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REVIEW

Antiviral Agent Therapy Optimization in Special Populations of COVID-19 Patients

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Abstract: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now a global outbreak of disease. The antiviral treatment acts as one of the most important means of SARS-CoV-2 infection. Alteration of physiological characteristics in special populations may lead to the change in drug pharmacokinetics, which may result in treatment failure or increased adverse drug reactions. Some potential drugs have shown antiviral effects on SARS-CoV-2 infections, such as chloroquine, hydroxychloroquine, favipiravir, lopinavir/ritonavir, arbidol, interferon alpha, and remedsivir. Here, we reviewed the literature on clinical effects in COVID-19 patients of these antiviral agents and provided the potential antiviral agent options for pregnant women, elderly patients, liver or renal dysfunction patients, and severe or critically ill patients receiving renal replacement therapy or ECMO after SARS-CoV-2 infection.

Keywords: coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, antiviral therapy, special population

Introduction

A novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China from December 2019, and quickly spread across the world. As of 20 April 2020, more than 2,246,200 coronavirus disease-19 (COVID-19) cases have been reported to WHO, and more than 152,700 patients have lost their lives.[1] COVID-19 has been found in over 210 countries, areas or territories, and is a global health crisis.

Medication treatment, oxygen therapy, support techniques such as extracorporeal membrane oxygenation (ECMO), are the main therapeutic means of SARS-CoV-2 infection. Antivirals are a class of small molecules that function as inhibitors of one or more stages of a virus life cycle.[2] Antiviral drug therapy is one of the most important parts of medical treatment. At the early transmission period of COVID-19, no antiviral agents for SARS-CoV2 infection have been proven to be effective. With the deepening of researches and accumulation of clinical experiences, several kinds of antiviral agents are regarded as potentially effective drugs for SARS-CoV2 infection.

According to the information from the Centers for Disease Control and Prevention,[3] the elderly are at higher risk for severe illness of COVID-19. Pregnant women experience immunologic and physiologic changes which might make them more susceptible to COVID-19. Both the elderly and pregnant women have special physiological characteristics and are at higher risks of medication treatment, especially the

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antiviral agents. Moreover, COVID-19 patients with hepatic or renal dysfunction, severe or critically ill patients receiving ECMO or renal replacement therapy would lead to changes in drug absorption, distribution, metabolism and elimination. In these populations mentioned above, the pharmacokinetic parameters of antiviral agents are likely to be altered, which may result in the failure of antiviral treatment or the increased adverse drug reactions. Antiviral agent selection and management in these special populations of COVID-19 patients have become therapeutic dilemmas for clinicians.

Here, we reviewed the articles focusing on antiviral agents in COVID-19 patients (Table 1) and summarized the potential antiviral options and dose optimization in special populations of COVID-19 patients (Table 2).

Effects of Antivirals on SARS-CoV-2 Infection

Chloroquine

Chloroquine, which acts as an anti-malarial and autoimmune disease drug, has been reported as a potential antiviral drug.[4] Chloroquine has been reported to inhibit the SARS-CoV by elevating endosomal pH and interfering with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2 (ACE2).[5] SARS-CoV-2 shares the same cellular receptor ACE2. Chloroquine functioned at both entry and post-entry stages, and showed inhibitory effects (EC_{50}= 1.13μM, EC_{90}= 6.90 μM) on SARS-CoV-2 in vitro.[6] Chloroquine could also interfere with proteolytic processing of the M protein, which may indirectly reduce the pro-inflammatory cytokines during SARS-CoV-2 infection.[7] Several clinical trials[8] (ChiCTR2000029609, ChiCTR2000029826, ChiCTR2000029837, ChiCTR2000029898, ChiCTR2000029899, ChiCTR2000029935, ChiCTR2000029939, ChiCTR2000029975, ChiCTR2000029988, ChiCTR2000029992, ChiCTR2000030031, ChiCTR2000030054, ChiCTR2000030417, ChiCTR2000030718, ChiCTR2000030987 and ChiCTR2000031204) are conducted in China to test the efficacy and safety of chloroquine in COVID-19. Results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control groups in inhibiting SARS-CoV-2 infection according to the news briefing.[9] Currently, chloroquine phosphate is recommended for adult patients under 65 years old by the Chinese National Health Committee. FDA also announces chloroquine is designated for expanded access to address the COVID-19.[10] Chloroquine is an old drug and could be easily obtained, but have more adverse reactions. The Chinese National Health Committee suggests that for COVID-19 patients weighing less than 50 kg, the recommended dose of chloroquine phosphate is 500 mg bid at the first 2 days, and 500 mg qd from day 3 to day 7; For COVID-19 patients weighing more than 50 kg, the recommended dose of chloroquine phosphate is 500 mg bid for 7 days.[11] A randomized clinical trial found that COVID-19 patients who receiving a high-dosage chloroquine (600 mg twice daily for 10 days) had a higher lethality and more instance of QTc interval than those who received a low-dosage chloroquine (450 mg twice daily on day 1 and once daily for 4 days).[12] Therefore, higher chloroquine dosage should not be recommended for critically ill patients with COVID-19. More clinical data about the effectiveness and safety of chloroquine are required for chloroquine dose optimization.

