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REVIEW

Drugs that Might Be Possibly Used for Treatment of COVID-19 Patients

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Abstract–The drug development process for Coronavirus disease (COVID-19) is the research process to create a preventive vaccine or therapeutic prescription drug to relieve the severity of 2019–2020 (COVID-19). In different stages of preclinical or clinical research, several hundred special scientific research centers, research organizations, and health agencies have developed and tried enormous numbers of vaccine candidates and new drugs for COVID-19 disease. In order to identify new therapies against COVID-19, several clinical trials have been in progress worldwide.

Keywords: Coronavirus disease, drug development process, trial of treatments, Favipiravir, Losartan

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INTRODUCTION

Humanity has been burdened by the advent of a novel coronavirus known as SARS-CoV-2 (severe acute respiratory syndrome, coronavirus 2) since the beginning of the new decade of the 21st century, 2020, which triggered a deadly outbreak of coronavirus disease (COVID-19) [1]. This novel virus was first described at the end of December 2019 and is related to a cluster of atypical cases of pneumonia (27 cases) identified in Wuhan, Hubei Province, China [2, 3]. On 11 March 2020, the virus was declared a pandemic by the World Health Organization (WHO) [4] and became an immediate public health issue. "After the SARS and MERS viruses that caused the" extreme acute respiratory syndrome "in 2002–2003 and the" Middle East respiratory syndrome in 2012, SARS-CoV-2 is the third highly pathogenic coronavirus that crossed the species barrier to cause fatal pneumonia in humans [1]. The SARS-CoV pandemic has been reported to have potentially resulted in up to 8000 cases of infection with a fatality rate of approximately 10% in the early 2000s, while MERS-CoV developed over 1700 cases and a fatality rate of approximately 36% later [5]. Nevertheless, the newly discovered coronavirus induces a higher rate of transmission, has already spread to all continents and has encountered more than 3430000 cases of infection up to the date of writing [6]. Therefore, as of the date of writing of this paper, the number of COVID-19 patients confirmed worldwide was 3435894 with 239604 deaths recorded (Fig. 1) [6], and these figures may be underestimated in the coming period, based on the trends observed in recent days.

1. DRUG DEVELOPMENT

The creation of drugs plays an important role in the discovery of a new infectious disease vaccine or therapeutic medication for needs, and the new drug has been identified by the drug discovery process [7]. It requires laboratory studies on microorganisms and animals, regulatory status filing, such as through the U.S. The Food and Drug Administration (FDA) may initiate clinical trials on humans for an investigational new drug and may require the step of obtaining regulatory approval for a new drug application to market the drug [8, 9]. The entire process usually takes more than a decade, from concept through preclinical laboratory testing to clinical trial creation, including phase I–III trials to approved vaccine or drug [7–9].

The production of a vaccine or therapeutic antiviral drug for COVID-19 starts with the combination of a chemical definition with the possible prophylactic mechanism of the future in vivo vaccine or antiviral activity [8, 9]. Figure 2 illustrates the mechanism of the drug development period.

2. ANTIVIRAL EIDD-2801

It is the β-D-N^4-hydroxycytidine isopropyl ester prodrug (Fig. 3). As it prevents phosphorylation of the N^4-hydroxyl group in the gastrointestinal tract, the

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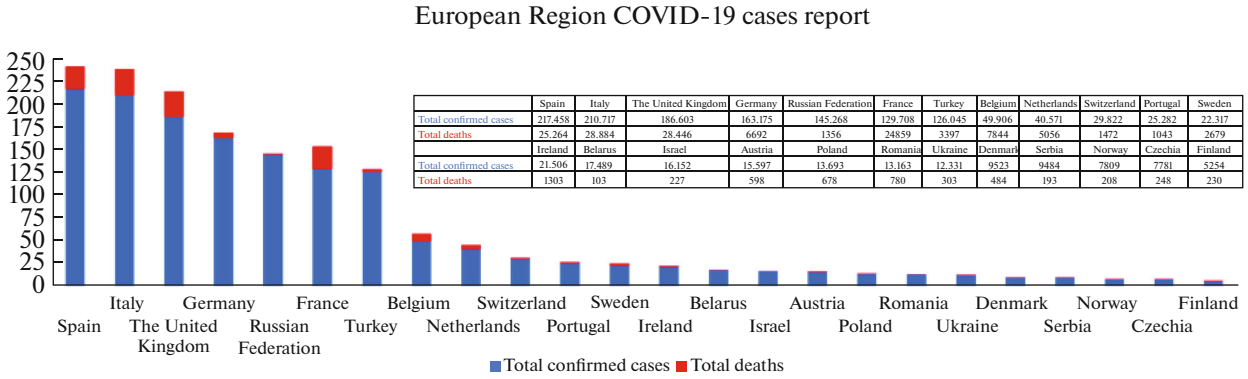


