Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 outbreak: Challenges in pharmacotherapy based on pharmacokinetic and pharmacodynamic aspects of drug therapy in patients with moderate to severe infection

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ABSTRACT

The new coronavirus (COVID-19) was first detected in Wuhan city of China in December 2019. Most patients infected with COVID-19 had clinical presentations of dry cough, fever, dyspnea, chest pain, fatigue and malaise, pneumonia, and bilateral infiltration in chest CT. Soon COVID-19 was spread around the world and became a pandemic. Now many patients around the world are suffering from this disease. Patients with predisposing diseases are highly prone to COVID-19 and manifesting severe infection especially with organ function damage such as acute respiratory distress syndrome, acute kidney injury, septic shock, ventilator-associated pneumonia, and death. Till now many drugs have been considered in the treatment of COVID-19 pneumonia, but pharmacotherapy in elderly patients and patients with pre-existing comorbidities is highly challenging. In this review, different potential drugs which have been considered in COVID-19 treatment have been discussed in detail. Also, challenges in the pharmacotherapy of COVID-19 pneumonia in patients with the underlying disease have been considered based on pharmacokinetic and pharmacodynamic aspects of these drugs.

New corona virus disease (COVID-19)

Coronaviruses are large viruses that are enveloped, non-segmented, and positive-sense single-stranded RNA viruses. Coronaviruses can be divided into four generations containing *alpha, beta, delta*, and *gamma*. Among these generations, *alpha* and *beta* are human coronaviruses (HCoVs)[1,2] In late December 2019, new cases of pneumonia caused by a new coronavirus (2019-nCoV), new human-infecting *Betacoronavirus*,[3] were introduced to the world from the Wuhan city of China. The most common clinical signs and symptoms of these patients were dry coughs, fever, dyspnea, and bilateral infiltration in chest CT. All these patients were associated with Wuhan's Huanan Seafood Wholesale Market which sells fish and other live animals such as bats, poultry, snakes, etc. The causative agent, new coronavirus, was first detected through a swab sample which was drawn from the throat of these patients.[4] This new coronavirus was subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Soon this disease, which called coronavirus disease 2019 (COVID-19) by World Health Organization (WHO), promptly spreads around the world,[5] and to date over 16.5 million cases have been diagnosed with COVID-19 and this disease became a pandemic. On the late January 2020 COVID-19 Chinese outbreak, were introduced as a public health emergency of international concern.[6] So although previously coronaviruses were considered as a potential cause of the common cold now we know that they are more than just the common cold![1]

COVID-19 signs and symptoms

Most of the COVID-19 infected patients have an average age of 50s, it is slightly more predominant in the male sex, approximately 25% of infected patients involved with severe disease were required to intensive care unit services and 10% of them were required to mechanical ventilation.[3] A published report from Italian patients revealed that COVID-19 was predominant in men (59.8% in male and 40.2% in female), most of the patients (about 75%) were over 50 years old, approximately 46% of all confirmed patients had mild disease, 25% had severe disease, 5% were in a critical situation, and rest of the patients showed few symptoms, unspecified symptoms or were

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completely asymptomatic.[7] According to recently published researches, the most common clinical presentations in COVID-19 patients were fever in 83% to 98% of patients, dry cough in 76 to 82%, and fatigue or myalgia in 11 to 44% of them. Other signs and symptoms which have been reported include sore throat, headache, confusion, rhinorrhea, sneezing, ageusia, anosmia, chest pain, hypoxemia, pneumonia, hemoptysis, acute cardiac injury, neurologic complications,[8, 9] and gastrointestinal presentations such as nausea, vomiting, diarrhea and abdominal pain.[3,10-12] Patients with underlying diseases are highly prone to present with severe infection especially with organ function damage such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), septic shock, and ventilator-associated pneumonia (VAP).[10,13] Severe COVID-19 could cause death due to huge alveolar damage and highly progressive respiratory failure.[14]

Transmission and spread

COVID-19 particles could spread through the respiratory mucosa[10] and fecal-oral route.[11] The nucleic acid of the virus was detected in stool, saliva, and respiratory specimens.[11] This virus could be transmitted between humans during the epidemic and then pandemic of COVID-19. Human-to-human transmission could highly accelerate the spread of this virus around the world. This type of transmission among humans is restricted to close contact and through sneezing or coughing of the infected patients who are capable to spread the respiratory droplets. Then these respiratory droplets could settle in oral mucosa and lung of the people who inhaled the contaminated air near (about 6 feet) to the infected patients.[15,16] Although some researches have been focused on the airborne transmission of this virus but this route of transmission has not been approved yet and further studies are required. Researches revealed that COVID-19 could also be transmitted through asymptomatic carriers with an incubation period of 1 to 19 days.[17] In order to prevent spreading of this new virus: hands should be washed frequently, the face should not be touched with unwashed hands, regular surface disinfecting is required, social distancing from people with respiratory symptoms is essential, sneezing or coughing should be done into the elbow or soft tissue if available.[16]

COVID-19 diagnosis

Based on the published reports, in most of the patients with COVID-19, the absolute value of lymphocytes was reduced, which indicated that this novel coronavirus (COVID-19) acts more on lymphocytes especially T lymphocytes, just similar to SARS coronavirus.[10] It seems that COVID-19 could induce a cytokine storm and activate immune responses which could be appeared as changes in the number of white blood cells and immune cells especially lymphocytes, the clinical outcome of such events would be respiratory distress syndrome, septic shock and finally end-organ damage.[10] COVID-19 could also affect the liver which could be presented as hypoproteinemia, elevated aminotransferases, and prolonged prothrombin time. Hepatotoxicity could be attributed to the higher expression of angiotensin converting enzyme II (ACE2) in cholangiocytes, ACE2 could act as an entry receptor for COVID-19. So it seems that this new virus can directly damage the intrahepatic bile ducts.[11] Pathological findings of a liver biopsy from a patient with COVID-19 showed moderate micro-vesicular steatosis and also a mild portal and lobular activity which could be a result of direct SARS-CoV-2 liver damage or antiviral drug-induced hepatotoxicity.[14] Almost all COVID-19 patients had abnormal lung CT when diagnosed. According to the recently published article, an average of 10.5±6.4 segments were involved in patients and the number of involved lung segments was significantly higher in symptomatic patients group in comparison to asymptomatic ones. CT findings revealed that affected COVID-19 patients could present as bilateral lung involvement, peripheral distribution, or diffuse distribution. The most common presentation in chest CT was ground-glass opacity pattern, consolidation, and ill-defined margins.[18,19] Laboratory confirmation of steatosis could be performed by real-time reverse-transcription polymerase chain reaction (rRT-PCR).[20,21] According to WHO approved laboratory testing for COVID-19 diagnosis is based on nucleic acid amplification test (NAAT) such as rRT-PCR which could detect the sequence of the RNA of COVID-19.[22]

Non-pharmacotherapy interventions

Governments need to appreciate people to obey social distancing and isolation. In some situations, quarantine of major cities is also suggestive. Global health governance should apply the least restrictive measures for people according to the International Health Regulations (IHR).[23,24]

COVID-19 potential treatments

Scientists around the world are looking for drugs that could be beneficial in COVID-19 treatment. Many drugs have been studied that are listed in Table 1 with the usual dosage ranges in adults and pediatrics. The latest Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia, have been suggested antiviral agents containing: Interferon alpha (IFN-α), lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol as potential options in COVID-19 treatment.[25] Drugs that have been considered in COVID-19 management have been classified as investigational drugs, drugs under clinical trials, and drugs that have received U.S. Food and Drug Administration (FDA) as shown in Table 2.