Hydroxychloroquine

Hydroxychloroquine is an analog of chloroquine and exhibits an antiviral effect similar to that of chloroquine.[13] A recent study demonstrated that hydroxychloroquine (EC50=0.72 μM) was found to be more potent than chloroquine in vitro.[14] The studies on the antiviral effects of hydroxychloroquine against SARS-CoV2 are controversial. An open-label non-randomized clinical trial showed that hydroxychloroquine (200 mg tid) combined azithromycin seems to be an alternative therapeutic strategy for SARS-CoV-2 elimination,[15] but the study had serious methodological flaws. A small, randomized clinical trial found that hydroxychloroquine (200 mg twice daily from day 1 to day 5) could shorten the time to clinical recovery and promote the absorption of pneumonia.[16] However, another small, randomized study in COVID-19 patients also found no difference in recovery rates between hydroxychloroquine treatment (400 mg daily) and other antivirals such as arbidol or lopinavir/ritonavir.[17] An open-label, randomized controlled trial enrolled 150 mild to moderate COVID-19 patients showed that hydroxychloroquine administrated at a loading dose of 1200 mg daily for 3 days followed by a maintenance dose of 800 mg daily did not result in a significantly higher probability of negative conversion than the standard of care alone in patients.[18] An observational study indicated that hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.[19] The effect of hydroxychloroquine remains uncertain. Hydroxychloroquine is one of the treatment options in "Solidarity" clinical trial of COVID-19 treatments, which is launched by the WHO and partners. On May 23, the WHO decided to implement a temporary

Table 1 Antiviral Information and Dosages of Potential Antiviral Agents for COVID-19 Patients

Antiviral Agents	Mode of Action	Numbers of Approved Clinical Trials in China	Antiviral Activities Against SARS-CoV-2	Suggest Dosage	References
Chloroquine phosphate	Block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors	16	Functioned at both entry and at post-entry stages of SARS-CoV-2 in vitro;	≤50kg, 500mg, twice daily at the first two days, 500mg once daily from day 3 to day 7; >50kg, the recommended dose of chloroquine phosphate is 500mg bid for 7 days; oral administration	[5,6,8,11]
Hydroxychloroquine	May be similar with chloroquine	14	More potent than chloroquine in vitro; shorten the time to clinical recovery and promote the absorption of pneumonia;	200mg, two or three times daily (daily dose do not exceed 6.5mg/kg weight), oral administration; the dosage is still need optimized.	[8,14–16]
Favipiravir	Mistakenly recognized by viral RNA polymerase as a purine nucleotide	8	Inhibit SARS-CoV-2 in vitro; favipiravir lead to faster viral clearance and presents better treatment effects on COVID-19 patients; favipiravir improved the latency to relief for pyrexia and cough	Loading dose: 1600mg, twice daily at first day, maintenance dose: 600mg, twice daily from day 2 to day 14; oral administration	[6,8,22–24,56]
Lopinavir/ritonavir	Inhibit 3CLpro protease activity of virus	11	Decreased SARS-CoV-2 loads after lopinavir/ritonavir treatment	400mg/100mg, twice daily; oral administration	[8,11,26,27]
Arbidol	Inhibit the virus-mediated fusion, and block virus entry into target cells; targets the SARS-CoV-2 spike glycoprotein and impedes its trimerization	5	Arbidol showed a tendency to the discharging rate and reduce mortality; Combination of arbidol and lopinavir/ritonavir showed antiviral effects in COVID-19; arbidol post-exposure prophylaxis was a protective factor against the development of COVID-19	200mg, three times daily; oral administration	[8,11,30–33,35,81]
IFN-α	Inhibit virus synthesis and produce a natural immune response	6	Combined with lopinavir/ritonavir or favipiravir to against SARS-CoV-2;	5 million units, twice daily; nebulization	[8,11,23,41]