	Spain	Italy	The United Kingdom	Germany	Russian Federation	France	Turkey	Belgium	Netherlands	Switzerland	Portugal	Sweden
Total confirmed cases	217.458	210.717	186.603	163.175	145.268	129.708	126.045	49.906	40.571	29.822	25.282	22.317
Total deaths	25.264	28.884	28.446	6692	1356	24859	3397	7844	5056	1472	1043	2679
	Ireland	Belarus	Israel	Austria	Poland	Romania	Ukraine	Denmark	Serbia	Norway	Czechia	Finland
Total confirmed cases	21.506	17.489	16.152	15.597	13.693	13.163	12.331	9523	9484	7809	7781	5254
Total deaths	1303	103	227	598	678	780	303	484	193	208	248	230

Fig. 1. According to World Health Organization (WHO) statistics, the situation of coronavirus disease in the European Region (COVID-19) was reported on May 4, 2020 (only countries with more than 5000 cases at that time are reported in the graph) [8].

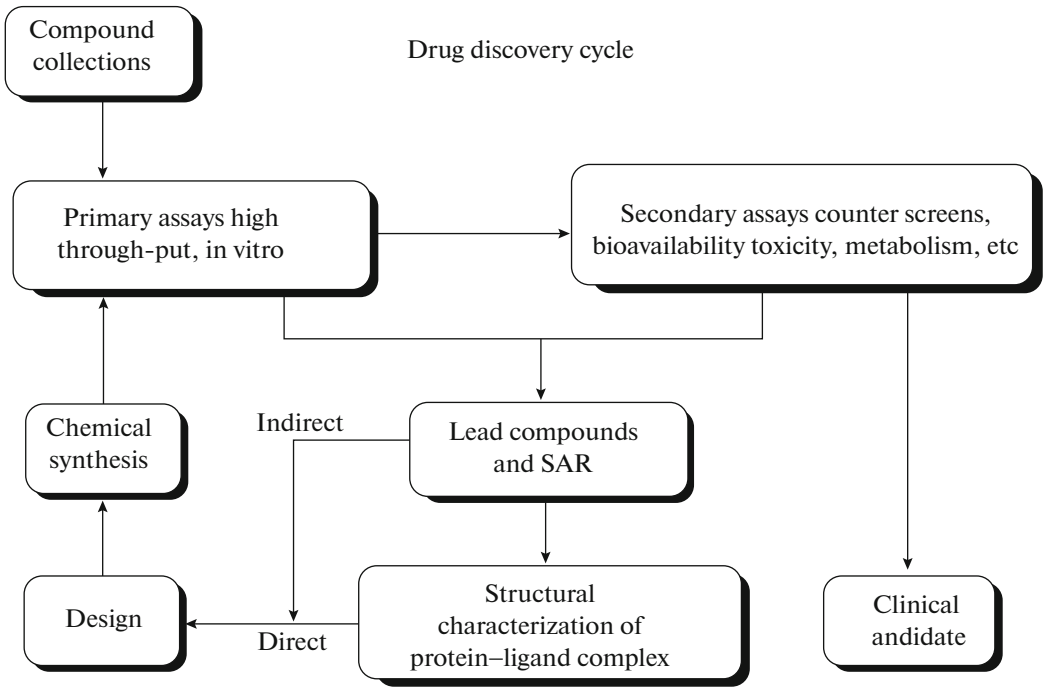


Fig. 2. The drug discovery cycle process.