Chloroquine/Hydroxychloroquine

Chloroquine and hydroxychloroquine are immunomodulant antimalarial agents with broad-spectrum antiviral effects which have been considered for potential benefits in COVID-19 treatment. Hydroxychloroquine is a common drug in many autoimmune disorders such as lupus and rheumatoid arthritis, also it has a strong immunomodulatory effect that can prevent inflammation flare-ups and avoid further organ damage related to COVID-19.[37,38] Previous *in vitro* studies confirmed the antiviral activity of chloroquine against COVID-19. Also, a recent publication from a Chinese clinical trial reported that the use of chloroquine phosphate in patients with COVID-19 is superior and have the potential of reversing exacerbation of 2019-nCoV-induced pneumonia, normalizing patients' lung CT scans, shortening the disease duration and length of hospitalization, and induction of virus-negative conversion. But still, more information and larger prospective clinical trials are required to confirm its beneficial effect in COVID-19 treatment.[37] The recommended dose of chloroquine in patients with mild, moderate, or severe COVID-19 pneumonia is 500 mg twice daily. Chloroquine is a safe, available, and clinically applicable drug for COVID-19 patients. Since hydroxychloroquine has the same mechanism of action to chloroquine, so it also could be an alternative agent with identical effects in the treatment of COVID-19 pneumonia.[39] 750 mg of chloroquine is equal to 1200 mg of hydroxychloroquine.[38] The recommended dose of hydroxychloroquine in COVID-19 is 200 mg twice daily. Chloroquine and hydroxychloroquine have been considered as potential candidates against COVID-19 pneumonia.[40,41] An open-label non-randomized clinical trial on hydroxychloroquine and azithromycin co-administration in COVID-19 patients was performed in France. Results revealed that hydroxychloroquine could significantly reduce the viral load and azithromycin could reinforce its clinical effect, but the main limitation of this clinical trial was its small sample size.[42] Although many previous studies emphasized the potential therapeutic effects of these drugs in COVID-19 management, unfortunately some recent publications reported that the efficacy of chloroquine/hydroxychloroquine in COVID-19 management is not consistent.

Table 1.
Drugs that have been studied in relief of COVID-19 clinical presentation.

Drug	Adult Dosage	Pediatric Dosage	Route of Administration
Chloroquine phosphate	500 mg (300 mg for chloroquine base) twice daily[25]	Not recommended	Oral
Hydroxychloroquine	200 mg twice daily[26]	Not recommended	Oral
Lopinavir/Ritonavir	400mg/100 mg (2 capsules each time) twice daily[26]	Lopinavir:BW[1] (kg): • 7–15 kg: 12 mg/3 mg/kg/time, twice daily for 1–2 weeks • 15–40: 10 mg/2.5 mg/kg/time, twice daily for 1–2 weeks • 40: 400 mg/100 mg/time, twice daily for 1–2 weeks[27]	Oral
Ribavirin	500 mg twice dailyin combination with IFN-α or lopinavir/ritonavir[25]	10 mg/kg every time (maximum 500 mg every time), 2–3 times daily [27]	IV infusion
IFN-α[2]	5 million U twice daily[25]	200,000–400,000 IU/kg or 2–4 μg/kg in 2 mL sterile water, twice daily for 5–7 days [27]	Vapor inhalation (nebulization)
Umifenovir	200 mgthree times daily[26]	Not recommended	Oral
Remdesivir	200 mg loading dose on the first day Followed by 100 mg once daily [28]	• BW[1] of 3.5-40 kg: 5 mg/kg loading dose on the first day followed by 2.5 mg/kg once daily from the second day • BW[1] of $\geq$ 40 kg: similar to the adult dosage[29].	IV infusion
Tocilizumab	8 mg/kg every 4 weeks [30]	Not recommended	IV infusion (during 60 min)
Teicoplanin	400 mg daily[31]	Not recommended	IV infusion
Favipiravir	1600-2400 mg loading dose on the first day Followed by 200-600 mg twice daily [26]	Not recommended	Oral

[1] Body weight
[2] Interferon alpha

Table 2
Classification of drugs that have been considered in COVID-19 management.

Status in COVID-19 management	Drugs/Approaches	Clinical considerations
FDA approved[32]	1. Remdesivir 2. Dexamethasone 3. Aviptadil	Severe cases of COVID-19 and COVID-19 induced ARDS
Under clinical trials[33]	1. Chloroquine 2. Hydroxychloroquine 3. Lopinavir/Ritonavir 4. IFN-α[1] 5. IFN-α2b[2] 6. Favipiravir 7. Umifenovir 8. Tocilizumab 9. IFN-ß1a[3] 10. Ribavirin 11. Convalescent plasma 12. ECMO[4] 13. High-dose vitamin C 14. Corticosteroids (Methylprednisolone)	Patients with confirmed COVID-19
Investigational and/or hypothesis	1. Desferrioxamine[34, 35] 2. Teicoplanin[31] 3. Etoposide[36]	-

[1] Interferon alpha
[2] Interferon alpha 2b
[3] Interferon beta 1a
[4] Extracorporeal membrane oxygenation

Also, their safety is still remaining a major concern for physicians and pharmacists, since chloroquine/hydroxychloroquine could cause QT prolongation and arrhythmia. Since the possible risks of these drugs could overweigh their potential benefits and efficacy, United States Food and Drug Administration (FDA) no longer recommended these two drugs as potential options for COVID-19 management.[43] Results of a systematic review on the efficacy of hydroxychloroquine or chloroquine on the prevention or treatment of COVID-19 revealed that the available evidences on their benefits and risks are weak and controversial.[44] Results of another systematic review and meta-analysis on 53 randomized clinical trials on administration of hydroxychloroquine in COVID-19 management revealed that hydroxychloroquine administration (case group) was significantly associated with higher incidence of total adverse effects in comparison to placebo or no treatment (control group) in overall population of patients with COVID-19.[45] So, the recruitment of chloroquine/hydroxychloroquine in COVID-19 management is still controversial and further larger multi-center randomized clinical trials are required to evaluate their efficacy, safety, risk-benefit ratio, dose and duration of individualized pharmacotherapy. Also, close patient monitoring, especially cardiac, ocular, and neurotoxicity assessments, are required and strongly recommended during drug administration.[46]