(*Continued*)

Table 1 (Continued).

Antiviral Agents	Mode of Action	Numbers of Approved Clinical Trials in China	Antiviral Activities Against SARS-CoV-2	Suggest Dosage	References
Remdesivir	Remdesivir triphosphate competes with the natural ATP substrate for incorporation into nascent RNA chains by the RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases.	4	Inhibit SARS-CoV-2 in vitro; remdesivir shorten the time to recovery, and clinical improvement was observed in remdesivir group;	≥40 kg: ① requiring invasive mechanical ventilation and/or ECMO: a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously for 9 days; ② not requiring invasive mechanical ventilation and/or ECMO: a single dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously for 4 days. 3.5 kg to <40 kg: ① requiring invasive mechanical ventilation and/or ECMO: a single loading dose of 5 mg/kg on Day 1 followed by 2.5 mg/kg once daily for 9 days; ② not requiring invasive mechanical ventilation and/or ECMO: a single loading dose of 5 mg/kg on Day 1 followed by 2.5 mg/kg once daily for 4 days; If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days.	[6,46,47,63,82]

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2 The Potentially Optional Antiviral Agents in Special Populations of COVID-19

	Pregnancy	Elderly	Liver Dysfunction	Renal Dysfunction	RRT	ECMO	References
Chloroquine phosphate	☒	×	Δ	Adjust the dose according to GFR	Dialysis: 50% of the dose; CRRT: No adjustment	No data	[11,65,71]
Hydroxychloroquine	☒	Δ	Δ	Adjust the dose according to GFR	Adjust according to residual renal function	No data	[66]
Favipiravir	×	Δ	Reduce dose in severe liver dysfunction	√	No adjustment	No data	[56,76]
Lopinavir/ritonavir	√	Δ	Δ	√	No adjustment	May need to increase the dosage	[57,60,79]
Arbidol	No data	√	Δ	Use with caution in severe renal dysfunction	No adjustment	No data	[64,70,73]
IFN-α	☒	Δ	Do not used in patients with autoimmune hepatitis or decompensated liver disease	√	No adjustment	No adjustment	[61,62]
Remdesivir	☒	Δ	☒Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline	eGFR≥30 mL/min: √eGFR < 30 mL/min: ☒	No data	Patients requiring ECMO are are always severely ill, and need to prolong the treatment course	[63]

Notes: × do not use; √ usable; Δ use with caution; ☒ use after weighing the advantages and disadvantages according to the actual clinical situation.
Abbreviations: COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

pause of the hydroxychloroquine arm of the trial, because of concerns raised about the safety of the drug. On 3 June 2020, WHO announced that on the basis of the available mortality data, there are no reasons to modify the trial protocol, including hydroxychloroquine.[20] A recent study also demonstrated that although hydroxychloroquine did not prevent illness compatible with COVID-19 when used as postexposure prophylaxis, no serious adverse reactions were reported after hydroxychloroquine administration (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days).[21] Randomized, controlled trials with larger sample numbers of COVID-19 patients to evaluate the efficiency and safety of hydroxychloroquine are needed.

