline or 5% glucose, respectively, can be administered. Often, the combination of ribavirin with α-interferon or lopinavir/ritonavir is also recommended by clinicians.

(4) Chloroquine phosphate: Patients aged between 18 to 65 years, suffering from mild COVID-19 associated pneumonia, and having a bodyweight of more than 50 kg are recommended to take 500 mg of chloroquine phosphate twice daily. However, patients weighing less than 50 kg are recommended to take 500 mg of chloroquine phosphate twice daily for the first two days, and subsequently once daily till the seventh day. It is often suggested to take chloroquine phosphate with food to reduce gastrointestinal adverse reactions and to promote drug absorption. Antacid drugs should not be taken four hours before and after the administration of chloroquine phosphate as antacids affect the absorption of chloroquine. In case of severe gastrointestinal reactions, the dose can be reduced to 500 mg once daily, or even discontinued [8].

(5) Arbidol tablets: 200 mg for adults once and thrice daily, 10 mg/kg/day for children aged >2 years, taken in four doses [1, 9]. Arbidol dispersible tablets can be chewed, or dissolved. It is recommended to take the tablet after meals to relieve gastrointestinal reactions.

4. Adverse Reactions and Corresponding Monitoring Indicators

(1) α-interferon is administered as a nebulizing inhalation in China. Since its excipients often contain preservatives, children tend to suffer from an irritating cough during nebulizing inhalation. Therefore, nebulization is not recommended for children [4]. Nebulized inhalation is often well-tolerated, albeit it has some adverse reactions such as mild fever.

(2) Common adverse reactions of lopinavir/ritonavir include diarrhea, nausea and vomiting, migraine, liver damage, pancreatitis, and rashes. Also, it can significantly increase blood triglyceride and cholesterol concentrations, resulting in lipid metabolism disorders. Previous observations suggest that lopinavir/ritonavir can increase PR interval, causing a second or third-degree cardiac block. Hence, patients may suffer from an abnormal conduction system and should be prescribed the medication cautiously. Patients suffering from severe diarrhea should be treated with fluid supplements and antidiarrheal medications such as montorite. In addition, liver enzymes, triacylglycerols and cholesterol are suggested to be monitored closely.

(3) Ribavirin can cause dose-dependent anemia. Therefore, it is crucial to evaluate the red blood cell count [10]. This dose-dependent anemia can be treated by reducing the dose of ribavirin and by eventually discontinuing or using erythropoietin [11]. Ribavirin leads to heart damage, causing dyspnea and chest pain in patients with respiratory diseases such as chronic obstructive pulmonary disease or asthma. Ribavirin is not recommended for patients with a significant or unstable history of heart disease and also for elderly individuals. Studies have shown that ribavirin can cause hypocalcemia, hypomagnesemia, hyperammonemia, and pancreatitis. Ribavirin is not recommended to be

used by pregnant women owing to its teratogenic effect. Gravidity should be avoided within six months of stopping ribavirin treatment. Patients with liver dysfunction like Child-Pugh B/C, or renal insufficiency having creatinine clearance <50 ml/min must avoid using ribavirin. While under ribavirin treatment, it is critical to monitor blood routine, electrolytes, blood ammonia, and blood amylase.

(4) It is crucial to ensure that the electrolyte levels (potassium, sodium, chloride), blood glucose, liver and kidney function, and electrocardiogram of the patients are normal before introducing chloroquine administration [5]. Chloroquine is known to induce hemolysis and acute renal failure in patients with G-6-PD deficiency, and hence, must not be administered with chloroquine [12]. The half-life of oral chloroquine phosphate in plasma is 2.5-10 days, and elimination half-life in tissues is even longer. Therefore, a higher dosage or longer treatment period leads to the accumulation of chloroquine in different organs, which results in dizziness, headache, nausea, vomiting, diarrhea, and rashes. Patients suffering from retinopathy and cardiotoxicity should be given adequate attention.

(5) Arbidol hydrochloride is safe and well-tolerated by most of the patients with adverse reactions shown by merely 6% of the recipients. The major adverse reactions include gastrointestinal symptoms [13-15] dizziness, elevated serum transaminase, and bradycardia. Liver function and electrocardiogram should be monitored in patients under arbidol hydrochloride administration. Arbidol hydrochloride should be used cautiously by pregnant and lactating women, patients with severe renal dysfunction, and patients with sinus dysfunction.

5. Interaction

(1) The combination of α-interferon and theophylline may cause theophylline poisoning due to inhibition of CYP1A2 activity.

(2) Lopinavir/ritonavir is an inhibitor of CYP3A, a cytochrome P450 isoform. Inhibiting CYP3A activity can increase the blood concentration of a wide array of drugs that are mainly metabolized by CYP3A. The concentrations of drugs such as atorvastatin, and erythromycin can be increased in blood upon co-administration with lopinavir/ritonavir. Thus, lopinavir/ritonavir should be prescribed cautiously. In addition to the above-mentioned changes, lopinavir/ritonavir can also reduce voriconazole levels in the blood, and hence, such a combination should be avoided.