Chloroquine/Hydrpxychloroquine mechanism of action in coronavirus treatment. Recently published studies revealed that chloroquine could highly reduce COVID-19 replication with an acceptable effective concentration (EC_{90}) value of 6.90 μM which could be easily achieved with standard doses of 500 mg twice daily. The most important advantage of chloroquine in COVID-19 treatment is good penetration to tissues especially lungs which are highly affected in COVID-19 pneumonia. Chloroquine could stop viral infection by enhancing the pH of endosomes which is required for virus-cell fusion and interfering with COVID-19 cellular receptor glycosylation which could interfere with post-translation modification of COVID-19 viruses (inhibition of entry and post-entry stages).[40] Chloroquine is a weak base that could be entrapped in organelles that are membrane-enclosed and have low-pH, so interfering with their acidification process. Therefore chloroquine could inhibit pH-dependent viral fusion and replication. Also, it might inhibit viral assembly in endoplasmic reticulum-Golgi intermediate like structures.[47] Another possible antiviral mechanism of chloroquine is its immunomodulatory effect through cell signaling pathways and regulating the action of pro-inflammatory cytokines that can enhance its antiviral effect synergistically[40,48,49] Chloroquine/hydroxychloroquine could prevent from COVID-19-induced ARDS by attenuating the pro-inflammatory cytokines and receptors.[47] Hydroxychloroquine can enhance intracellular pH and avoid lysosomal activity in antigen presenting cells containing B cells, also they can avoid antigen processing and MHC-II presentation to T cells. So, T cell activation could be reduced by the

action of hydroxychloroquine. It can suppress the cytokine release syndrome (CRS), which is a result of immune system over-activation, caused by COVID-19. According to this mechanism, hydroxychloroquine could alleviate symptoms of mild to severe COVID-19 pneumonia.[38]

Chloroquine/Hydroxychloroquine adverse reactions. Chloroquine has different adverse reactions such as cardiovascular adverse reactions (atrioventricular block, cardiac arrhythmia, QT prolongation, torsades de pointes, etc.), ophthalmic adverse drug reactions (blurred vision, corneal opacity, macular degeneration, maculopathy and retinopathy [which are depends on cumulative doses of chloroquine], nocturnal amblyopia, accommodation disturbances, etc), otic adverse drug reactions (deafness, hearing loss and tinnitus), central nervous system (CNS) adverse reactions (agitation, anxiety, confusion, etc.), endocrine and metabolic adverse reactions such as hypoglycemia, hematologic and oncologic (agranulocytosis, aplastic or hemolytic anemia, neutropenia, pancytopenia, etc.), gastrointestinal adverse reactions, hepatic adverse reactions (hepatitis and increased liver enzymes), etc. Results of a recent case report emphasized that chloroquine/hydroxychloroquine administration could induce severe dermatologic side effects such as Stevens Johnson syndrome (SJS) in a patient with COVID-19.[50] Also the results of a systematic review on dermatologic adverse effects of hydroxychloroquine emphasized that the most common dermatologic reactions due to hydroxychloroquine administration were rash, SJS,toxic epidermal necrolysis (TEN), pruritus, hyperpigmentation, and hair loss. These dermatologic reactions were mostly occurred after cumulative dosages of hydroxychloroquine.[51] In overall, since hydroxychloroquine has lower tissue accumulation potential in comparison with chloroquine, it has fewer adverse drug reactions and would be better choice.[38]

Chloroquine/Hydroxychloroquine contraindications. Contraindications in chloroquine use contains hypersensitivity to chloroquine (4-aminoquinolone compounds) and the presence of retinal or visual field changes.[52]

Chloroquine/Hydroxychloroquine pharmacokinetics. Chloroquine and hydroxychloroquine can distribute widely in the whole body after oral administration. Hydroxychloroquine has incomplete and variable (about 70%) absorption, while chloroquine has rapid and almost complete absorption. Both have moderate plasma protein binding. Both have hepatic metabolism. Chloroquine has an elimination half-life of 4 to 5 days while hydroxychloroquine has an elimination half-life of about 40 days. The main route of drug excretion for both of them is renal excretion, which could be increased with urine acidification.[52]

Patients with predisposing diseases and special conditions. Cardiovascular diseases. Chloroquine and hydroxychloroquine have a narrow therapeutic index and poisoning could be occurred with cardiovascular features so it should be used with caution in patients with predisposing cardiovascular disease.[37] Long-term exposure to these drugs could induce cardiomyopathy.[38] Chloroquine in patients consuming heparin, prone the patients to risk of bleeding. Also, chloroquine in patients with digitalization (using digoxin) could cause cardiac block.[27]

Liver diseases. There is no dosage adjustment available for chloroquine or hydroxychloroquine in patients with hepatic failure but it should be used with caution.[52]

Kidney diseases. There is no dosage adjustments available for chloroquine in patients with renal failure from the manufacture's labeling but according to UpToDate some clinicians use the following guideline [52]:

A) Patients with GFR $\geq$ 10 ml/min: No dosage adjustment is required.
B) Patients with GFR $<$ 10 ml/min: Dosage should be reduced to 50%.
C) Patients with peritoneal- or hemodialysis: Dosage should be reduced to 50%.
D) Patients with continuous renal replacement therapy (CRRT): No dosage adjustment is required.

There is no dosage adjustments available for hydroxychloroquine in renal failure but it should be used with caution.[52]

Pregnancy. Although some studies showed a low risk of congenital abnormalities in patients receiving chloroquine during pregnancy because of the lack of a pattern in these congenital defects, the possible association is unlikely and it seems that the benefits of its use are higher than risks.[53]

Hydroxychloroquine use during pregnancy could not be accompanied by risks for fetuses, especially in low doses. But patient monitoring during pregnancy is required.[53]

In general, since chloroquine may induce severe side effects during fetal development, so hydroxychloroquine would be a better option in pregnant women with COVID-19 infection because of its safety profile during pregnancy.[38]

Lactation. According to the American Academy of Pediatrics, chloroquine is compatible with breastfeeding. Although it could be excreted into the milk, this amount was not considered harmful for nursing infants.[53]

According to the American Academy of Pediatrics, hydroxychloroquine is compatible with breastfeeding. Small amounts of hydroxychloroquine could be excreted to the milk, but because of the slow elimination rate and the possibility of drug accumulation and toxicity, breastfeeding during hydroxychloroquine therapy should be done with caution.[53]

Umifenovir (Arbidol®)

Umifenovir is a broad-spectrum antiviral agent which is effective against enveloped and non-enveloped RNA or DNA viruses especially against influenza virus type A and B, respiratory syncytial virus, SARS-CoV, adenovirus, hepatitis C virus (HCV), etc. Umifenovir was first developed in Russia and now its usage is more common in Russia and China and is less common in western countries. Its possible antiviral mechanism is the inhibition of viral fusion with targeted membrane and preventing from the viral entrance to targeted cells.[54]