Favipiravir

Favipiravir is a nucleotide analog that approved for a novel or re-emerging influenza in Japan and has been demonstrated as a broad-spectrum inhibitor of RNA virus. Favipiravir phosphoribosylated by cellular enzymes to favipiravir-ribofuranosyl-5′-triphosphate, which then mistakenly recognized by viral RNA polymerase as a purine nucleotide.[22]

A high concentration of favipiravir (EC_{50}= 61.88 μM, CC_{50}> 400 μM, SI > 6.46) was required to reduce the SARS-CoV-2 infection in vitro.[6] Recently, an open-label control study was conducted to evaluate the clinical effects of favipiravir in COVID-19 patients, and the dose regimen of favipiravir in this study was 1600 mg twice daily at the first day, and then 600 mg twice daily from day 2 to day 14.[23] The study indicated that favipiravir was independently associated with faster viral clearance and presented better treatment effects on COVID-19 patients. A randomized clinical trial showed that compared to arbidol, favipiravir did not significantly improve the clinical recovery rate at Day 7, but significantly improved the latency to relief for pyrexia and cough.[24] Favipiravir is a relatively safe potential antiviral agent for COVID-19, but the antiviral effects need to be further validated. Additionally, in some regions, it is not easy to mobilize against COVID-

19. Of note, previous studies demonstrated that the plasma concentration of favipiravir in USA patients was 50% of that in Japanese patients, which suggested a possible regional difference in the pharmacokinetics of favipiravir.-[25] Therefore, the dose regimen for COVID-19 patients should be carefully considered.

Lopinavir/Ritonavir

Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor and ritonavir is combined to increase the half-life time of lopinavir. Lopinavir/ritonavir showed inhibitory effects on SARS-CoV through inhibiting 3CLpro protease activity.[26] Some researchers have reported the treatment effects of lopinavir/ritonavir on COVID-19. A case report showed that SARS-CoV-2 loads significantly decreased after one-day treatment of lopinavir/ritonavir (400 mg/100 mg, twice daily), and no or little coronavirus titers have been observed since then.[27] A randomized, controlled, open-label trial was conducted to evaluate the clinical effects of lopinavir/ritonavir in severe COVID-19 patients, and they were orally administrated at a dose of 400 mg/100 mg twice daily for 14 days in this study.[28] The result showed that treatment with lopinavir/ritonavir was not associated with a difference from standard care in the time to clinical improvement. However, the 28-day mortality was numerically lower and patients had a shorter stay in the intensive care unit (ICU) in the lopinavir/ritonavir group than those in the standard care group. The author has indicated that after the exclusion of three patients who died within 24 hours after randomization and did not receive lopinavir/ritonavir, the time to clinical improvement in the lopinavir/ritonavir group was 1 day shorter than that in the control group using the modified intention-to-treat analysis.[29] The lopinavir/ritonavir combination is relatively safe and could be easily mobilized against COVID-19. Additional clinical trials with a larger sample size involving patients with milder disease, earlier drug administration, and an extended treatment course may be helpful in further evaluating the effectiveness of lopinavir/ritonavir against COVID-19. On the other hand, some studies indicated that COVID-19 patients may get benefit from lopinavir/ritonavir combined arbidol treatment, see section "Arbidol".

Arbidol

Arbidol is a small indole-derivative molecule and involves inhibition of virus-mediated fusion with the target membrane and a resulting block of virus entry into target cells.[30] A retrospective study including 69 adults revealed that arbidol showed a tendency to the discharging rate and reduce mortality.[31] Combination of arbidol and lopinavir/ritonavir has applied as the basic regimen for antiviral treatment in some hospitals and showed antiviral effects in COVID-19.[32] A single-center retrospective cohort study revealed that oral arbidol and lopinavir/ritonavir in the combination group was associated with a significant elevated negative conversion rate of coronavirus' test in 7-day and 14-day, in comparison with lopinavir/ritonavir only in the monotherapy group. Furthermore, combination therapy is associated with a significantly improved the chest CT scans in 7-day.[33] A retrospective study found that COVID-19 patients treated with arbidol had a shorter duration of positive RNA test compared to those treated with lopinavir/ritonavir.[34] A recent study found that arbidol post-exposure prophylaxis was a protective factor against the development of COVID-19,[35] arbidol might reduce the infection risk of the COVID-19 in hospital and family settings. Arbidol is a relatively safe potential antiviral agent for COVID-19, but in some regions, it is not easy to obtain.