(3) Combination of ribavirin with nucleoside analogues or didanosine can cause lactic acidosis. It has been reported that ribavirin can inhibit the conversion of zidovudine phosphate from zidovudine indicating antagonism while used in combination.

(4) Till date, a wide range of drugs are banned from being used in combination with chloroquine phosphate [8]. These drugs include cardiovascular drugs such as digitalis, antiarrhythmic drugs (class Ia: quinidine, procainamide, class III: amiodarone, sotalol, ibutilide, dronedarone), bepridil, hydrochlorothiazide, and indapamide, antibiotics such as quinolones, macrolides, triazole antifungal drugs, penicillamine, and streptomycin, drugs of the central nervous system such as methadone, tricyclic antidepressants, citalopram, antipsychotics; monoamine oxidase inhibitors, gastrokinetic drugs (domperidone, cisapride), antiemetics (ondansetron, dolasetron), and others such as phenylbutazone, heparin, astemizole, ammonium chloride, apomorphine, octreotide, terfenadine, and arsenic trioxide.

(5) The combination of arbidol with aluminium-containing preparations affect the absorption of arbidol. It is recommended to have an interval of at least 1-2 hours between the administration of the two compounds. However, the combination with probenecid eventually extends the half-life of arbidol while the concentration of theophylline is increased in plasma when co-administered with arbidol. Arbidol is known to be metabolized by the liver enzyme CYP3A4. Hence, it is recommended to be careful while using drugs inhibiting CYP3A4 like lopinavir/ritonavir in combination with arbidol.

6. Combination Medication

Application of multidrug combination is a critical strategy against COVID-19 [16], especially for severe cases. The antiviral mechanisms of the five drugs mentioned above are different and unique. Therefore, presumably, the efficacy can be enhanced when used in combination. However, the effect of the combined use of antiviral drugs is still controversial [17-18]. The "New Coronary Virus Pneumonia Diagnosis and Treatment Plan (Trial Version 6)" [1] issued by the National Health and Medical Commission recommends that three or more antiviral drugs are not used together, simultaneously.

Based on the superposition of drug interactions and adverse reactions, we propose that aerosolized inhaled α-interferon can generally be used in combination with four other antiviral drugs. Combination of chloroquine phosphate and lopinavir/ritonavir leads to gastrointestinal response and liver toxicity, and the interaction between the two drugs is not clear, which results in adverse events such as death. The combination of ribavirin and chloroquine phosphate can cause cardiac arrest and hemolytic anemia, and hence, forbidden. Some healthy subjects manifested bradycardia, 3 hours post drug intake during the human bioequivalence test of arbidol preparations conducted in China. Cardiac toxicity should be monitored when arbidol is used in combination with chloroquine phosphate as

chloroquine phosphate can cause cardiac conduction block and sudden cardiac arrest. Lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol show hepatotoxicity. Therefore, liver function should be monitored when they are used in any kind of combination. Oral administration of lopinavir/ritonavir, chloroquine phosphate, and arbidol can cause gastrointestinal reactions, and higher incidences of diarrhea when combined. These factors must be taken into consideration while introducing combinatorial multidrug therapy in patients.

7. Efficacy Evaluation Indicators

A wide variety of clinical, biochemical indicators can be used to evaluate the efficacy of a given therapy either alone or in combination. The indicators under consideration include individual supportive treatment, vital signs, respiratory symptoms, finger oxygen saturation, blood routine, erythrocyte sedimentation, CRP, PCT, coagulation function, arterial blood gas analysis, pulmonary CT, viral nucleic acid and organ functions (such as liver enzymes, bilirubin, myocardial enzymes, creatinine, urea nitrogen, urine output).

The discharge criteria for COVID-19 associated pneumonia [6] are as follows: body temperature returning to normalcy for at least three days; significant improvement of respiratory symptoms; significant improvement of acute exudative lesions shown in pulmonary imaging examination; two consecutive viral nucleic acid detection tests of respiratory specimens should be negative (The sampling interval should be at least one day). Additionally, the COVID-19 nucleic acid test of the fecal specimens should also be negative. Lastly, the total treatment and supervision duration must be more than two weeks.

8. Conclusion

No effective antiviral drugs have been confirmed for SARS-COV2, but they are recommended based on existing research results and the diagnosis and treatment guidelines of the National Health Commission，α-interferon (nebulization), lopinavir/ritonavir, ribavirin (recommended in combination with α-interferon or lopinavir/ritonavir), chloroquine phosphate, and arbidol can be attemped.

Rational use of antiviral drugs to treat SARS-CoV2 in China including medication timing and duration of treatment, usage and dosage, adverse reactions and corresponding monitoring indicators, drug interactions, combination medication, and efficacy evaluation.

Authorship Contribution

Naiju Zhang: wrote the manuscript, Tianping Chen: wrote and modified the manuscript, Kuihua Xu: modified the manuscript, Chuanmiao Liu: modified the manuscript, Shousong Zhao: modified the manuscript, Wei Li: consulted and collected the literature.

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Conflict of Interest Statement

The authors declare that they have no competing interests.

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