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Review

An overview of the safety assessment of medicines currently used in the COVID-19 disease treatment

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ABSTRACT

On 11th March 2020, the pandemic of the new coronavirus was declared by the World Health Organization. At the moment, there are no new registered medicines that can effectively treat the coronavirus infection. However, a number of ongoing clinical trials are investigating the efficacy and safety of the medicines which have already been registered and used for the treatment of other diseases, in the treatment of the coronavirus infection. The proposed combinations of these medicines could potentially present a safety risk, since most of these medicines have the potential to cause numerous side or toxic effects, even when used in monotherapy. Thus, the aim of this study was to review and evaluate the literature data on the toxicity of the selected individual drugs (ritonavir, lopinavir, remdesivir, chloroquine, and umifenovir) and the available clinical data concerning the possible adverse effects of the selected drug combinations (lopinavir/ritonavir + umifenovir, lopinavir/ritonavir + interferon β, chloroquine + remdesivir, and chloroquine + azithromycin).

The most often reported toxic effects of these medicines such as hepatotoxicity, retinal damage, nephrotoxicity, and cardiotoxicity, together with the fact that the health status of the patients with COVID-19 disease is often complicated by co-existing illnesses and therapy implicate that the decision on the therapeutic strategy should be made with caution.

1. Introduction

The occurrence of pneumonia of unknown etiology was registered in Wuhan, province Hubei, China, on December 2019. On the 31st December 2019, there were 27 such cases (Lu et al., 2020). The virus had originally been named 2019-novel coronavirus (2019-nCoV) but was later renamed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Perrella et al., 2020). The disease caused by this virus was named COVID-19 by the World Health Organization. On 11th March 2020, there were 118,319 reported cases and 4,292 deaths due to the infection with new coronavirus, and the pandemic of the new coronavirus was declared. At that moment, there were confirmed cases in 113 countries/territories/areas outside of China (World Health Organization, 2020a,b). On 3rd May 2020, there were 3,349,786 reported cases and 238,628 deaths due to the infection (World Health Organization, 2020).

Twelve European hospitals recruited patients with COVID-19 in a study aimed at confirming the occurrence of olfactory and gustatory dysfunctions. The most common symptoms in 417 patients from Europe were cough, muscle pain, appetite loss, facial pain and nasal congestion. Olfactory dysfunction occurred in 85.6% of patients and gustatory dysfunctions occurred in 88% of patients, while 11,8% of patients experienced olfactory dysfunction as the first symptom of COVID-19. Olfactory and gustatory dysfunction occurrence was more common in women (Lechien et al., 2020). Anxiety, depression and stress were common in patients with COVID-19, possibly due to sleep disorders (Rajkumar, 2020). Out of 651 patients from Wuhan (mean age 46.14) included in another study, 74 experienced nausea, vomiting or diarrhea. Patients with gastrointestinal symptoms had a higher incidence of fever (above 38.5 °C), headache, fatigue, and shortness of breath (Jin et al., 2020). Patients from Wuhan region experienced complications such as Acute Respiratory Distress Syndrome, RNAaemia, acute heart failure and secondary infections. Ten percent of patients required mechanical ventilation support (Huang et al., 2020).

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Table 1
An overview of the combinations of medicines used in COVID-19 therapy.

Medicines	Reference
Lopinavir/ritonavir	Cao et al. (2020)
Lopinavir/ritonavir + umifenovir	Deng et al. (2020)
Lopinavir/ritonavir + interferon beta	Momattin et al. (2019)
Lopinavir/ritonavir + interferon beta + umifenovir	Jaihua et al. (2020)
Hydroxychloroquine + azithromycin	Gautret et al. (2020)
Lopinavir/ritonavir + interferon alpha-2b	(Lythgoe and Middleton, 2020)*
Interferon alpha + umifenovir	(Lythgoe and Middleton, 2020)*
lopinavir/ritonavir + ribavirin + interferon beta-1b	(Lythgoe and Middleton, 2020)*
Lopinavir/ritonavir + novaferon	(Zhang et al., 2020)*
Favipiravir + interferon-alpha	(Zhang et al., 2020)*
ASC09F + ritonavir + oseltamivir	(Zhang et al., 2020)*
Favipiravir + baloxavir + marboxil	(Zhang et al., 2020)*
Lopinavir/ritonavir + interferon alpha + glucocorticoid	(Zhang et al., 2020)*
Lopinavir/ritonavir + umifenovir + novaferon	(Zhang et al., 2020)*
Hydroxychloroquine + umifenovir	(Zhang et al., 2020)*
Favipiravir + bromhexin + umifenovir + interferon alpha-2b	(Mina et al., 2020)*
Favipiravir + tocilizumab	(Mina et al., 2020)*
ASC09 + oseltamivir	(Mina et al., 2020)*
Darunavir + cobicistat + thymosin	(Mina et al., 2020)*