Umifenovir mechanism of action in coronavirus treatment. Umifenovirhas a dual pharmacologic action: First is its beneficial effect on respiratory viruses such as the COVID-19 virus and the second is its immune-stimulating function which can activate serum interferon and phagocytes. Since 2004, umifenovir was patented for its beneficial effect in the treatment of severe acute respiratory distress (SARS) coronavirus-induced atypical pneumonia.[55] Results revealed that umifenovircan induce direct viricidal effect so it would be a promising direct-acting antiviral (DAA) agent. Umifenovircould affect critical stages of viral life cycles such as cell attachment, cell internalization, viral replication, assembly, and budding so it also would be a promising host targeting agent (HTA). Its dual pharmacologic function is related to its potential interaction with both cell membranes and with cellular and viral lipids and proteins.[55]

Umifenovir adverse reactions. The most important adverse reactions associated with umifenovirare diarrhea, nausea, vomiting, dizziness, confusion, and elevated liver enzymes (serum aminotransferases).[27]

Umifenovir pharmacokinetics. Umifenoviris an indole derivative with poor water solubility which could affect its bioavailability and pharmacokinetics. After oral administration of umifenovir, it could rapidly

distribute to organs and tissues, maximum plasma concentration (C_{max}) was achieved after 1 to 1.5 hours. In the Russian population, it had elimination half-life (t $^1/_2$) of 17 to 21 hours, but t $^1/_2$ was shorter in the Chinese population. After multiple-dose administration of umifenovir, little drug accumulation could be predictable. The main site of drug metabolization is the liver. Umifenovircould undergo several metabolism pathways such as oxidation at the S site, N-demethylation, glucuronidation, and conjugation at 5-hydroxy moiety. The potential antiviral effects of umifenovirmetabolites are unknown until now.[55]

Patients with predisposing diseases and special conditions. Liver diseases. Since the major site of umifenovirmetabolization is in the liver, so it should be used with caution in patients with predisposing liver diseases.

Pregnancy. Animal data revealed that umifenovirtherapy couldn't induce embryo-toxic effects during pregnancy. According to these results umifenovirwould be a promising safe and well-tolerated antiviral agent in pregnancy with a wide therapeutic index in administration for a few days up to one month.[55]

Ribavirin

Ribavirin is a nucleoside antihepaciviral agent (anti-HCV) which has been suggested for COVID-19 treatment. Ribavirin is a direct-acting antiviral (DAA) agent.[56]

Ribavirin mechanism of action in coronavirus treatment. Ribavirin is a nucleoside analog that has antiviral action against a variety of RNA and DNA viruses. The potential antiviral activity of ribavirin is inhibition of inosine monophosphate dehydrogenase (IMPDH) cellular protein and therefore intracellular GTP would be diminished which inhibits RNA replication of viral genomes, so viral growth might be stopped. Another possible antiviral activity of ribavirin is its immunomodulatory effects by suppression of IL-10.[57] Ribavirin also could inhibit RNA polymerase activity and therefore inhibition of RNA fragments' initiation and elongation, so viral protein synthesis could be inhibited.

Ribavirin adverse reactions. The most common adverse reactions of ribavirin are CNS adverse reactions (headache, fatigue, insomnia, nervousness, etc.), dermatologic complications (alopecia, pruritus, skin rash, etc.), endocrine and metabolic adverse reactions (growth suppression in children and adolescents and weight loss), gastrointestinal adverse effects, hematologic effects (anemia, lymphocytopenia, neutropenia, and hemolytic anemia), hepatic adverse reactions (elevated serum bilirubin level), respiratory adverse reactions (flu-like symptoms, upper respiratory tract infection, dyspnea, cough, pharyngitis, sinusitis, etc.), weakness, muscle pain, etc. The less common adverse reactions are cardiovascular events such as chest pain and flushing.[52]

Ribavirin contraindications. Ribavirin is contraindicated in patients with hypersensitivity to ribavirin, pregnant women and their partner, patients with severe renal failure, patients with severe hepatic failure, and patients with major hemoglobinopathies such as sickle cell anemia and major thalassemia.[52]

Ribavirin pharmacokinetics. Ribavirin distribution could significantly prolonged in erythrocytes for about 16 to 40 days, which is responsible for ribavirin-induced anemia.[58] Ribavirin has hepatic metabolism. Its oral bioavailability (F) is about 64%. Ribavirin elimination half-life (t $^1/_2$) in the normal population is 24 hours but in patients with pre-existing chronic hepatitis C infection, half-life could be increased to 44 hours. So because of its prolonged half-life and potential overdose toxicity, ribavirin is contraindicated in patients with hepatic failure (Child-Pugh class B and C). Time to peak level (T_{max}) after oral administration is between 2 to 3 hours. Ribavirin excretion could take place through both urine and feces routes. Because of its renal elimination, dose adjustment in patients with underlying kidney disease is highly essential. According to the previous pharmacokinetic/pharmacodynamic study, Bayesian therapeutic drug monitoring would be a suitable approach to control ribavirin-induced anemia [41].

Patients with predisposing diseases and special conditions. Cardiovascular diseases. One of the most important side effects of ribavirin is hemolytic anemia which could worsen cardiac disease in patients with underlying cardiac diseases and it could induce fatal or non-fatal myocardial infarction in them. So ribavirin should be avoided in patients with a history of unstable or severe cardiac diseases.

Liver diseases. Ribavirin is contraindicated in patients with hepatic decompensation (Child-Pugh class B and C).

Kidney diseases. Ribavirin dosage adjustment in patients with renal failure highly depends on different formulations which are available. These data are shown in Table 3[52]. In children, if serum creatinine level rises over 2 mg/dl during administration, ribavirin should be discontinued promptly.[27]

Pregnancy. Ribavirin has teratogenic and mutagenic effects. So it is a high-risk drug in pregnancy according to animal data. Also because of its half-life of 12 hours in multiple-dose drug therapy and the possibility of drug accumulation in tissue compartments for up to 6 months, ribavirin administration is contraindicated in pregnant women and also in men who are pregnant women's partner. It was suggested that pregnancy should be avoided during ribavirin therapy and at least 6 months after completion of therapy in women or men.[53]

Lactation. Ribavirin because of the prolonged plasma elimination half-life and molecular weight of 244 Da, potentially would have toxicity in nursing infants but there are no human data available.[53]

Patients have undergone solid organ transplantation. Ribavirin may precipitate hematologic adverse effects of organ transplantation regimen such as immunosuppressive agents (mycophenolate mofetil, azathioprine, mTOR inhibitors), Trimethoprim/sulfamethoxazole, and valganciclovir. These hematologic adverse reactions would also worsen hematologic reactions related to COVID-19. So close patient monitoring is essential.

Lopinavir/Ritonavir

Lopinavir/Ritonavir are protease inhibitor antiretroviral agents (anti-HIV). Previous researches proved the *in vitro* efficacy of lopinavir against SARS-CoV.[59] Ritonavir can enhance lopinavir's elimination half-life (t $^1/_2$) by inhibition of CYP450. Lopinavir itself showed antiviral effects against MERS-CoV.[60] Also, results revealed that lopinavir/ritonavir in combination with ribavirin and IFN-α could promote viral

Table 3.
Ribavirin dose adjustment based on renal function.