prodrug has increased oral bioavailability. To release the parent (EIDD-1931), which distributes into tissues, it is hydrolyzed in vivo, and it becomes the active triphosphate type upon tri-phosphorylation. By the action of RdRp, the active form is incorporated into the genome of RNA Wide-spectrum antiviral activity against various RNA viruses, including influenza, Ebola, Venezuelan equine encephalitis virus, MERS-CoV, SARS-CoV, SARS-CoV-2 and associated zoonotic group 2b or 2c bat coronaviruses, has been observed in the triphosphorylated form [10, 11]. Increased potency against coronavirus with Remdesivir resistance mutations was also shown [12]. Viruses, contributing to the accumulation of mutations known as the tragedy of viral error [10]. There are two versions of the active form (Fig. 5b): the oxime form, which mimics uridine and adenosine pairs, while the other tautomer mimics cytidine and guanosine pairs [11]. EIDD-2801 administration was found to decrease virus titer and body weight loss in mice infected with MERS-CoV or SARS-CoV and to enhance pulmonary function [10]. In vitro and in vivo, the decreased MERS-CoV yield was attributed to an increase in the frequency of transition mutations in viral RNA alone. In human airway epithelial cells, the drug recorded similar results. As a prophylactic and as a therapy, the medication showed similar results [10].

The drug was developed at the Emory Institute for Drug Development and it was tested in a phase 1 ran-

domized, double-blind, placebo-controlled, first-in-human study designed to evaluate its safety, tolerability, and pharmacokinetics following oral administration to healthy volunteers (NCT04392219. $n = 130$). It is now being tested in two phase 2 trials in COVID-19 patients (NCT04405570. $n = 44$ and NCT04405739. $n = 60$) [12].

3. REMDESIVIR IS AN ANTIVIRAL MEDICATION

Remdesivir(2-ethylbutyl (2*S*)-2-{[(*S*)-{[(2*R*,3*S*,4*R*,5*R*)-5-(4aminopyrrolo[2,1-*f*] [1,2, 4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl] methoxy}(phenoxy) phosphoryl] amino} propanoate). The most promising therapy for SARS-CoV-2 infection is considered at this stage (Fig. 4, see brief summary in Table 1), based on the latest results obtained in the phase III clinical trials funded by the manufacturer [12] and the National Institute of Allergy and Infectious Diseases (NIAID) in the Adaptive COVID-19 Treatment Trial (ACTT) [13].

RDV is the C-adenosine nucleoside analog GS-441524 monophosphoramidate prodrug (1^J-cyano 4-aza-7,9-dideazaadenosine C-nucleoside, a compound recommended as a treatment for bacterial peritonitis in cats and felines, a feline coronavirus-determined disease) [14, 15]. This drug was developed by Gilead Sciences, Inc. as an antiviral candidate against the Ebola virus, but has also been shown to be highly effective in vitro against paramyxoviridae (parainfluenza type 3 virus, measles and mumps virus, nipah virus, among others) and pneumoviridae (respiratory syncytial virus), as well as positive sense viruses, coronaviridae (respiratory syncytial virus), as well as positive sense viruses [16–18].

Using the free web tool SwissADME, the absorption, distribution, metabolism and excretion (ADME) profile was achieved. The red highlighted region is the required physicochemical space for oral bioavailability covering LIPO (lipophility) value intervals: $-0.7 <$ XLOGP3 $< +5.0$, SIZE: 150 g/mol $<$ MV $<$ 500 g/mol, POLAR (polarity): 20 Å^2 $<$ TPSA $<$ 130 Å^2, INSOLU (insolubility): $0 <$ log S(ESOL) < 6, INSATU (insaturation): $0.25 <$ Fraction Csp3 < 1, FLEX (flexibility): $0 <$ Num. Rotatable bonds < 9, whereas the overlapped green highlighted area shows the calculated ADME profile for the molecule [19].