*Ongoing clinical trial, ASC09F - a new protease inhibitor.

At the moment, there are no registered medicines that can effectively treat SARS-CoV-2 infection (Li and De Clercq, 2020). However, several clinical trials have been registered with the aim to examine the efficacy of the already registered medicines used for the treatment of other mostly virus-related diseases and conditions (Maxmen, 2020). The approach of the old drugs repositioning allows faster release of the medicines on the market since many clinical trial steps become redundant, especially in phases I and II. Additionally, the existing supply chains for such drugs are already present in the pharmaceutical industry. The possibility of combining multiple registered medicines present on the market, in order to increase the effectiveness of the therapy, is yet another advantage of the approach (Pushpakom et al., 2018). However, these new combinations of medications certainly present a safety risk, since most of these medicines have the potential to cause numerous side effects when used in monotherapy and their combined used can produce new or more pronounced toxic effects as it is the case with chemicals (Hernandez et al., 2019; Karri et al., 2020; Kostoff et al., 2020; Tsatsakis et al., 2019). Moreover, the health status of patients with COVID-19 disease is often complicated by co-existing illnesses, so particular attention should be paid to the adverse/toxic effects of the drugs and their combinations used in potential therapeutic strategies. Thus, the aim of this study was to evaluate the safety of drugs or drug combinations, currently referred in the studies as potential effective therapy options for the treatment of COVID-19. This review was based on the literature data on the toxicity of individual drugs as well as the available clinical data concerning the possible adverse effects of the selected drug combinations.

2. Use of medicines in COVID-19 therapy

Several medicines were reported to have been used to treat patients with COVID-19. A recent paper states that over 30 agents are considered potentially effective in the treatment of COVID-19, listing interferon alpha, lopinavir/ritonavir, chloroquine phosphate, ribavirin, umifenovir, favipiravir, remdesivir, darunavir, and imatinib (Dong et al., 2020). A number of these medicines are currently undergoing clinical trials for application in COVID-19 therapy. Another paper additionally lists saquinavir, indinavir, atazanavir, carfilzomib, fosamprenavir, tipranavir, presatovir, abacavir, enzaplatovir, maribavir, elvitegravir, raltegravir, bortezomib, montelukast, tideglusib, cyclosporin A, deoxyrhapontin, disulfiram, carmofur, chalcone, polydatin, cinanserin shikonin and ebselen as compounds which might have antiviral activity against SARS-CoV-2, as well as several Chinese herbal medicines (Shanghai Institute of Materia Medica website and Sciences, 2020). At the First Affiliated Hospital, Zheijang University School of Medicine, early antiviral treatment was found to decrease the incidence of severe COVID-19 cases. A few antiviral medicines have been used, among which were lopinavir/ritonavir, umifenovir, and an antimalarial medicine chloroquine (Tingbo, 2020). However, based on growing data some new already registered medicines warrant attention and have been included in clinical trials procedures. Phase III of the clinical trial, for remdesivir was started on 4th February 2020 in Wuhan (Liu et al., 2020). The administration of antibiotics such as azithromycin with hydroxychloroquine were found useful in the treatment of bacterial super-infections in SARS-CoV-2 positive patients (Gautret et al., 2020). Another study reported the efficacy of chloroquine and remdesivir to inhibit SARS-CoV-2 infection *in vitro*. So far, the therapeutic strategies of the combination of medicines in the COVD-19 disease were based mainly on the experience in the treatment of other coronavirus infections (SARS and MERS) (Rosa and Santos, 2020). Some of these combinations include interferons, implying that interferons may be beneficial in the COVID-19 treatment (Sallard et al., 2020). An overview of these combinations of medicines is given in Table 1. Considering all available data, this review is focused on the following medicines/combinations of medicines: ritonavir, lopinavir, remdesivir, chloroquine, umifenovir, lopinavir/ritonavir, lopinavir/ritonavir + umifenovir, lopinavir/ritonavir + interferon beta, chloroquine + remdesivir, chloroquine + azithromycin.