Interferon Alpha (IFN-α)

Previous in vitro studies found that IFN-α and IFN-β showed antiviral effect against SARS-CoV.[36] Both IFN-α and IFN-β were applied during MERS-CoV infection.[37] A nonrandomized single-arm intervention study found that IFN-α2b combined with ribavirin showed lower crude 14-day mortality rate than supportive care.[38] A retrospective cohort study found that IFN-α was not associated with crude mortality rate, while an increase in crude mortality rate was observed in MERS-CoV infection patients who treated with IFN-β.[39] Another nonrandomized single-arm intervention study showed that no difference was observed in the unadjusted mortality rate between IFN-α2a and IFNβ1a, where all MERS-CoV patients were co-treated with ribavirin.[40] Due to the lacking of evidence in the early period of COVID-19 outbreak, only IFN-α nebulization is recommended as a potential antiviral treatment method for SARS-CoV-2 infection by the Chinese National Health Committee.[11] IFN-α is always used as one of the combination therapy drugs during COVID-19 treatment. In clinical trials, IFN-α often combined with other antivirals, such as favipiravir,[23] lopinavir/ritonavir.[41] There are no clinical trials about the effects of IFN-α monotherapy on SATS-CoV-2 infection. The recommended dose is 5 million units twice daily by aerosol inhalation. IFN-α nebulization should be performed in negative-pressure wards rather than general wards due to

the possibility of aerosol transmission.[32] The denaturation of IFN-α would be related to the heating of nebulizer solution; therefore, ultrasonic nebulization should be avoided.[42]

Remdesivir

Remdesivir, an adenosine analog, is a monophosphoramidate prodrug and metabolized into its active form, which can obscure viral RNA polymerase and evade proofreading by viral exonuclease, thereby causing a decrease in viral RNA production.[43] A model for SARS-CoV-2 RdRp was constructed and the results suggested that remdesivir was a potent drug against the newly emerged COVID-19 disease.[44] In vitro study showed that remdesivir (EC50= 0.77 μM; CC50>100 μM; SI > 129.87) potently blocked SARS-CoV-2 infection at low concentration and showed the high SI.[6] Compassionate use was reported on a deteriorating case with good recovery.[45] Currently, a randomized, controlled, double-blind trial (https://clinicaltrials.gov/ct2/show/NCT04252664) involving hospitalized adult patients with mild and moderate COVID-19 disease in China has been suspended. A newly published study demonstrated that clinical improvement was observed in 68% severe COVID-19 patients who were treated with compassionate-use remdesivir.[46] A recent double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 showed that Remdesivir was superior to placebo in shortening the time to recovery.[47] FDA issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.[48] Remdesivir seems to be one of the most promising antivirals against SARS-CoV-2 infection, but it is still an investigated drug with unknown adverse effects and is relatively hard to obtain. Evaluation of remdesivir efficacy still requires ongoing randomized, placebo-controlled trials of remdesivir therapy.

Antiviral Agents in Pregnant COVID-19 Patients

An animal study indicated that chloroquine could pass across the placenta and accumulated in melanin structures of the fetal eyes.[49] Moreover, a pharmacokinetic study of chloroquine based on a population pharmacokinetic modeling showed that pregnancy significantly reduced exposure to chloroquine.[50] Pregnancy may lead to the failure of chloroquine treatment. Nevertheless, chloroquine has been a choice for malaria prevention and treatment in pregnant women.[51,52] A study revealed that chloroquine can be safe in pregnant women after a dosage of 500 mg/day.[53] We suggested that a daily dosage of chloroquine higher than 500 mg should be avoided in pregnant women.

Hydroxychloroquine treatment could improve the pregnancy outcome in women with antiphospholipid antibodies.[54] However, the dose of hydroxychloroquine (200 mg bid) was lower than that recommended in COVID-19 (200 mg bid to tid). Hydroxychloroquine could be detected in the cord blood, and the concentrations were similar to those in the maternal serum.[55] Higher concentrations of hydroxychloroquine may result in drug accumulation in the fetus. Considering the lower adverse drug reactions of hydroxychloroquine,[13] we suggest that the advantages and disadvantages should be carefully evaluated before using hydroxychloroquine in pregnant women with COVID-19.