Important evidence supporting the efficacy of RDV against SARS-CoV-2 virus has recently been collected: (i) In vitro, Wang et al. [17, 20]. demonstrated that RDV prevented viral infection efficiently at low micromolar concentrations in two separate cell lines (Vero E6 and Huh-7) with a notable half-maximal efficacy (EC50) value of 0.77 μM. (ii) In vivo studies in animal models of SARS-CoV and MERS-CoV have verified the antiviral ability of RDV by reducing clinical signs of infection [21]. (iii) In clinical efficacy studies of RDV in patients with extreme COVID-19, improved clinical results have been observed, but some adverse effects have also been reported in the RDV-treated group [22, 23]. Phase I, phase II and phase III clinical trials in healthy volunteers and patients with Ebola virus infection have demonstrated the pharmacokinetic properties and safety profile of the compound (high human tolerance, absence of cytotoxicity, hepatotoxicity or renal toxicity and absence of / reduced serious adverse reactions) [18]. Currently, RDV is tested in multiple ongoing phase 3 clinical trials for COVID-19 treatment (NCT04252664, NCT04257656, NCT04292730, NCT04292899, NCT04280705, Solidarity trial (WHO). Discovery trial (INSERM) in Belgium, and so on) and Article 83, which includes guidelines on the humane use of RDV for COVID-19 care in the European Union, was adopted by the European Medicine Agency (EMA) [24]. Two randomized, open-label, multi-center phase 3 clinical trials (also known as SIMPLE studies) developed in countries with a significant number of cases were funded by the manufacturer of Remdesivir, Gilead Sciences, Inc.: (1) SIMPLE Study 1 was developed on extreme COVID-19 patients to assess the efficacy and safety of 5-day versus 10-day RDV (first dose-200200) therapy. In addition to standard care, and (2) Easy Study 2 conducted on patients with mild symptomatology of COVID-19 to assess the efficacy and safety of a 5- or 10-day RDV treatment versus standard care, findings will be available by the end of May [12]. In a press release dated April 29, 2020, Gilead Sciences, Inc. reported the preliminary results obtained in SIMPLE Study 1 for severe patients with COVID-19 as follows: (i) a similar clinical improvement after 5 or 10 days of RDV treatment. (ii) An earlier start of treatment with RDV (within 10 days of the onset of symptoms) decreases the period of hospitalization. (iii) In most patients, high tolerance of RDV (both experimental settings: 5- or 10-day treatment) was observed, but some side effects occurred occasionally, such as nausea (10% of patients), acute respiratory failure (a higher percentage in the 10-day group: 10.7% versus 6%), elevated liver enzyme (ALT) values (7.3% of patients), And discontinuation of treatment due to liver damage in 3% of patients (high enzyme values) [12]. On June 1, 2020, Gilead Sciences, Inc. announced the findings of SIMPLE Study 2, as follows: (i) the 5-day RDV therapy resulted in a substantial improvement in clinical status in patients with mild symptomatology of COVID-19 on day 11 relative to the standard care community (65% of patients). (ii) In terms of safety and adverse effects observed, RDV treatment was well tolerated and nausea (10% of patients), diarrhea (5%) and headache (5% of patients) were the most common adverse effects observed, and no deaths were reported compared to the standard care group, which reported four deaths [24]. Moreover, since May 7, 2020. Remdesivir (Veklury ®) has been approved as a treatment in Japan