The use of other medicines in COVID-19 treatment has also been suggested, such as Rho kinase inhibitors. It was suggested that these medicines, e.g. fasudil, could counter events such as inflammation, immune cell migration, apoptosis and other major events leading to lung damage. Although such medicines do not target the virus itself, they can potentially prevent certain consequences of SARS-CoV-2 infection, undoubtedly to the benefit of patients (Abedi et al., 2020). Bearing in mind that a large number of medicines is being investigated, we have focused this review on the medicines either targeting the virus itself or medicines which have initially been investigated or available to the health professionals in the initial virus outbreak areas.

3. The toxicity of the selected medicines in COVID-19 therapy

3.1. Ritonavir

The use of ritonavir, a member of a group of the newer protease inhibitors was approved in 2000 by FDA (Chandwani and Shuter, 2008; Lv et al., 2015). In a prospective cohort study involving approximately 300 subjects, the initial therapy with ritonavir resulted in hepatotoxicity in 30% of patients (95% confidence interval 17.9–44.6%) (Nolan et al., 2005; Sulkowski et al., 2000). Hepatotoxicity was assessed by monitoring the activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The odds ratio for hepatotoxicity following ritonavir administration in full dose i.e. 400 mg was 6.2 (95% confidence interval 2.8–13.7) (Sulkowski et al., 2000). Hepatotoxicity manifested through non-specific gastrointestinal symptoms (upper and lower abdominal pain, nausea, vomiting and diarrhea), as well as jaundice and hepatomegaly. Shortly after the introduction of the protease inhibitor drug to the therapy, several cases of frequent and severe bleeding were observed in patients with hemophilia. The mechanisms responsible for bleeding have not yet been clarified. The characteristic places where the bleeding occurred were the small joints of the hands as well as the soft tissue of the palms (Nolan et al., 2005).

In a study conducted by Tebas et al. (2000), subjects who received a protease inhibitor (24% of subjects received ritonavir) had lower bone mineral density t-scores of the lumbar spine ($P = 0.02$), than the subjects who did not use a protease inhibitor, and healthy subjects. Bone mineral

density median z-score of the lumbar spine and femoral neck were also lower in the study population. The relative risk for osteoporosis was 2.19 (95% confidence interval 1.13–4.23) (Tebas et al., 2000).

Dyslipidemia in antiretroviral therapy is characterized by an increase in total cholesterol with decreased high-density lipoprotein (HDL) cholesterol levels, increased triglyceride levels and increased low-density lipoprotein (LDL) cholesterol levels. These effects of protease inhibitors were explained by the binding of lipoprotein particles or the blocking of their binding to the LDL receptor, which disrupts the mechanisms responsible for intracellular synthesis, storage and release of cholesterol (Nolan et al., 2005). Administration of drugs from the protease inhibitor group leads to sequestration of endoplasmic reticulum-derived transcription factor that are involved in lipogenesis and to deficiency of adiponectin (Lv et al., 2015). The inhibition of proteasomal degradation of apolipoprotein B is another mechanism that is associated with the onset of dyslipidemia in patients who receive this group of drugs (Anđelković et al., 2016; Lv et al., 2015).