Favipiravir is prohibited for pregnant women. Animal experiments showed that early embryonic lethality (rat) and teratogenicity (monkey, mouse, rat and rabbit) were observed at doses similar to or lower than clinical exposure.[56]

The use of the lopinavir/ritonavir by pregnant women did not increase the rate of preterm birth and low birth weight.[57] Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol. Therefore, the oral solution is not recommended for use during pregnancy. It was reported that a reduction in lopinavir plasma concentrations during pregnancy of around 30% compared with those in non-pregnant adults.[58] Increasing the dose of lopinavir/ritonavir during pregnancy to 600 mg/150 mg resulted in lopinavir plasma concentrations equivalent to those in non-pregnant adults receiving standard doses (400 mg/100 mg). Based on these data, the US Department of Health and Human Services guidelines recommends increasing lopinavir/ritonavir dose to 600 mg/150 mg twice daily in the third trimester.[59] However, FDA recommends taking lopinavir/ritonavir 400/100 mg twice daily in pregnant women with no documented lopinavir-associated resistance substitutions, and no dose adjustment of lopinavir/ritonavir is required for patients during the postpartum period.[60] We suggest that lopinavir/ritonavir tablets could be used during pregnancy, and if lopinavir/ritonavir were used with standard doses during pregnancy, SARS-CoV-2 loads and drug concentration of lopinavir should be monitored.

IFN-α is assumed to have abortifacient potential. IFN-α is used by aerosol inhalation for COVID-19 treatment,

which may indicate less systemic distribution. However, the previous study showed that adverse reactions and blood concentration were related to inhaled dosage.[61] Three million units daily administered by aerosol induced a significant biological activity of IFN-α.[62] Considering the recommended dose (5 million twice daily) is higher, we suggest that IFN-α aerosol inhalation therapy is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Currently, there is no related research on the application of arbidol in pregnant women. Therefore, we suggest that arbidol is not recommended in COVID-19 patients during pregnancy.

According to the fact sheet of remdesivir for health care providers, remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.[63]

Antiviral Agents in Elderly COVID-19 Patients

Elderly patients are more likely to have decreased renal function, thereby may lead to chloroquine accumulation. The Chinese National Health Committee did not recommend elderly COVID-19 patients to receive chloroquine treatment.[11] We suggest taking care of dose selection and closely monitor renal function as well as other adverse effects such as cardiac disorders and ocular disorders.

Hydroxychloroquine has a lower level of tissue accumulation than chloroquine, thereby, has few adverse reactions.[13] Hydroxychloroquine could be used in elder COVID-19 patients, and adverse drug reactions such as cardiac disorders, ocular disorders and renal function should be monitored.

Considering the declined physiological function, older adults should be closely monitored after taking favipiravir.

Lopinavir/ritonavir clinical trials did not include a sufficient number of subjects age ≥65 years.[60] Considering the declined physiological function, the adverse effects and the drug interactions should be closely monitored after older adults taking lopinavir/ritonavir.

It was reported that the use of arbidol in patients over 65 years old reduced the incidence of nosocomial pneumonia, and adverse reactions associated with the arbidol were not identified in the study.[64] We suggest that elderly COVID-19 patients could use arbidol. Besides, arbidol is metabolized by CYP3A4, and ritonavir is a CYP3A inhibitor; therefore, a combination of ritonavir and arbidol may increase the arbidol serum concentration. Adverse effects such as elevation of serum transaminase in elderly COVID-19 patients who receiving combination treatment of arbidol and lopinavir/ritonavir.

IFN-α could be used in elderly patients. However, adverse reactions such as fever, influenza-like symptoms, nausea, flush, and headache were observed in patients receiving IFN-α inhalation.[61] Adverse reactions may be more severe in the elderly patients, and caution should be exercised in the use of IFN-α.