Ribavirin formulations	GFR ≥ 50 ml/min	GFR 30 to 50 ml/min	GFR < 30 ml/min	ESRD[1] patients with hemodialysis
Rebetol® capsule/solution and Ribasphere® capsule	No dosage adjustment is required	Contraindicated	Contraindicated	Contraindicated
Copegus®, Moderiba®, and Ribasphere® tablets	No dosage adjustment is required	Alternate 200 mg and 400 mg every other day	200 mg once daily	200 mg once daily

[1] End stage renal disease

clearance and enhance patients' survival. The results of a recent clinical trial revealed that the addition of lopinavir/ritonavir to the standard supportive care was related to neither clinical improvement nor mortality rate reduction in patients with COVID-19 infection. But the most important limitation of this study was the heterogeneity of the sample population according to disease severity and duration of the COVID-19 course.[61] So further larger clinical trials are required to confirm lopinavir/ritonavir's clinical efficacy against COVID-19 infection. The recommended daily dose of lopinavir /ritonavir is 400 and 100 mg respectively twice daily. Another report from Korea showed that lopinavir/ritonavir administration in patients with COVID-19 could improve clinical symptoms and reduce viral load. Lopinavir/ritonavir would be a promising agent in high-risk patients, such as elderly groups and patients with the underlying disease who are infected with COVID-19.[62] Also, lopinavir would be a promising drug of choice in children with COVID-19.[27]

Lopinavir/Ritonavir mechanism of action in coronavirus treatment. Lopinavir/ritonavir are protease inhibitor, anti-retroviral agents. The potential antiviral mechanism of lopinavir/ritonavir is inhibition of viral protease, which is a critical enzyme in viral maturation and infectivity. Low dose ritonavir in combination with lopinavir act as a pharmacokinetic enhancer by inhibition of lopinavir inactivation metabolism.[63]

Lopinavir/Ritonavir adverse reactions. The most common adverse drug reactions of lopinavir/ritonavir are dermatologic reactions such as skin rash, endocrine, and metabolic adverse reactions such as hypercholesterolemia and hypertriglyceridemia, gastrointestinal and digestive adverse reactions, hepatic adverse reactions such as elevated serum ALT level, and upper respiratory tract infections. Other less common adverse reactions contains cardiovascular events such as vasodilation, elevated AST level, hematologic adverse reactions (thrombocytopenia and neutropenia), weakness, etc. may occur with lopinavir/ritonavir. When clinicians administer this drug they should consider digestive adverse effects and hypokalemia in patients with COVID-19 infection.[64]

Lopinavir/Ritonavir drug interactions. Since lopinavir undergoes hepatic metabolism through CYP3A4 enzyme, potential drug-drug interactions could occur with all drugs that are strong inhibitors or inducers of CYP3A4 enzyme and P-glycoprotein inhibitors. Also, ritonavir has hepatic metabolism via CYP3A4 and CYP2D6. Ritonavir has serious and life-threatening drug interactions with sedative-hypnotic agents, antiarrhythmic drugs, and ergot alkaloid agents because of the effect of ritonavir on their hepatic metabolism through CYP3A4 AND CYP2D6. Concurrent use of these agents with ritonavir is absolutely contraindicated and should be avoided.[52]

Lopinavir/Ritonavir contraindications. Lopinavir/ritonaviris contraindicated in patients with a history of hypersensitivity reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, angioedema, etc. to lopinavir/ritonavir or its components.[52]

Lopinavir/Ritonavir pharmacokinetics. Lopinavir has high plasma protein binding (about 98 to 99 %), it has hepatic metabolism via CYP3A4 through its drug interaction with all inducers and inhibitors of CYP3A4. Lopinavir has an elimination half-life of 5 to 6 hours which indicates that a suitable dosage interval would be 12 hours. Time to peak (T_{max}) is about 4 hours. The main route of drug excretion is feces (about 83%) and the remaining amounts could be excreted through urine. Because of its low renal elimination, no dosage adjustment is required in patients with underlying kidney disease and it could be administered safely.[52]

Ritonavir also has high protein binding (about 98 to 99 %) and undergo hepatic metabolism through CYP3A4 and CYP2D6. Low-dose of ritonavir in combination with lopinavir as a fixed-dose agent (1:4 ratio) acts as a pharmacokinetic enhancer by inhibition of lopinavir inactivation metabolism through inhibition of liver and intestinal CYP3A4 and inhibition of P-glycoprotein efflux pump.[65] Ritonavir could induce high serum and lymph node concentration with a volume of distribution of 0.41±0.25 L/kg. It has an elimination half-life of 3 to 5 hours. Ritonavir's absorption and oral bioavailability are highly affected by fasting or fed state, its absorption, bioavailability, and peak level (C_{max}) could be significantly increased with food. But food can delay T_{max} from 2 hours in fasting state to 4 hours in the fed state. Ritonavir also has small renal elimination so dosage adjustment is not required in patients with underlying kidney disease.[52]

Patients with predisposing diseases and special conditions. Cardiovascular diseases. Lopinavir/ritonavir have major interactions with drugs used in cardiovascular diseases such as anti-coagulating agents (anti-factor Xa inhibitors), none dihydropyridine calcium channel blockers, digoxin, antiarrhythmic agents such as amiodarone, etc. So close patient monitoring is required in COVID-19 patients with pre-existing cardiovascular disease who are planned to treat with lopinavir/ritonavir and sometimes alternative drugs might be considered.[52]

Liver diseases. In patients with mild to severe hepatic failure, there is no dosage adjustments available but lopinavir has primary liver metabolism and its AUC will be increase by about 30 %, so it should be used with caution.[52]

Kidney diseases. There is no dosage adjustments based on renal function according to the manufacture's labeling.[52]

Pregnancy. Results revealed that embryo-fetal risk of lopinavir/ritonavir is low, so it is compatible with pregnancy and should not be stopped during pregnancy.[53]

Lactation. Lopinavir and ritonavir with a molecular weight of 629 and 721 Da respectively and their lipid solubility nature, are good candidates for excretion to milk during lactation period but their high plasma protein binding could limit this excretion. A comprehensive data is not available yet. It has been recommended that breast-feeding during lopinavir/ritonavir therapy is better to be avoided especially in developed countries.[53]

Patients have undergone solid organ transplantation. Immunosuppressive agents are critical drugs in patients undergone solid organ transplantation. Lopinavir/ritonavir cannot be administered in combination with immunosuppressive agents because of the occurrence of strong drug interactions. Lopinavir/ritonavir can enhance the plasma level of immunosuppressive agents such as calcineurin inhibitors and mTOR inhibitors. So if co-administration is essential, immunosuppressive agents dose reduction and therapeutic drug monitoring, to maintain optimum immunosuppressive plasma level, is highly recommended. It has been suggested that during COVID-19 treatment, calcineurin inhibitors (ex. cyclosporine and tacrolimus) and mTOR inhibitors (ex. sirolimus and everolimus) could be discontinued and replaced with lopinavir/ritonavir but it seems that the benefit of this drug discontinuation could not overlay the risk of allograft transplant rejection.[66]

