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ANTIVIRAL AGENTS AND THEIR EFFECT ON SPECIAL POPULATION OF COVID 19 PATIENTS

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Abstract:

Antiviral are a class of drugs that are used to treat viral infections currently available antiviral infection. Currently available antiviral drugs target only main groups of viruses that are: herpes, hepatitis and influenza viruses most disease caused by viruses tend to end without treatment and do not require antiviral therapy. Acyclovir, Brivudine, Docosanol, Trifluridine, valacyclovir etc. are the examples of common antiviral drugs.

Due to viruses a wide range of human diseases causes, ranging from acute self-resolving conditions to acute fatal diseases. The propensity for chronic conditions can also increase after the long arise of primary infection which may lead to the development of cancer. Our understanding of recent advances for viral pathogenesis, to improve vaccination strategies and developing the newer along with more effective treatment for patient in all over the world due to virology and pathology. The review has focus on interface in between virology and pathology and to hold the aspects of clinical pathology of viral disease and the mechanisms of disease underlying. The articles based on prominent diseases caused by viruses such as Ebola virus, Marburg virus, coronaviruses (SARS and MERS), Nipah virus and noroviruses are followed by reviews of enteroviruses, HIV infection, human respiratory syncytial virus (RSV), influenza, cytomegalovirus (CMV) and varicella zoster virus (VZV). The issue have been concluded with a series of articles by reviewing the relationship between viruses and cancer, including the role played by Epstein-Barr virus (EBV) in the pathogenesis of lymphoma and carcinoma; which reveal how human papillomaviruses (HPVs) are involved in the development of skin cancer as well as the involvement of hepatitis B virus infection in hepatocellular carcinoma; and the mechanisms with Kaposi's sarcoma-associated herpesvirus (KSHV) leads to Kaposi's sarcoma. Hopefully this collection of articles will help the scientists and clinicians at a time while there is a renaissance in the appreciation of the power of pathology as virologists dissect the processes of disease.

Keywords: *CMV; EBV; HPV; KSHV; MERS; Marburg virus; RSV; SARS; VZV; coronavirus; enterovirus; measles.*

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INTRODUCTION:

New Drug Delivery Systems:

Increased drug resistance and viral repetition have always been the subject of important lessons about the use of nanotechnology in the treatment of antimicrobials. Nanomatadiums offer unique physico-chemical compounds that combine the benefits of drug delivery as effective tools for viral therapy [1]. Currently, different types of nanomaterials namely nanoparticles, liposomes, nanospheres, nanogels, nanosuspensions and nanoemulsions were analyzed in vitro or in vivo to deliver the antiviral agents expected to be translated into clinical practice. This review highlights the drug delivery nanosystems that include large antiviral classes and their transport across all specific cellular and intracellular barriers. Important reflections on nanomedicines currently approved or investigated for the treatment of bacterial infections are also discussed. Finally, the authors present a summary of the design requirements for antimicrobial nanotherapeutics [2].

The guanine-based antiviral drug Acyclovir (ACV) is one of the oldest market-leading molecules up to date, available for sale in a variety of oral, topical and parenteral doses. Clinical use of this drug is superior to new antivirals due to its potential risks such as repetitive suppression, safety profile, low drug interaction, and low cost. ACV is slightly soluble in water, less invasive and less bioavailable, yet a potentially powerful antiviral molecule, physicochemical modification and novel measurement methods that have led to more than 100 research studies over a decade. The literature review showed major reports on the development of ACV formulations, including modified tablets, partial drug delivery, vesicular drug delivery, polymeric nanoparticles, bioadhesive systems, floating dose forms, in situ gelling systems, delivery. transdermal, artificial systems, emulsified volume forms, polymeric films / episodes, etc. Since the drug could be administered in multiple channels of site-targeted action at various doses, and attracted the attention of many studies, a review of current ACV delivery methods would be of great benefit to new scientists. This paper is a review of recent research which highlight the development of new techniques and types of ACV novel dosages for better therapeutic efficacy, aimed at improving its solubility, penetration and bioavailability [3].