The pharmacokinetics of remdesivir have not been evaluated in patients >65 years of age. In general, appropriate caution should be exercised in the administration of remdesivir and monitoring of elderly patients.[63]

Antiviral Agents in COVID-19 Patients with Liver Dysfunction

Chloroquine could deposit in liver tissues in considerable amounts. It should be used with caution in patients with liver dysfunction.[65]

Hydroxychloroquine is metabolized by the liver. Although there are no dosage adjustments provided in the manufacturer's labeling, hydroxychloroquine should be used with caution in patients with liver dysfunction.[66]

Favipiravir is mainly metabolized to the hydroxylated form by aldehyde oxidase and partly by xanthine oxidase.[67] Patients with severe liver dysfunction (Child-Pugh C) showed an increase in AUC (6.3 fold) and C_{max} (2.1 fold).[56] We suggested that COVID-19 patients with severe liver function impairment should reduce favipiravir dosage.

Lopinavir is principally metabolized by CYP3A and ritonavir is an inhibitor of CYP3A.[68] Mild to moderate liver function impairment led to a 30% increase in AUC of lopinavir, but no clear correlation between the increase and clinical treatment was observed.[69] Lopinavir/ritonavir has not been studied in patients with severe hepatic impairment.[69] Based on the fact that lopinavir/ritonavir can lead to elevated liver enzymes and bilirubin, lopinavir/ritonavir may worsen liver dysfunction. Therefore, we suggest that caution should be exercised when administering lopinavir/ritonavir in COVID-19 patients with hepatic impairment.

Presently, arbidol has not been studied in patients with liver function impairment, and there is no relevant recommendation in the manufacturer's labeling either. Considering that arbidol is mainly metabolized by CYP3A4 and UGT1A9,[70] we suggest that COVID-19 patients with liver function impairment should use arbidol with clinical caution.

IFN-α is contraindicated in patients with autoimmune hepatitis or decompensated liver disease. Although it is administrated by aerosol inhalation, we suggested that it should not be used in COVID-19 with autoimmune hepatitis or decompensated liver disease.

The pharmacokinetics (PK) of remdesivir in humans is not clear. According to the PK study in rhesus monkeys, remdesivir exhibits a short plasma half-life with faster systemic elimination and rapidly distributed in peripheral blood mononuclear cells. In vitro study indicated low cytotoxicity of remdesivir in human primary hepatocytes.[43] It is not known if dosage adjustment is needed in patients with hepatic impairment and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.[63] One of the main adverse reactions of remdesivir is the increased liver transaminases; therefore, remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline.[63] Further study is needed for the safety of remdesivir in patients with liver dysfunction.

Antiviral Agents in COVID-19 Patients with Renal Dysfunction

Chloroquine and its metabolites excreted from urine. Slightly more than half of the urinary drug products can be accounted for as unchanged chloroquine. When the glomerular filtration rate (GFR) is less than 10 mL/min, the dose of chloroquine should reduce by half.[71]

Hydroxychloroquine is excreted by urine as metabolites and unchanged drug (up to 60%). Dosage should be adjusted according to GFR: when GFR ranges from 20 to 50 mL/min, the maximum daily dose of hydroxychloroquine should be 75 mg, when GFR ranges from 10 to 20 mL/min, the maximum daily dose of hydroxychloroquine should be 50 mg; when GFR is less than 10 mL/min, the hydroxychloroquine is contraindicated.[72]

Favipiravir is mainly excreted in the urine as the hydroxylated form, little is excreted as unchanged drug. We suggested that COVID-19 patients with renal function impairment should not adjust the dose regimen.

Lopinavir PK has not been studied in patients with renal impairment; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal impairment. We suggest that COVID-19 patients with renal function impairment should not adjust the dose regimen.

Arbidol has not been studied in patients with renal function impairment. It was reported that in human urine, glucuronide and sulfate conjugates of arbidol were detected as the major metabolites, accounting for 6.3% of the dose excreted within 0 to 96 h after drug administration. The fecal specimens mainly contained the unchanged arbidol, accounting for 32.4% of the dose.[70] Therefore, we speculate that COVID-19 patients with mild to moderate renal function impairment should not adjust the dose regimen, and the manufacturer's labeling[73] suggested that patients with severe renal function impairment should use arbidol with clinical caution.

Since IFN-α is administrated by aerosol inhalation, we suggest that dose adjustment is not needed in patients with renal dysfunction.