Other drugs

Tocilizumab. Tocilizumab is an interleukin-6 (IL-6) inhibitor which is a disease modifying anti-rheumatic agent.[67] A small retrospective observational study on COVID-19 pneumonia patients receiving tocilizumab revealed that this drug would have potential benefits in these patients such as improvement in CT scan abnormalities, normalizing C-reactive protein (CRP), and lymphocyte levels, and enhancing O_2 saturation. Tocilizumab mechanisms of action in COVID-19 pneumonia is attributed to the critical role of IL-6 in the hyper-inflammatory state after infection with COVID-19, so the blockers of IL-6 would be a promising option in the management of COVID-19 pneumonia, especially ARDS condition.[30] Since the number of pro-inflammatory cytokines in COVID-19-induced cytokine release

syndrome (CRS), is inversely related to absolute lymphocyte count, so tocilizumab, as an IL-6 antagonist, would be a promising agent to enhance viral clearance and relieve COVID-19 pneumonia complications,[68,69] Further clinical trial results are required to confirm its clinical efficacy and safety. In COVID-19 patients, T cell counts have been reduced significantly and also the remaining T cells are highly exhausted. Since an active immune response against respiratory viruses such as COVID-19 is highly dependent on cytotoxic T cells' action, so in patients with total T cell count of fewer than 800 cells/μL, aggressive intervention is essential. One of the possible approaches in enhancing T cell count in these patients is the administration of tocilizomab, because there is a reverse relationship between T cell count and the number of cytokines such as IL-6.[70]

Interferon alpha (IFN-α). IFN-α is a broad-spectrum antiviral agent that is commonly used in hepatitis management. After the confirmation of the *in vitro* efficacy of IFN-α against COVID-19, it has been recommended by the Chinese Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia. The route of administration of IFN-α in COVID-19 patients is vapor inhalation with an adult dosage of 5 million U twice daily.[25] Subcutaneous administration of pegylated IFN-α-2a and pegylated IFN-α-2b would be beneficial in patients with COVID-19 by stimulation of innate antiviral responses. Since IFN-α has many adverse reactions, close patient monitoring is required during IFN-α therapy.[71] IFN-α, in dosage form of nebulization or oral/nasal spray, is a drug of choice which has been recommended in children with mild symptoms of COVID-19 pneumonia. The recommended dose in children is 200000 to 400000 U/kg twice daily for up to 5 to 7 days. IFN-α overdosing in children could cause elevated liver enzyme levels, bleeding, acute kidney injury and renal failure, etc. Another concern about the administration of IFN-α in combination with ritonavir in children is inhibition of development and growth which also should be considered by clinicians and experts. IFN-α could also enhance suicidal ideation in children and there is a warning/caution in co-administration of IFN-α with sedative-hypnotic agents.[27]

Teicoplanin. Teicoplanin is a glycopeptide antibiotic. It is commonly used in Gram-positive bacterial infections. Recent *in vitro* studies showed that teicoplanin could be effective in COVID-19 treatment. A possible antiviral (anti-COVID-19) mechanism of teicoplanin is the enhancement of the endosomal pH and thereby inhibition of low-pH viral spike protein cleavage in endosome by Cathepsin L, this process results in avoidance of genomic RNA release and replication of viral life cycle which would be stopped at early stages. The recommended daily dose of teicoplanin is 400 mg daily which could obtain a serum level of 8.78 μM/L, this level is significantly higher than its IC_{50} of 1.66 μM/L. According to these results, teicoplanin would be a promising alternative in COVID-19 pneumonia treatment but further randomized clinical trials are required to confirm its efficacy.[31]

Azithromycin. Azithromycin is a macrolide antibiotic. Previous *in vitro* studies revealed the antiviral activity of azithromycin and also it could prevent severe viral respiratory tract infections in patients infected with respiratory viruses. A recent publication showed that azithromycin in combination with hydroxychloroquine could have synergistic effects against COVID-19 infection. But the most important concern about these two compounds is the increased risk of QT prolongation and Torsades de points.[42] especially in patients with underlying cardiovascular diseases. So, close patient monitoring is required during the concomitant administration. An open-label non-randomized clinical trial in France revealed that co-administration of azithromycin with hydroxychloroquine in COVID-19 patients was accompanied by reinforcement of the effect of hydroxychloroquine monotherapy, but the main limitation of this clinical trial was its small sample size.[42] So, further larger clinical trials are required to confirm these combinations' safety and efficacy in COVID-19 treatment.

Remdesivir. Remdesivir is a new antiviral agent that is effective against RNA viruses such as COVID-19. Its potential effects on SARS/MERS coronaviruses are just confirmed in cell culture and animal models (mice), still no clinical data available on its efficacy against COVID-19. Remdesivir is an adenosine analog with antiviral activity. A possible mechanism of antiviral action of remdesivir is its incorporation into the nascent RNA chain of the virus and causing premature viral cycle termination, but this stage is a post virus entry stage. A recent publication showed the efficacy of remdesivir in cell culture in the inhibition of COVID-19 infection.[49] On 1st May 2020, the US Food and Drug Administration (FDA) approved the emergency use of remdesivir for the treatment of suspected or confirmed COVID-19 patients both in adults and children with severe disease. While there is limited information about the safety and clinical efficacy of remdesivir in the management of hospitalized patients with COVID-19, but according to the latest clinical trial results, this drug could shorten the recovery time of COVID-19 patients and received FDA approval for management of severe cases.[72] Although this preliminary and observational study revealed the reduction in recovery time of some patients receiving remdesivir, but still there are controversies about its safety and efficacy. Results of a randomized, double-blind, placebo-control clinical trial in China, from the 6th February to 12th March 2020, revealed that remdesivir administration in adult COVID-19 patients with severe disease was not significantly associated with shorter recovery time and clinical benefit.[73] Also results of a United States clinical trial on remdesivir have not been published till now for further evaluation of remdesivir efficacy in severe cases of COVID-19. Although the results of a previous cohort study on compassionate-use of remdesivir in patients with severe COVID-19 revealed that remdesivir therapy could cause clinical improvement in about 68% of the patients who were recruited in this study. The authors suggested that prospective, randomized, placebo-controlled clinical trials are essential in order to evaluate the efficacy of remdesivir therapy in severe cases of COVID-19.[74]

Corticosteroids and NSAIDs. Corticosteroids are a double-edged sword, they can inhibit our immune response and so the clearance of COVID-19 could be delayed, but on the other hand, they can suppress our inflammatory response which is highly responsive to the lung damage and ARDS during viral infection. Although corticosteroids were used in the management of SARS/MERS-CoV outbreaks, corticosteroids have the disadvantage of increased incidence of secondary bacterial and fungal infections and also increase the length of patient's staying in the intensive care unit. In overall, there are no sufficient data available to recommend the use of corticosteroids in the management of COVID-19 complications and WHO in the recent guideline in the treatment of COVID-19 advice against the use of corticosteroids.[68]