Novel drug delivery approaches on antiviral agents:

Germs have the ability to replicate very quickly in a host cell. It may attack any part of the host cell. Therefore, the clinical efficacy of antimicrobial drugs and their bioavailability are very important considerations in the treatment of bacterial infections [4]. Oral and parental drug administration routes have several shortcomings, however, which can lead to searches for better delivery programs. Now, the Novel Drug Delivery Systems (NDDS) of the day has proven to be the best way to improve the effectiveness of antivirals and improve patient compliance and reduce adverse effects [5].

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

Coronavirus 2019 (COVID-19) caused by acute acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now a global epidemic. Antiviral treatment serves as one of the most important means of infection with SARS-CoV-2. Mutations in specific individuals can lead to changes in the pharmacokinetics of the drug, which may result in treatment failure or an increase in adverse drug reactions. Other potential drugs have shown antimicrobial effects on SARS-CoV-2 infections, such as chloroquine, hydroxychloroquine, favipiravir, lopinavir / ritonavir, arbidol, interferon alpha, and remedsivir. Here, we reviewed the clinical outcome literature on COVID-19 patients of these antiviral agents and provided options for antiviral agent for pregnant women, elderly patients, liver or kidney function patients, and critically ill or critically ill patients receiving kidney transplant treatment or ECMO, After SARS-CoV-2 infection.

Medication, oxygen therapy, supportive techniques such as extracorporeal membrane oxygenation (ECMO), is the main treatments for SARS-CoV-2 infections. Antivirals are a class of small molecules that act as shortcuts for one or more stages of the viral life cycle.2 Antiretroviral therapy is one of the most important parts of treatment. In the early stages of COVID-19 transmission, no SARS-CoV2 infection antiviral agents were found to be effective. With the depth of research and the accumulation of clinical experience, several types of antiviral are considered as potential drugs with SARS-CoV2 infection.

According to information from the Centers for Disease Control and Prevention, 3 adults are at high risk of serious illness COVID-19. Pregnant women experience immunologic and physiologic changes that can make them more susceptible to COVID-19. Both the elderly and pregnant women have special physical characteristics and are at high risk for medical treatment, especially antiviral agents. In addition, COVID-19 patients with liver or kidney dysfunction, critically ill or severely ill patients

receiving ECMO or kidney transplant treatment may lead to changes in drug absorption, circulation, metabolism and elimination. In the above-mentioned statistics, the pharmacokinetic parameters of the antiviral agents are likely to change, which may result in failure of antiretroviral treatment or increase in adverse drug reactions. The selection and management of an antimicrobial agent in these special numbers of COVID-19 patients has become a medical problem.

Effects of Antivirals on SARS-CoV-2 Infection:

Chloroquine:

Chloroquine, which acts as an anti-malarial and autoimmune disease, has been reported as a potential antiviral drug.4 Chloroquine has been reported to inhibit SARS-CoV by increasing endosomal pH and disrupting the glycosylation of the cell receptor, i - angiotensin- converting enzyme 2 (ACE2) .5 SARS-CoV-2 shares the same cellular receptor ACE2. Chloroquine is active in both the entry and post-entry stages, and has shown inhibitory effects (EC50 = 1.13μM, EC90 = 6.90 μM) in SARS-CoV-2 in vitro.6 Chloroquine may also interfere with M-proteolytic processing of M protein, which may indirectly reduce the inflammatory cytokines pro at the time of the SARS-CoV 2 infection.7 several clinical trials8 (ChiCTR2000029609, ChiCTR2000029826, ChiCTR2000029837, ChiCTR2000029898, ChiCTR2000029899, ChiCTR2000029935, ChiCTR2000029939, ChiCTR2000029975, ChiCTR2000029988, ChiCTR2000029992, ChiCTR2000030031, ChiCTR2000030054, ChiCTR2000030417, ChiCTR2000030718, ChiCTR2000030987 and ChiCTR2000031204) was developed in China to test the effectiveness and safety of chloroquine in COVID-19. Results from more than 100 patients showed that chloroquine phosphate was superior to control groups in the prevention of SARS-CoV-2 infection according to a press release.9 Currently, chloroquine phosphate is recommended for patients under the age of 65 Committee. The FDA has also announced that chloroquine is designed for extended access to COVID-19.10 Chloroquine is an old and easily available drug, but has a very serious reaction. China National Health Committee recommends that for COVID-19 patients weighing less than 50 kg, the recommended dose of chloroquine phosphate is 500 mg of bids for the first 2 days, and 500 mg qd from day 3 to day 7 ; In patients with COVID-19 weighing more than 50 kg, the recommended dose of chloroquine phosphate is 500 mg of bid for 7 days. days) have a higher risk and more frequent QTc intervals than those who received a lower dose of chloroquine (450 mg twice daily 1 day once daily for 4 days) .12 Therefore, high doses of chloroquine should not be recommended in humans very sick. patients with COVID-19. Additional clinical data regarding the efficacy and safety of chloroquine are required for the use of chloroquine dosage.