The elimination of remdesivir in humans is not clear. In vitro study showed low cytotoxicity of remdesivir in renal proximal tubular epithelial cells.[43] Patients with eGFR greater than or equal to 30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment of remdesivir, and remdesivir is not recommended in adult patients with eGFR less than 30 mL/min unless the potential benefit outweighs the potential risk.[63]

Antiviral Agents in COVID-19 Patients Receiving Renal Replacement Therapy

Renal replacement therapy (RRT), especially the continuous renal replacement therapy (CRRT), could keep a stable mean arterial pressure and effective renal perfusion, maintain the fluid, electrolyte, and acid–alkaline balance in efficient and smooth manners, and is often required in critically ill patients. (10.3389/fphar.2020.00786) According to the recent report, about 17% of the critically ill COVID-19 patients received RRT.[74] Pharmacokinetics of drugs could be altered during RRT.[75]

For patients receiving hemodialysis or peritoneal dialysis, the dosage of chloroquine should be as same as patients with GFR< 10 mL/min, namely, administer 50% of the original dose. For patients receiving CRRT, no dosage adjustment is necessary.[71]

A case report investigated the effects of continuous venovenous haemofiltration (CVVH) on patients taking favipiravir and showed that CVVH had no clinically relevant contribution to total clearance of favipiravir.[76] Reducing the dose regimen of favipiravir during CVVH may be not appropriate.

Pharmacokinetics of hydroxychloroquine, lopinavir/ritonavir, and arbidol have not been studied in patients

with renal replacement therapy. Lopinavir and ritonavir are 98–99% bound to the blood plasma protein albumin and alpha-1-acid-glycoprotein.[59] We speculate that renal replacement therapy would not affect the plasma concentration of lopinavir/ritonavir. Considering arbidol, lopinavir/ritonavir are mainly metabolized by liver and excreted by fecal, we speculate that adjusting the dose regimens of these two agents in COVID-19 patients with RRT is not needed. Hydroxychloroquine is eliminated by kidney. Considering its low molecular weight, we confer that it could be cleared by CRRT. Dose adjustment could be applied according to residual renal function.

RRT has little effects on drug concentration in lung tissues; therefore, we speculated that no drug dosage adjustment is needed for IFN-α inhalation.

Antiviral Agents in COVID-19 Patients Receiving ECMO

ECMO is a life-support modality used in patients with refractory cardiac and/or respiratory failure. Recently study indicated that ECMO may have a role in the management of COVID-19 patients who have refractory hypoxemic respiratory failure.[74,77] Drug pharmacokinetics alterations during ECMO were demonstrated.[78] A case report investigated the effect of ECMO on patients taking ritonavir. Ritonavir has administrated 100 mg once daily before ECMO and 100 mg twice daily during ECMO. The result exhibited that the drug levels of ritonavir were lower than the expected concentrations for a typical individual in the population, suggesting that the PK of ritonavir changed during ECMO.[79] We suggest that COVID-19 patients with ECMO may need to increase the dose regimen of lopinavir/ritonavir and conduct therapeutic drug monitoring to achieve personalized treatment. Considering IFN-α is used as topical administration, we conferred that dosing adjustment is not required during ECMO.

Little is known about the alteration of other antivirals during ECMO. It has been reported that significant absorption of drugs occurs in the ECMO circuit, which is correlated with increased lipophilicity of the drug.[80] Among these antivirals, lopinavir, ritonavir, and arbidol are hydrophobic; therefore, increased dose regimen may be needed during ECMO.

According to the information about using remdesivir in treating COVID-19, the suggested dosages are the same in patients with or without ECMO.[63] On the other hand, COVID-19 patients who receiving ECMO are more likely to be accompanied by severe symptoms, therefore need a prolonged treatment course.[63]

Conclusion

As a novel infection disease, the treatment of COVID-19 is continuously being explored and improved. Due to the alteration of physiological characteristics in special populations, individual antiviral treatment should be performed to achieve better clinical outcomes and avoid adverse drug reactions. Further studies of antiviral agents in special populations of COVID-19 patients are required.

Author Contributions

All authors contributed toward conception and design, acquisition of data, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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