Dexamethasone could have an immediate impact on most severe cases of COVID-19. Recent results revealed that this drug could reduce the mortality rate to one-third and one-fifth in COVID-19 patients who are on ventilators and supplemental oxygen respectively. Dexamethasone didn't show any significant beneficial effect in patients who did not require respiratory support.[75] There are controversial comments on the usage of NSAIDs in the treatment of COVID-19. A possible disadvantage of NSAIDs such as Ibuprofen in COVID-19 infection is their potential effects in over-expression of ACE2 and enhancement of angiotensin II, which could worsen the clinical course of COVID-19 pneumonia. Another possible disadvantage of NSAIDs is their masking effect which can delay the diagnosis of COVID-19 infection.[68]

Favipiravir. Favipiravir, a guanine analog, is an RNA-dependent RNA polymerase (RdRp) inhibitor. It has antiviral effects against variant RNA viruses such as Coronaviruses and Influenza viruses. Favipiravir in the body could be metabolized to an active form called favipiravir-RTP (a phosphorylated form of favipiravir), which is a substrate for viral RNA polymerases. By adhesion of favipiravir to viral RNA polymerase, RNA polymerase activity would be inhibited. With this theory, favipiravir would be a promising antiviral agent against COVID-19 which is an RNA virus. Results of a small clinical trial revealed that favipiravir in comparison with lopinavir/ritonavir was more potent and had fewer adverse drug reactions. But further clinical trial results are required for deciding its efficacy and safety in COVID-19 pneumonia.[25,71]

Convalescent plasma therapy

Convalescent plasma or immunoglobulins would be a promising therapy in COVID-19 patients. Previous results revealed that convalescent plasma therapy during viral infection outbreaks, could improve patients' survival rate, shorten the duration of hospitalization, reduce viral load, and reduce the mortality rate. A potential mechanism of convalescent plasma in COVID-19 is that the antibodies which are present in convalescent plasma could avoid viremia. Viremia could reach its peak state during the first week of viral infection, so convalescent plasma therapy should be done at the early stages of COVID-19 infection to reach its most efficacy. According to the recent evidence, convalescent plasma from patients who are recently recovered from COVID-19 would be a promising option in COVID-19 infection treatment. This approach has been considered safe with no severe adverse reactions.[76] A recent pilot study reported that transfusion of a dose of 200 ml convalescent plasma, from patients recently recovered from COVID-19, in addition to antiviral therapy and supportive care, could improve clinical symptoms (such as fever, cough, chest pain, etc.), improve pulmonary abnormalities on chest CT, and normalize laboratory data (such as C-reactive protein (CRP) level and lymphocyte counts) within three days. Also, results of this study revealed that convalescent plasma therapy would be a safe method in COVID-19 management which could reduce viral load. So, convalescent plasma therapy has been suggested as a well-tolerated and feasible approach in patients with severe COVID-19 pneumonia through neutralizing of viremia.[77]

Aviptadil

Aviptadil is a vasoactive intestinal polypeptide (VIP) which is administered in Europe to treat erectile dysfunction. According to the results, aviptadil could be highly concentrated in the lung also it could block inflammatory cytokines. This drug has been received US and EU orphan drug designation to treat ARDS. Aviptadil received FDA approval phase II clinical trial in patients with COVID-19-related ARDS. This study was done on severe cases of COVID-19 who were on mechanical ventilation.[78]

Supportive therapy

Vitamin C. Ascorbic acid (vitamin C), is an antioxidant agent and might act as a co-factor of many physiological reactions such as immune augmentation. The results of a previous meta-analysis revealed that high dose intravenous (IV) vitamin C would be a promising agent in sepsis and septic shock management. ARDS could be a life-threatening consequence of sepsis or septic shock. High dose vitamin C has dual effects; it can act as a pro-oxidant agent for immune cells and as an antioxidant agent for lung epithelial cells. Another possible mechanism of vitamin C is inhibition of lactate secretion from immune cells and therefore preserve the innate immunity of alveolar epithelial cells type II.[79] So high dose IV vitamin C would be a promising option in COVID-19-induced ARDS management. The recommended dose of vitamin C in patients with severe COVID-19 pneumonia is 50 mg/kg IV every 6 hours for 4 days. In this protocol, hydrocortisone (50 mg IV every 6 hours for 7 days) should be added to avoid vitamin C-induced local inflammation in the alveolar medium.[79] The results of this study were based on a mechanistic approach, so further studies and clinical trials are required to confirm its efficacy and safety in COVID-19 patients. Some recent studies revealed that vitamin C could have a preventive role in COVID-19 lower respiratory tract infection. So supplementation with a moderate amount of vitamin C has been suggested as a promising preventive option.[80]

Extracorporeal membrane oxygenation. It has been recommended that patients with COVID-19 who are suffering from refractory hypoxemia should be managed with extracorporeal membrane oxygenation (ECMO). ECMO is a form of cardiopulmonary bypass machine which has been used in patients with refractory respiratory or cardiac failure. In this approach, oxygen would be supplied and carbon dioxide would be removed from the blood. Results revealed that ECMO could reduce the mortality rate in patients with ARDS, just like severe cases of COVID-19 pneumonia. But the exact efficacy of ECMO in COVID-19 management is still unknown. In critically ill COVID-19 patients with refractory hypoxemia and/or refractory multi-organ failure and those with underlying cardiac diseases such as ischemic heart disease or heart failure, ECMO might be considered as a potential option especially in patients who develop cardiac arrhythmia and septic shock during COVID-19 pneumonia.[81]

Deferoxamine. Iron toxicity has a multi-stage clinical course. First patients have gastrointestinal symptoms including nausea, vomiting, diarrhea, etc. After an apparent recovery phase, clinical presentations of shock and end-organ damage (renal failure, liver damage, and cardiomyopathy) would be occur. After that enhancement of liver aminotransferases would be appear. The adhesion of SARS-CoV-2 protein to heme could results in the removal of iron from hemoglobin and convert it to porphyrin, so the excess free iron could induce iron toxicity. This iron toxicity leads to alveolar macrophage inflammation and chest infiltrations. In moderate to severe cases of COVID-19 pneumonia, symptoms of iron overload such as shock, end-organ damage (renal failure, hepatic failure, and cardiac events), and elevation of liver aminotransferases would be appeared. It seems that the recruitment of deferoxamine, as an iron-chelating agent, could relieve iron toxicity presentations in COVID-19 patients.[34,35]

Recommended regimens for confirmed COVID-19 based on disease severity

In some European countries, patients with confirmed COVID-19 could be treated according to the degree of disease severity through the regimens as listed below:

Mild to moderate disease in no risk group

Mild to moderate disease refers to the condition that there is no oxygen supply required and no evidence of pneumonia. In this group, antiviral treatment is not required. They should be managed with supportive care and symptomatic therapy.[82]