Hydroxychloroquine:

Hydroxychloroquine is an analogue of chloroquine and exhibits an antimicrobial effect similar to that of chloroquine.13 Recent studies have shown that hydroxychloroquine (EC50 = 0.72 μM) has been found to be more potent than chloroquine in vitro.14 A study of the antiviral effects of hydroxychloroquine and SARS-CoV2 are controversial. Clinical trials study with a randomized placebo-controlled trial showed that hydroxychloroquine (200 mg tid) when combined with azithromycin appeared to be a different treatment strategy for the elimination of SARS-CoV-2,15 but the study also had significant methodological errors. A small, randomized clinical trial found that hydroxychloroquine (200 mg twice daily from day 1 to day 5) shorten the time to clinical recovery and promote the absorption of pneumonia.16

However, other small, randomized studies in COVID-19 patients also found no difference in recovery rates between hydroxychloroquine treatment (400 mg daily) and other antiretroviral drugs such as arbidol or lopinavir / ritonavir. in COVID-19 moderate patients showed that hydroxychloroquine administered with a loading dose of 1200 mg daily for three days followed by a corrective dose of 800 mg daily did not lead to significantly higher risk of adverse reactions than patient care alone. 18 Experimental studies have shown that the administration of hydroxychloroquine was not associated with a significantly reduced or increased risk of end-stage intubation or death.19 The effect of hydroxychloroquine remains uncertain. Hydroxychloroquine is one of the treatments found in the “Solidarity” clinical trial of COVID-19, presented by WHO and partners. On May 23, the WHO decided to use a temporary suspension of the case for hydroxychloroquine, due to concerns raised over drug safety. On June 3, 2020, the WHO announced that on the basis of available data, there were no grounds for changing the test procedure, including hydroxychloroquine. as postexposure prophylaxis, no adverse reactions were reported after administration of hydroxychloroquine (800 mg once, followed by 600 mg for 6 to 8 hours, then 600 mg daily for an additional 4 days). 19 patients are required to evaluate the efficacy and safety of hydroxychloroquine.

Favipiravir:
Favipiravir is an analog of a nucleotide that has been approved to be a novel or flu recurrence in Japan and has been shown to be a broad-spectrum inhibitor of the RNA virus. Favipiravir phosphoribosylated is the cellular enzyme in favipiravir-ribofuranosyl-5′-triphosphate, which has been mistakenly identified by viral RNA polymerase as a purine nucleotide.22

High concentrations of favipiravir (EC50 = 61.88 μM, CC50> 400 μM, SI> 6.46) were required to reduce SARS-CoV-2 infection in vitro.6 Recently, an open label control study was conducted to evaluate clinical outcomes of favipiravir in COVID-19 patients, and the dosage of favipiravir in this study was 1600 mg twice daily on the first day, and then 600 mg twice daily from day two to day fourteen.23 The study was showed that favipiravir independently associated with and rapid infection approves and presents the best treatment outcomes for COVID-19 patients. A randomized clinical trial showed that compared with arbidol, favipiravir did not significantly improve clinical recovery at Day 7, but significantly improved delay in pyrexia relief and coughing. antiviral effects require further verification. Additionally, in some regions, it is not easy to assemble against COVID-19. Notably, previous studies have shown that the concentration of favipiravir in plasma in USA patients was 50% of that in Japanese patients, suggesting a potential regional difference in the pharmacokinetics of favipiravir.25 therefore, the dose range for COVID-19 patients it must be careful considered.