3.2. Lopinavir

Lopinavir is antiretroviral of the protease inhibitor class, used in combination with other antiviral drugs for HIV-1 infection treatment, and recognized as potential medicine for COVID-19 disease (Gautret et al., 2020). In the study performed on 120 HIV-positive patients, the low incidence of severe liver injury attributable to lopinavir blood levels was observed (González-Requena et al., 2004). Similar results were obtained in another study where the incidence of hepatotoxicity after the administration of 200 mg/day of lopinavir was also low, which can be explained by low blood levels and fast metabolism of lopinavir by cytochrome P450 3A4 (Núñez, 2006). Toxic blood lopinavir levels were reported after simultaneous administration of herb medicines that may inhibit P450 enzymes. In this case, only gastrointestinal adverse effects were manifested (Beukel Van Den Bout-Van Den et al., 2008). Lopinavir is most used as the coformulation with ritonavir to maintain therapeutic drug concentration, making it the second line of antiretroviral therapy. Hence, there are limited cases of adverse or toxic effects of single lopinavir treatment. Safety data of the combination of lopinavir/ritonavir is presented in part 4.1.

3.3. Remdesivir

Remdesivir is broad-spectrum antiviral prodrug that acts as adenosine nucleotide analogue, used for RNA virus infections treatment (Wang et al., 2020). A recent study by Grein et al. (2020) revealed that the elevation of hepatic enzymes, hypotension, renal impairment, rash and diarrhea were the most common adverse effects associated with remdesivir administration in COVID-19 patients (200 mg iv on the first day, plus 100 mg for the remaining nine days). The occurrence of adverse effects was reported in 60% of subjects. Serious adverse effects, such as acute kidney injury, hypotension, septic shock and multiple organ dysfunction syndrome were reported in 12% of subjects. Four patients discontinued the treatment because of multiple organ failure, elevated hepatic enzymes and maculopapular rash (Grein et al., 2020). Another study on Ebola patients reported AST and ALT elevation as well, in patients who received intravenous remdesivir. The same study also reported a single case of hypotension, which was followed by the discontinuation of the treatment and cardiac arrest, however, the exact cause of death could not be differentiated from the existing Ebola virus disease (Mulangu et al., 2019). The patients in this study received a loading dose on the first day (200 mg in adults, adjusted for body weight in pediatric patients), followed by 100 mg in adults on the next day for the remaining nine or thirteen days, depending on the viral load.

However, WHO recognized the safety of intravenous remdesivir administration, based on the evidence from controlled clinical trials. Remdesivir was also found to be tolerable in repeated doses. Reversible ALT and AST increase was observed, however, no abnormalities in total bilirubin, alkaline phosphatase or albumin occurred. In these trials, remdesivir displayed no effect on kidneys either (WHO, 2018).

In vitro studies have shown that remdesivir hepatotoxicity is caused by increased membrane permeability and intracellular drug metabolism. Remdesivir also caused an increase in respiratory rate in experimental animals, whereas it had no effect on the central nervous system and cardiovascular function. In toxicity studies where experimental animals were treated with remdesivir for four weeks, interestingly however, kidneys were identified as the target organs of toxicity. No changes in hepatic function were observed in rats and cynomolgus monkeys (WHO, 2018).

3.4. Chloroquine and hydroxychloroquine

Chloroquine (its sulfate and phosphate salts) is a medicine used in the prevention and treatment of malaria. Due to its potential antiviral activity and relatively mild side effects (Touret and de Lamballerie, 2020), it has been recommended as the second therapy choice in the treatment of SARS-CoV-2 infections (Tingbo, 2020). In 2018, the Royal College of Ophthalmologists issued recommendations for screening for retinotoxicity in patients taking chloroquine and hydroxychloroquine. Many patients are taking 400 mg of hydroxychloroquine daily, which is higher than recommended for any patient weighing less than 80 kg. Current evidence suggests the highest risk of retinopathy in patients taking more than 5 mg/kg of hydroxychloroquine daily. Prescribers should be aware of the recommendations regarding hydroxychloroquine dosage (less than 5 mg/kg daily), although no dose is absolutely safe (Yusuf et al., 2018).