Mild to moderate disease in the risk group

This group also categorized as mild to moderate disease but patients have risk factors such as the age of over 60 years and patients with underlying diseases (ex. liver disease, kidney disease, heart disease, diabetes, chronic obstructive pulmonary disease, hypertension, etc.) In this group, lopinavir/ritonavir plus chloroquine or hydroxychloroquine would be considered. Also according to the therapeutic protocol in each country, each of these drugs may be administered as monotherapy. The recommended duration of therapy in this group is 5 to 7 days.[82]

Severe disease

COVID-19 could be categorized as a severe disease if one or more of the following conditions have occurred: Tachypnea (respiratory rate of over than 30 breaths/min in adults), oxygen saturation of less than 93%, PaO_2/FiO_2 ratio of less than 300, and over than 50% lung infiltration during 24 to 48 hours. In this group, a combination of remdesivir plus chloroquine or hydroxychloroquine or monotherapy of remdesivir are considered as the first choice. If remdesivir is not available, lopinavir/ritonavir plus chloroquine has been suggested as a second choice of therapy. Duration of therapy in this group could vary between 5 to 20 days which is dependent on the monitoring of viral excretion.[82]

Critical disease

COVID-19 could be categorized as a critical disease if one or more of the following conditions have occurred: ARDS, sepsis, altered mental status, and multi-organ failure. In this group, a combination of remdesivir plus chloroquine or hydroxychloroquine or monotherapy of remdesivir are considered as the first choice. If remdesivir is not available, lopinavir/ritonavir plus chloroquine has been suggested as a second choice of therapy. Duration of therapy in this group could vary between 5 to 20 days which is dependent on the monitoring of viral excretion. In some countries such as Switzerland, tocilizumab has been considered in patients with multi-organ failure and inotropic support.[82]

COVID-19 in patients with underlying diseases

Cardiovascular disease

ACE2 has a critical role in cardiac and immune systems. ACE2 is related to heart function and it could be a potential cause of hypertension and diabetes mellitus development.[83] Since ACE2 is a functional receptor for COVID-19, in patients with underlying cardiovascular diseases, clinical symptoms of COVID-19 are more severe and fatal than the general population because, in cardiovascular diseases, ACE2 secretion might be enhanced. Administration of renin-angiotensin-aldosterone system inhibitors, such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) could enhance ACE2 level. Thiazolidinediones and Ibuprofen might also enhance the ACE2 level.[83] So the potential safety of administration of these drugs in COVID-19 patients with underlying cardiovascular disease, hypertension, and diabetes mellitus is still controversial and further studies are required for making decisions.[84,85] A recent publication declared that calcium channel blockers would be suitable alternative of these drugs in patients with cardiovascular disease who are infected with COVID-19.[83] The previous meta-analysis revealed that patients with cardiovascular diseases are more likely prone to MERS-CoV infection. Also, recent studies showed that elderly group with comorbidities such as coronary heart disease, hypertension, and diabetes mellitus are more prone to COVID-19 infection[86] and in these patients, COVID-19 could induce more severe systemic symptoms and more severe pneumonia and a large number of COVID-19 deaths were associated with cardiovascular diseases. COVID-19 infection could act as a precipitating factor in patients with the acute coronary syndrome (ACS), in which necrosis and myocardial ischemia have occurred. In cases with ACS, COVID-19 infection could deteriorate patients' condition and lead to death. Coronary heart disease is related to COVID-19-induced acute cardiac events and these patients are poor prognosis after COVID-19 infection. In general, new-onset or worsening heart failure, new-onset or worsening arrhythmia, and myocardial infarction would be common features of patients with pneumonia such as COVID-19.[86] So cardiovascular protection with suitable pharmacotherapy options is essential in COVID-19 patients with underlying cardiovascular diseases.[84,85] As a hypothesis, it seems that ACEIs could precipitate COVID-19 pneumonia but ARBs, through blockade of angiotensin receptors, may have beneficial effects in these patients.

Kidney disease

Most of the hepatic metabolites of drugs considered in COVID-19 treatment such as chloroquine, hydroxychloroquine, and lopinavir/ritonavir would be found in urine due to renal elimination. So in patients with chronic kidney disease (CKD), the accumulation of drug metabolites would be expected if administered in routinely recommended doses for the normal population. Therefore, individualized dose adjustment based on kidney function is required for each drug as mentioned above.[87] A small study on COVID-19 patients with end-stage renal disease (ESRD) who undergone hemodialysis, revealed that the number of total T cells (cytotoxic and helper T cells), natural killer (NK) cells, and inflammatory cytokines were significantly lower than these levels in non-hemodialysis patients with COVID-19. This study revealed that ESRD patients with hemodialysis who infected with COVID-19 had a good prognosis and they had mild symptoms of pneumonia, it might be related to the fewer number of inflammatory cytokines and reduced immune function which can avoid CRS but further studies are required to confirm this hypothesis.[66]

Liver disease

According to the recent studies, liver abnormalities (such as elevated AST and ALT serum levels) have been occurred after and during infection with COVID-19. These abnormalities would be related to viral infection pathogenesis and direct liver injury or it may be drug-induced.[88] Almost all of the potential drugs in COVID-19 treatment containing chloroquine, hydroxychloroquine, ribavirin, and lopinavir/ritonavir have hepatic metabolism. So injury to the liver because of pre-existing liver disease or acute hepatic failure would impair drug metabolism and therefore drug accumulation and enhancement in plasma level, which can lead to drug toxicity. In these patients, frequent liver function monitoring is essential to achieve an optimal serum drug level.[87] Also, dosage adjustment for each drug should be done individually according to the patients' liver function as mentioned above. The impact of chronic liver diseases such as chronic viral hepatitis, alcoholic and non-alcoholic liver diseases on occurrence of liver injury related to COVID-19 infection, still is not clear. It seems that in patients with underlying liver disease, with the immunocompromised condition, who infected with COVID-19, more intensive and individualized pharmacotherapy is required. Further studies would be also helpful to explain the exact role of pre-existing liver diseases in COVID-19 prognosis.[88]

Conclusion

The new coronavirus (COVID-19) was first detected in Wuhan city of China in December 2019. Soon this coronavirus disease 2019 (COVID-19) spreads around the world and became a pandemic. Now many patients around the world are suffering from this disease. Patients with underlying diseases are highly prone to severe COVID-19 pneumonia. Till now many drugs have been considered in the treatment of COVID-19 pneumonia, but pharmacotherapy in patients with pre-existing comorbidities is highly challenging. In this review, different potential drugs which have been considered in COVID-19 treatment have been discussed in detail. Also, challenges in the pharmacotherapy of COVID-19 pneumonia in patients with underlying disease especially heart diseases have been considered based on pharmacokinetic and pharmacodynamic aspects of drugs. Patients with COVID-19 who have cardiac diseases such as coronary heart disease and those who are ACEIs consumers should be highly considered in treatment options. Also, patients with liver and kidney disease and those with organ transplants should be considered to avoid the occurrence of drug overdose toxicities and potential drug-drug interactions.

Contributors

P.G. and S.M. were contributed equally in data gathering, writing-original draft, reviewing, and revising the final version of this manuscript.

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