Lopinavir/Ritonavir:
Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor and ritonavir is synthesized to extend the lopinavir half-life. Lopinavir / ritonavir has shown inhibitory effects on SARS-CoV by inhibiting the activity of 3CLpro protease.26 Some researchers have reported the therapeutic effects of lopinavir / ritonavir on COVID-19. The case report showed that SARS-CoV-2 loads decreased significantly after one-day treatment of lopinavir / ritonavir (400 mg / 100 mg, twice a day), and no or less coronavirus titers have been detected since then. , an open-label study was performed to evaluate the clinical effects of lopinavir / ritonavir in severe patients with COVID-19, and were given orally at a dose of 400 mg / 100 mg twice daily for 14 days in this study.28 The result showed. that lopinavir / ritonavir treatment was not related to the difference from standard care at the time to clinical improvement. However, the 28-day mortality rate was lower and patients stayed shorter in the intensive care unit (ICU) in the lopinavir / ritonavir group than those in the conventional care group. The author noted that after discharge of three patients who died within 24 hours of randomization and did not receive lopinavir / ritonavir, the clinical development time in the lopinavir / ritonavir group was shorter by 1 day than that in the modified control group. therapeutic objective analysis.29 The combination of lopinavir / ritonavir is relatively safe and can be easily synthesized against COVID-19. Additional clinical trials with a larger sample size involving patients with chronic disease, previous drug administration, and an extended treatment course may be helpful in evaluating the efficacy of lopinavir / ritonavir against COVID-19. On the other hand, some studies have suggested that COVID-19 patients may benefit from combination therapy with lopinavir / ritonavir, see the section “Arbidol”.

Arbidol:
Arbidol is a small cell that leaks out of the indole and involves blocking the interaction between the virus and the target membrane as well as the effect of blocking the entry of the virus into target cells. death.31 The combination of arbidol and lopinavir / ritonavir has been used as a basic antiretroviral therapy in some hospitals and has shown antimicrobial effects in COVID-19.32 A single retrospective cohort study revealed that oral arbidol and lopinavir / ritonavir are grouped together. with a higher rate of adverse reversal of coronavirus testing at 7 days and 14 days, compared with lopinavir / ritonavir only in the monotherapy group. In addition, combined treatment was associated with significant improvement in breast CT scan at 7.33 days a previous study found that COVID-19 patients treated with arbidol had a shorter RNA-RNA test compared to those treated with lopinavir / ritonavir. 34. Recent research has found that arbidol post-exposure prophylaxis has been protective against the development of COVID-19,35 arbidol may reduce the risk of COVID-19 infection in the hospital and family. Arbidol is a potent and potent anti-COVID-19 agent, but in some regions it is not easy to find.

Interferon Alpha (IFN-α):
A previous in vitro study found that IFN-α and IFN-β showed an antiviral effect against SARS-CoV.36 Both IFN-α and IFN-β were used during MERS-CoV infection .37 One unauthorized intervention study found that IFN-α2b combined with rakuvirin showed a 14-day lower mortality rate than supportive care.38 A previous cohort study found that IFN-α was not associated with a higher mortality rate, while an increase was increased. of the rate of contagious mortality observed in MERS-CoV infection patients treated with IFN-β.39 Another study of

nonrandomized single-arm intervention showed that no difference was observed in the unresolved mortality rate between IFN-α2a and IFNβ1a, in which all patients -MERS-CoV were treated in combination with rivatirin.40 Due to the lack of evidence in the early stages of COVID-19 outbreak, only IFN-α nebulization is recommended as an anti-inflammatory drug. a potential source of SARS-CoV-2 infection by the China National Health Committee.11 IFN-α is often used as one of the combination of therapeutic drugs during COVID-19 treatment. In clinical trials, IFN-α is often combined with other antivirals, such as favipiravir, 23 lopinavir / ritonavir.41 There are no clinical trials regarding the effects of IFN-α monotherapy on SATS-CoV-2 infections. Recommended dose 5 million units twice a day by inhaling aerosol. IFN-α nebulization should be performed in wards with negative pressure than conventional wards due to possible aerosol transfer.32 The denaturation of IFN-α will be associated with the temperature of the nebulizer solution; therefore, ultrasonic nebulization should be avoided.42