A study published in 2019 found that glial cell damage was due to the production of reactive oxygen species, with reduced glutamate uptake. The damage was reduced when ascorbic acid was added to cell cultures (Oliveira et al., 2019). Chloroquine, deposited in the cornea, lead to turbidity of the posterior subcapsular part of the lens, dysfunction of the ciliary body and macular pigmentation disorders, manifested by partial vision loss and blurred vision. The mechanism of damage could involve the binding of chloroquine to melanin in retinal pigment epithelium, which would ultimately lead to cell migration to other retinal layers, irreversible photoreceptor loss and atrophy of retinal pigment epithelium (Arndt et al., 2018). Chloroquine has a long elimination half-life (approximately one month), whereas complete elimination takes about six months (Hickley et al., 2011; Kalia and Dutz, 2007). Chloroquine passes the placental barrier, but there is no indication that it damages the fetus. It is also excreted via breast milk (Rainsford et al., 2015). A study in laboratory mice found that it accumulated in the retina of pups, but the accumulation was temporary and did not cause permanent damage (Ullberg et al., 1970). In addition to visual impairment, effects like dizziness, headache, nausea, vomiting, diarrhea and skin rash also occur. The most serious complication of chloroquine administration is cardiac arrest, which is why regular electrocardiographic monitoring is advised. In a recent study, it was suggested that chloroquine prolonged corrected QT interval (QTc) significantly (Van den Broek et al., 2020). It should not be administered in people with history of arrhythmia and retinal or hearing impairment (Tingbo, 2020).

3.5. Umifenovir

Umifenovir (registered as Arbidol) is RNA polymerase inhibitor approved for influenza treatment only in Russia and China. Due to mechanism of action, the medicine has been recognized as potential therapy for novel SARS-CoV-2 infection (Chen et al., 2020). Umifenovir was shown to be safe, even for use in pregnant women and showed no teratogenic effects (Belokrinitskaya et al., 2012; Guskova and Glushkov, 1999). Umifenovir has a broad therapeutic index, thus it could be expected that it is also well tolerated. Administration of 200 mg to volunteers demonstrated excellent tolerability. The usage over several days to one month was also well tolerated. A study shown no toxic effect

occurrence during chronic administration of this drug (Blaising et al., 2014). Certain adverse effects were reported, prominently gastrointestinal adverse effects and increased transaminase levels (Wang et al., 2004).

In a study of umifenovir and paracetamol combination toxicity in experimental animals, oral no observed adverse effect level (NOAEL) was determined at 200 mg/kg per day (Wang et al., 2010). In another study, a safe dose of umifenovir was found to be 350 mg/kg, while weight loss and hair loss occurred at a dose of 1200 mg/kg (Zhou et al., 2006). Similar data have been obtained in other studies (Blaising et al., 2014; Guskova and Glushkov, 1999).

4. The toxicity of the selected combinations of medicines in COVID-19 therapy

4.1. Lopinavir/ritonavir

Due to the low dose of ritonavir used in combination with lopinavir, there are few cases in which ritonavir toxicity has been reported (Findlay, 2007). Several reports have mentioned toxic effects in the form of retinal damage (Louie and Jones, 2019; Papavasileiou et al., 2017). Some authors state that the cause of the toxic effects of ritonavir is the existing liver dysfunction. Liver dysfunction leads to the accumulation of ritonavir in blood plasma, where it is otherwise 99% protein-bound (Tu et al., 2016). Certain recommendations advise avoiding the use of this combination of medicines, if possible. When these medicines are used in combination, it is advised to monitor side effects such as nausea, diarrhea, vomiting, elevated transaminase and lactate levels, icterus and dyslipidemia (Tingbo, 2020). The same sources describe the withdrawal of side effects following the discontinuation of the therapy.

Another group of authors found that after six months of therapy with the combination lopinavir/ritonavir, the risk of pancreatitis was negligible, but the elevated triglyceride levels indicated that a significantly increased risk of cardiovascular diseases was present. The standard dosage was 400 mg of lopinavir and 100 mg of ritonavir (Greffrath, 2016; Greffrath et al., 2018). The same group of authors recommended constant monitoring of triglyceride levels, serum amylase and other comorbidity markers, such as HbA1c and thyroid function markers. According to current data, the duration of COVID-19 therapy with these antivirals is approximately two weeks (Tingbo, 2020).