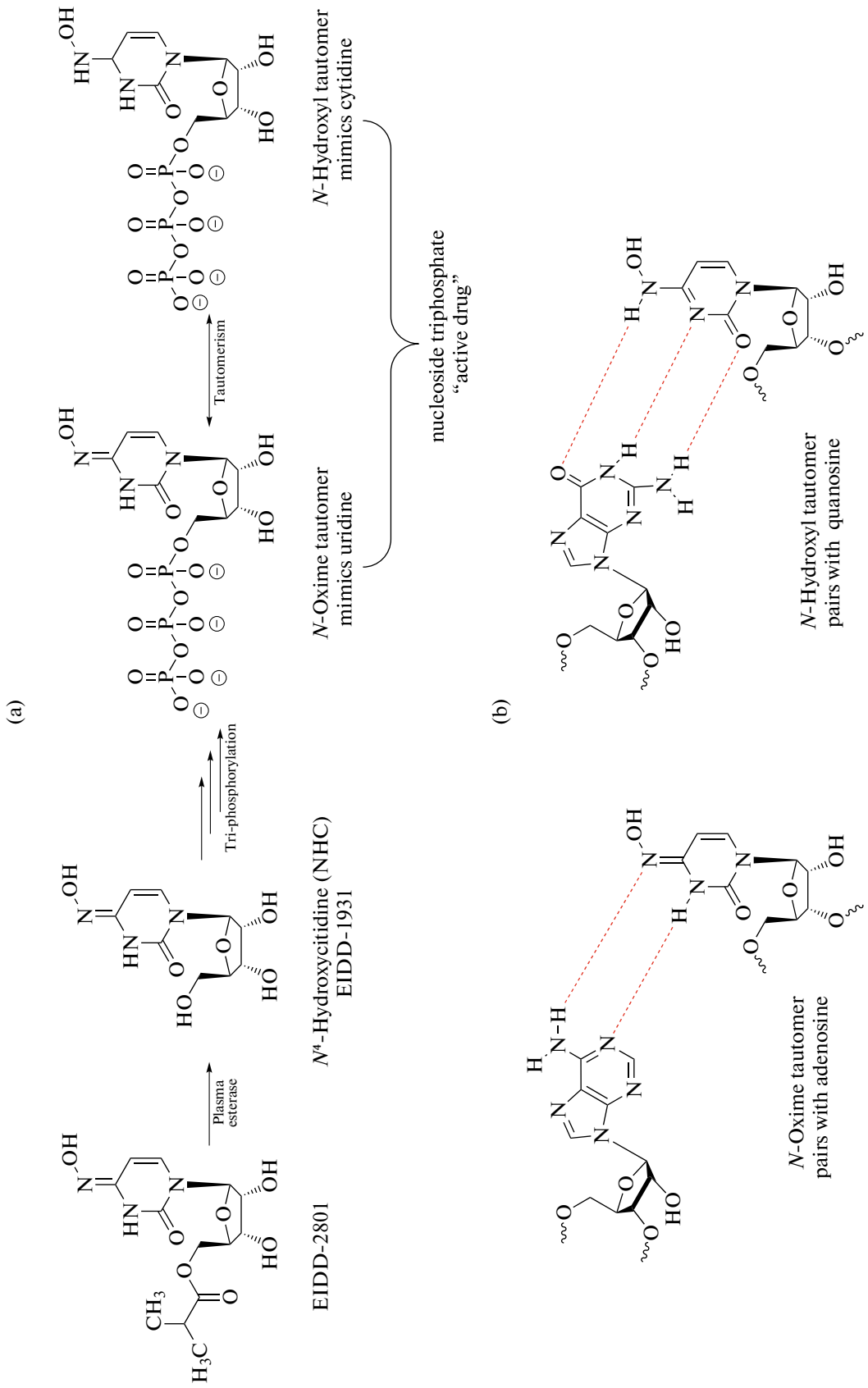


Fig. 3. (a) Chemical composition of EIDD-2801, a ribonucleoside isopropyl ester prodrug analog of β-D-N^4-hydroxycytidine. EIDD-2801 is a nucleoside derivative orally bioavailable for SARS-CoV-2 that is being created. Its activation to the corresponding tri-phosphorylated form showing a broad-spectrum antiviral activity against different RNA viruses, including coronaviruses with Remdesivir resistance mutations, is also shown. (b) There are two variants of the active form: the oxime form that imitates uridine and adenosine pairs, while the other tautomer imitates cytidine and guanosine pairs. The medicine inevitably leads to a tragedy of viral malfunction.