Remdesivir:

Remdesivir, an adenosine analog, is a monophosphoramidate prodrug and is metabolized into its active form, which can suppress viral RNA polymerase and prevent viral exonuclease testing, thereby causing a decrease in viral RNA production.43 Model of SARS-CoV-2 RdRp had been developed and the results suggested that remdesivir is a potent drug for the recent outbreak of COVID-19.44 In vitro studies have shown that remdesivir (EC50 = 0.77 μM; CC50> 100 μM; SI > 129.87) strongly inhibited SARS-CoV-2 infection at low concentrations and showed high SI use.6 Compassionately reported in a deteriorating condition with good recovery.45 Currently, randomized, controlled, double-blind tests (https://clinicaltrials.gov/ ct2 / show / NCT04252664) which includes hospitalized adult patients with COVID-19 syndrome in China has been suspended. A recently published study showed that clinical improvement was seen in 68% of severe COVID-19 severe patients treated with compassionate remdesivir has shown that Remdesivir was better than placebo in shortening the recovery time.47 The FDA has issued an urgent approval for the use of the antiretroviral drug remdesivir for the treatment of COVID-19 which is suspected to be a proven laboratory for adults and children hospitalized with serious illness.48 Remdesivir is one of the most promising antiretroviral drugs against SARS-CoV-2 infection, but it is still the most widely investigated drug with unknown side effects and difficult to detect. Effective trials of remdesivir still require continuous randomized, placebo-controlled trials of remdesivir treatment.

Antiviral Agents in Pregnant COVID-19 Patients:

Animal studies have shown that chloroquine can pass through the placenta and accumulate in the fetal melanin structures of the fetus.49 In addition; pharmacokinetic studies of chloroquine based on human pharmacokinetic composition have shown that pregnancy significantly reduces chloroquine exposure.50 Pregnancy may led to the failure of chloroquine treatment. However, chloroquine was the preferred prevention and treatment of malaria for pregnant women.51,52 Research has shown that chloroquine may be safe for pregnant women after a dose of 500 mg / day.53 We suggested that the daily dose of chloroquine is higher than 500 mg should be avoided in pregnant women.

Hydroxychloroquine treatment may improve the effect of pregnancy on 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 not be found in the bloodstream, and the concentration was similar to that in the mother's serum.55 High concentrations of hydroxychloroquine may cause drug accumulation in the fetus. Considering the low drug reactions to hydroxychloroquine, 13 we suggest that the benefits and disadvantages should be carefully evaluated before using hydroxychloroquine in pregnant women with COVID-19.

Favipiravir is not approved for pregnant women. Animal studies have shown that early embryonic death (mouse) and teratogenicity (monkey, mouse, mouse and rabbit) were detected in doses similar to or lower than clinical exposure.56

The use of lopinavir / ritonavir by pregnant women did not increase premature birth and low birth weight.57 Lopinavir / ritonavir oral solution contains 42.4% (volume / volume) of alcohol and 15.3% (weight / volume) propylene glycol. Therefore, an oral solution is not recommended for use during pregnancy. It has been reported that a decrease in lopinavir concentration in the plasma of lopinavir during pregnancy by about 30% compared to non-pregnant adults.58 increasing the dose of lopinavir / ritonavir during pregnancy to 600 mg / 150 mg led to the concentration of lopinavir in -plasma equivalent to those in the abdomen. Non-pregnant adults receive standard doses (400 mg / 100 mg). Based on this data, US Department of Health and Human Services

guidelines recommend increasing the dose of lopinavir / ritonavir to 600 mg / 150 mg twice daily in the third trimester.59 However, the FDA recommends taking lopinavir / ritonavir 400 / 100 mg twice daily for pregnant women. Women who do not have a prescribed lopinavir-related resistance, and no dose adjustment of lopinavir / ritonavir is required in patients during postpartum period.60 We suggest that lopinavir / ritonavir pills may be used during pregnancy, and if lopinavir / ritonavir were used normally. doses during pregnancy, loads of SARS-CoV-2 and overdose of lopinavir should be monitored.