In a clinical trial (Phase II and III) involving more than 500 subjects, the administration of lopinavir/ritonavir was followed by mild gastrointestinal disorders (diarrhea 12–27%, nausea 4–15%, asthenia 4–11%, abdominal pain 0–8%, vomiting 1–5%, headache 1–8% and rash 2–4%). Dyslipidemia was accompanied by an increase in total cholesterol and triglyceride concentrations in 10–40% of subjects. The incidence of a double increase in serum amylase activity was seen in 4–9% of subjects, and the increase in serum glucose concentration in 2–6% of subjects. Hepatotoxicity was observed by the increase in AST and ALT activity in 3–11% of subjects. Lipodystrophy followed by lipid redistribution and central obesity occurred in 7–20% of subjects (Corbett et al., 2002).

In a study by Bongiovanni et al. approximately 400 HIV-positive individuals were included, and it was shown that the treatment with lopinavir/ritonavir (400/100 mg twice daily) resulted in gastrointestinal disorders in 51.9% of patients (nausea, vomiting, diarrhea) and dyslipidemia in 35.1% of patients. An increase in aminotransferase activity (13.0%) was also observed and was the reason for the discontinuation of the therapy. The total number of subjects who reported these side effects was 71.9%, while 18.5% stopped receiving therapy (Bongiovanni et al., 2005).

One report suggests a possible association between the administration of lopinavir and ritonavir with the toxic effects on the hearts of premature twins (McArthur et al., 2009). A low incidence of the toxic effect of lopinavir on the liver has been observed, which may nevertheless be increased in patients with hepatitis C infection. Hepatotoxicity and other effects associated with the administration of protease inhibitors were not related to lopinavir plasma levels (González-Requena et al., 2004).

4.2. Lopinavir/ritonavir + umifenovir

The combination of lopinavir and ritonavir with umifenovir was one of the first choices of the treatment of COVID-19 reported in the Handbook based on clinical experience in the First Affiliated Hospital, Zheijang University School of Medicine (Tingbo, 2020). However, this combination induced liver damage in about 50% of treated patients including the increase of serum aminotransferase enzymes and jaundice. On the contrary, in the retrospective cohort study, researchers reported that this combination of drugs were more effective than lopinavir/ritonavir combination, but led to similar adverse effects: higher bilirubin levels, mild diarrhea and nausea (Deng et al., 2020).

4.3. Lopinavir/ritonavir + interferon beta

A clinical trial titled "Middle East Respiratory Syndrome with a combination of lopinavir, ritonavir and interferon beta-1b (MIRACLE trial)" is expected to examine the efficacy and safety of a given drug combination in the treatment of MERS-CoV coronavirus infection originally recorded in 2012. The dosage used in this study will include 400/100 mg of lopinavir/ritonavir as 5 mL suspension applied through nasogastric tube and 0.25 mg/mL of interferon beta-1b applied subcutaneously (Arabi et al., 2018). The authors state that lopinavir is used to prolong the half-life of ritonavir and to evaluate the combination of lopinavir and ritonavir with interferon beta in future findings. An update on the statistical analysis plan for the trial has been published recently (Arabi et al., 2020).

4.4. Chloroquine + azithromycin

There are limited data concerning the efficacy and safety of the combination of chloroquine and azithromycin in COVID-19 therapy. In a study conducted in France, combined hydroxychloroquine and azithromycin therapy was far more successful compared to untreated patients or treatment with hydroxychloroquine alone. Hydroxychloroquine was chosen, rather than chloroquine, because of its lower toxicity, higher safety and higher dose capability (Liu et al., 2020). The results obtained in this study suggest a synergistic effect of the two drugs. The researchers report that only 6 of 20 treated patients received azithromycin with hydroxychloroquine to prevent bacterial superinfection with daily monitoring of cardiac output by electrocardiogram due to the potential, but low, risk of a prolonged QT interval. The results of the above study regarding the safety of administered medicines have not yet been published (Gautret et al., 2020). These results refer to the application of 200 mg of hydroxychloroquine sulfate orally, three times a day for ten days, while 500 mg of azithromycin was administered on the first day, followed by 250 mg for the next four days, with constant ECG monitoring. In an animal study based on a model of cardiac instability in guinea pigs, azithromycin alone or in combination with chloroquine did not produce a proarrhythmogenic effect, unlike the administration of chloroquine alone (Fossa et al., 2007).