IFN-α is thought to have abortive potential. IFN-α is used to inhale aerosol in the treatment of COVID-19, which may indicate a slower systemic distribution. However, previous studies have shown that adverse reactions and blood pressure were associated with an elevated dose.61 Three million daily aerosol-controlled units perform vital biological function of IFN-α.62 Considering the recommended dose (5 million twice daily) is high , we suggest that IFN-α aerosol inhalation therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the baby.

Currently, there are no studies related to arbidol use in pregnant women. Therefore, we suggest that it arbidol is not recommended in patients with COVID-19 during pregnancy.

According to the health-care provider's Remdesivir paper, remdesivir should only be used during pregnancy if the potential benefits justify the potential risks to the mother and baby.63

Antiviral Agents in Elderly COVID-19 Patients

Elderly patients are more likely to have kidney failure, thus leading to chloroquine accumulation. The China National Health Committee not recommends elderly patients with COVID-19 to receive chloroquine treatment.

Hydroxychloroquine has a lower rate of tissue accumulation than chloroquine, hence, it has fewer adverse reactions.13 Hydroxychloroquine may be used in older patients with COVID-19, and adverse drug reactions such as heart failure, eye disorders and kidney function should be noted.

Considering reduced body function, older adults should monitored closely after taking favipiravir.

Clinical trials of Lopinavir / ritonavir did not include a sufficient number of subjects aged ≥65.60 In view of reduced physical activity, side effects and drug interactions should be monitored closely after older adults were taking lopinavir / ritonavir.

It is reported that the use of arbidol in patients over the age of 65 reduces the incidence of nosocomial pneumonia, and arbidol-related adverse reactions were not detected in the study.64 We suggest that older COVID-19 patients may use arbidol. In addition, arbidol is made up of CYP3A4, while ritonavir is a CYP3A inhibitor; therefore, a combination of ritonavir and arbidol may increase the concentration of arbidol serum. Side effects such as elevated serum transaminase in elderly COVID-19 patients receiving combination therapy with arbidol and lopinavir / ritonavir.

IFN-α can be used in elderly patients. However, adverse reactions such as fever, symptoms such as fever, nausea, dizziness, and headache are seen in patients receiving IFN-α inhalation.61 Adverse reactions may be more severe in elderly patients, and monitoring should be used with IFN-α.

The pharmacokinetics of remdesivir have not been evaluated in patients over 65 years of age. Generally, appropriate precautions should be taken when administering remdesivir and monitoring elderly patients.63

Antiviral Agents in COVID-19 Patients with Liver Disfunction:

Chloroquine can enter the liver tissue in large amounts. It should be used with caution in patients with liver failure.65

Hydroxychloroquine is produced by the liver. Although no dose adjustment is provided in the manufacturer's prescription, hydroxychloroquine should be used with caution in patients with liver failure.66

Favipiravir is metabolized to a form of hydroxylated by aldehyde oxidase and in part xanthine oxidase. 19 patients with severe liver failure should reduce the dose of favipiravir.

Lopinavir is primarily produced by CYP3A and ritonavir is a inhibitor of CYP3A.68 Medium to moderate liver failure that led to a 30% increase in AUC of lopinavir, but there is no clear correlation between the increase and treatment seen.69 Lopinavir / ritonavir has been detected. has not been studied in patients with severe hepatic impairment.69 Based on the fact that lopinavir / ritonavir can lead to an increase in liver enzymes and bilirubin, lopinavir / ritonavir may worsen liver dysfunction. Therefore,

we recommend the caution when giving lopinavir / ritonavir to COVID-19 patients with liver failure.

Currently, arbidol has not been evaluated in patients with liver function defects, and there is no valid recommendation in the manufacturer's label. Considering that arbidol is highly digested by CYP3A4 and UGT1A9,70 we suggest that COVID-19 patients with liver failure should use arbidol with clinical caution.
IFN-α is contraindicated in patients with autoimmune hepatitis or chronic liver disease. Although it is controlled by an aerosol inhalation, we have suggested that it should not be used in COVID-19 for autoimmune hepatitis or reduced liver disease.