Chloroquine + azithromycin combination of drugs has been used earlier. In a clinical trial conducted in Africa, the combination proved to be safe in malaria therapy, where only one patient had a serious side effect of vomiting. Most other side effects were mild or very mild (Sagara et al., 2014).

4.5. Chloroquine + remdesivir

Recent *in vitro* study reported effective inhibition of SARS-CoV-2, which implicate the potential use of the drugs in COVID-19 therapy (Wang et al., 2020). Still, there are no published data considering the combination of these drugs, either safety or efficacy.

Table 2
Summary of data analyzing toxic/adverse effects of potential therapy for COVID-19 disease.

Medicine(s)	Study type	Toxic/adverse effect	Reference
Ritonavir	*In vivo* (humans)	Hepatotoxicity/ abdominal pain, nausea, vomiting diarrhea and jaundice	Sulkowski et al. (2000)
	In vivo (humans)	Severe bleeding in patients with hemophilia	Nolan et al. (2005)
	In vivo (humans)	Lower bone mineral density	Tebas et al. (2000)
	In vivo (humans)	Decrease in HDL Increase in LDL	Nolan et al. (2005)
Lopinavir	*In vivo* (humans)	Hepatotoxicity	Núñez (2006)
Remdesivir	*In vitro*	Hepatotoxicity	WHO (2018)
	In vivo (animals)	Nephrotoxicity	WHO (2018)
	In vivo (humans)	Reproductive toxicity	WHO (2018)
	In vivo (humans)	Hepatic enzymes elevation, hypotension, renal impairment, rash, diarrhea, acute kidney injury, hypotension, septic shock and multiple organ dysfunction syndrome	Grein et al. (2020)
	In vivo (humans)	AST and ALT elevation, hypotension	Mulangu et al. (2019)
Chloroquine	*In vivo* (humans)	Retinotoxicity, headache, nausea, vomiting, diarrhea and skin rash	Yusuf et al. (2018)
	In vivo (humans)	Cardiac arrest	Tingbo (2020)
Umifenovir	*In vivo* (humans)	Transaminase elevation, gastrointestinal symptoms	Wang et al. (2004)
	In vivo (animals)	Weight loss and hair loss	Zhou et al. (2006)
Lopinavir/ ritonavir	*In vivo* (humans)	Retinal damage	(Louie and Jones, 2019; Papavasileiou et al., 2017)
	In vivo (humans)	Elevated triglyceride levels	Greffrath et al. (2018)
	In vivo (humans)	Hepatotoxicity/increased AST and ALT Dyslipidemia diarrhea, nausea asthenia, abdominal pain, vomiting headache and rash	Corbett et al. (2002)
	In vivo (humans)	Cardiotoxicity in premature twins	McArthur et al. (2009)
Lopinavir/ ritonavir + interferon beta	/	/	/
Chloroquine + azithromycin	*In vivo* (humans)	Serious side effect of vomiting	Sagara et al. (2014)
Chloroquine + remdesivir	/	/	/

/– no reported data.

5. Conclusion and remarks

In this review we summarized the toxicity of medicines that are currently recognized as potential effective therapy options for the treatment of COVID-19 disease. The most important studies reviewed in this paper are summarized in Table 2.

Having in mind that the health status of patients with COVID-19 disease is often complicated by existing illnesses and conditions, understanding the toxicity of medicines, especially their combinations intended for the therapy is of crucial importance in building the successful therapeutic strategies. Some of the most often reported toxic effects such as, hepatotoxicity, retinal damage, nephrotoxicity and cardiotoxicity urge the plea for rationale and cautious decision on COVID-19 treatment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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