The pharmacokinetics (PK) of remdesivir in humans is unclear. According to PK studies in rhesus monkeys, remdesivir exhibits a shorter half-life of plasma by rapidly depleting the system and rapidly distributing it to mononuclear blood cells. In vitro studies have shown low cytotoxicity of remdesivir in primary human hepatocytes.43 It is not known if dose adjustment is needed in patients with liver failure and remdesivir should only be used in patients with liver failure if the potential benefit outweighs the potential risk.63 One main side effects of remdesivir is an increase in liver transaminases; therefore, remdesivir should not be started on patients with ALT $\geq$ 5 times more than the usual limit at baseline.63 Further research is needed to secure remdesivir in patients with liver failure.

Antiviral Agents in COVID-19 Patients Receiving Renal Replacement Therapy:
Renal replacement therapy (RRT), especially continuous renal replacement therapy (CRRT), can maintain stable arterial pressure and effective renal perfusion, retaining fluid, electrolyte, and acid-alkaline balance effectively and smoothly, and is often required. in critically ill patients. (10.3389 / fphar.2020.00786) According to a recent report, approximately 17% of critically ill COVID-19 patients who received RRT.74 Pharmacokinetics of the drug could be replaced during RRT.75

In patients those receiving hemodialysis or peritoneal dialysis, the dose of chloroquine should be the same as in patients with GFR <10 mL / min, that is, giving 50% of the initial dose. In patients receiving CRRT, no dose adjustment is required.71

A case report is investigated the effects of continuous venovenous haemofiltration (CVVH) in patients taking favipiravir and showed that CVVH did not have a significant clinical contribution to the complete release of favipiravir.76 Reducing the dose of favipiravir during CVVH may not be appropriate.

The pharmacokinetics of hydroxychloroquine, lopinavir / ritonavir, and arbidol have not been studied in patients with renal transplant therapy. Lopinavir and ritonavir are 98–99% bound to blood plasma proteins albumin and alpha-1-acid-glycoprotein.59 We think that kidney replacement therapy will not affect the concentration of lopinavir / ritonavir in plasma. Considering arbidol, lopinavir / ritonavir is mainly metabolized by the liver and released by fecal, we speculate that dose adjustment of these two agents in COVID-19 patients with RRT is not required. Hydroxychloroquine is excreted by the kidneys. Considering its low molecular weight, it offers that it can be removed by CRRT. Dosage adjustment can be done depending on the remaining kidney function.

RRT has little effect on the concentration of the drug in the lung tissue; therefore, we hypothesized that no dose adjustment is required for IFN-α inhalation.

Antiviral Agents in COVID-19 Patients Receiving ECMO:
ECMO is a health support system used for patients with congestive heart failure and / or respiration. Recent studies have shown that ECMO may play a role in regulating COVID-19 patients with hypoxemic refractory respiratory failure.74,77 Modification of Drug pharmacokinetics during ECMO was demonstrated.78 Case report investigated the effect of ECMO on patients taking ritonavir. Ritonavir was given 100 mg once daily before ECMO and 100 mg twice daily during ECMO. The result showed that the levels of ritonavir drugs were lower than expected in the general population, suggesting that the PK of ritonavir changed during ECMO.79 We suggest that COVID-19 patients with ECMO may need to increase dose. of lopinavir / ritonavir and conduct medical drug monitoring to gain personal treatment. Considering IFN-α is used as a topical administration, we have provided that dose adjustment is not required during ECMO.

Little is known about the alternatives to other antivirals during ECMO. It has been reported that significant drug absorption occurs in the ECMO cycle, which is accompanied by an increase in drug lipophilicity.80 Among these drugs, lopinavir, ritonavir, and arbidol are hydrophobic; therefore, an additional dose regimen may be required during ECMO.

According to information about the use of remdesivir in the treatment of COVID-19, the recommended doses are the same in patients with ECMO.63 or without. On the other hand, COVID-19 patients receiving ECMO may experience severe symptoms, therefore. they need a longer course of treatment.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.

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