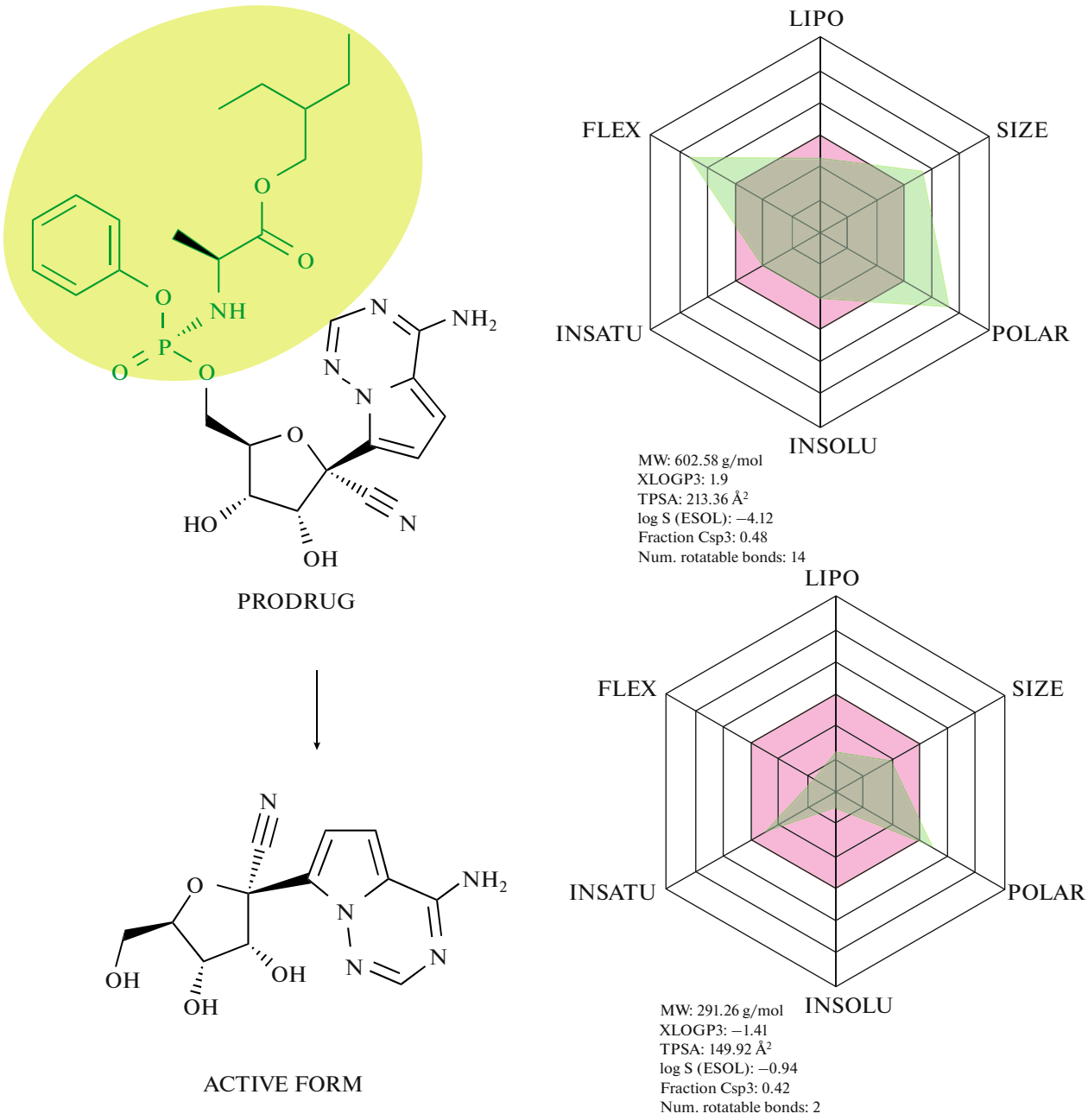


Fig. 4. Chemical structure and active form of the prodrug remdesivir (RDV), GS-441524.

for patients with serious COVID-19 disease [24]. The Adaptive COVID-19 Treatment Trial (ACTT) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID, part of the National Institutes of Health), a clinical trial that included 1063 patients, also obtained promising results regarding the efficacy of RDV as a treatment for COVID-19 patients: (i) RDV-treated patients (10 days, first day 200 mg/day intravenously, followed by 100 mg/day for 9 days) recovered faster (31%) compared to placebo-treated patients. in addition, the mortality rate was lower compared to placebo in the RDV-treated group (8% versus 11.6%, respectively) [13]. Beigel et al. [25]. released the preliminary report findings of the ACTT analysis in The New England Journal of Medicine on May 22, 2020. On the basis of these positive preliminary results, the European Medicine Agency (EMA) launched a "rolling study" for RDV, which culminated in an acceleration of the RDV marketing authorization assessment process [27], while the Food and Drug Administration (FDA) approved RDV for emergency use as a treatment for COVID-19 hospitalized patients [24]. These latest data on the efficacy of RDV against SARS-CoV-2 infection are stimulating,

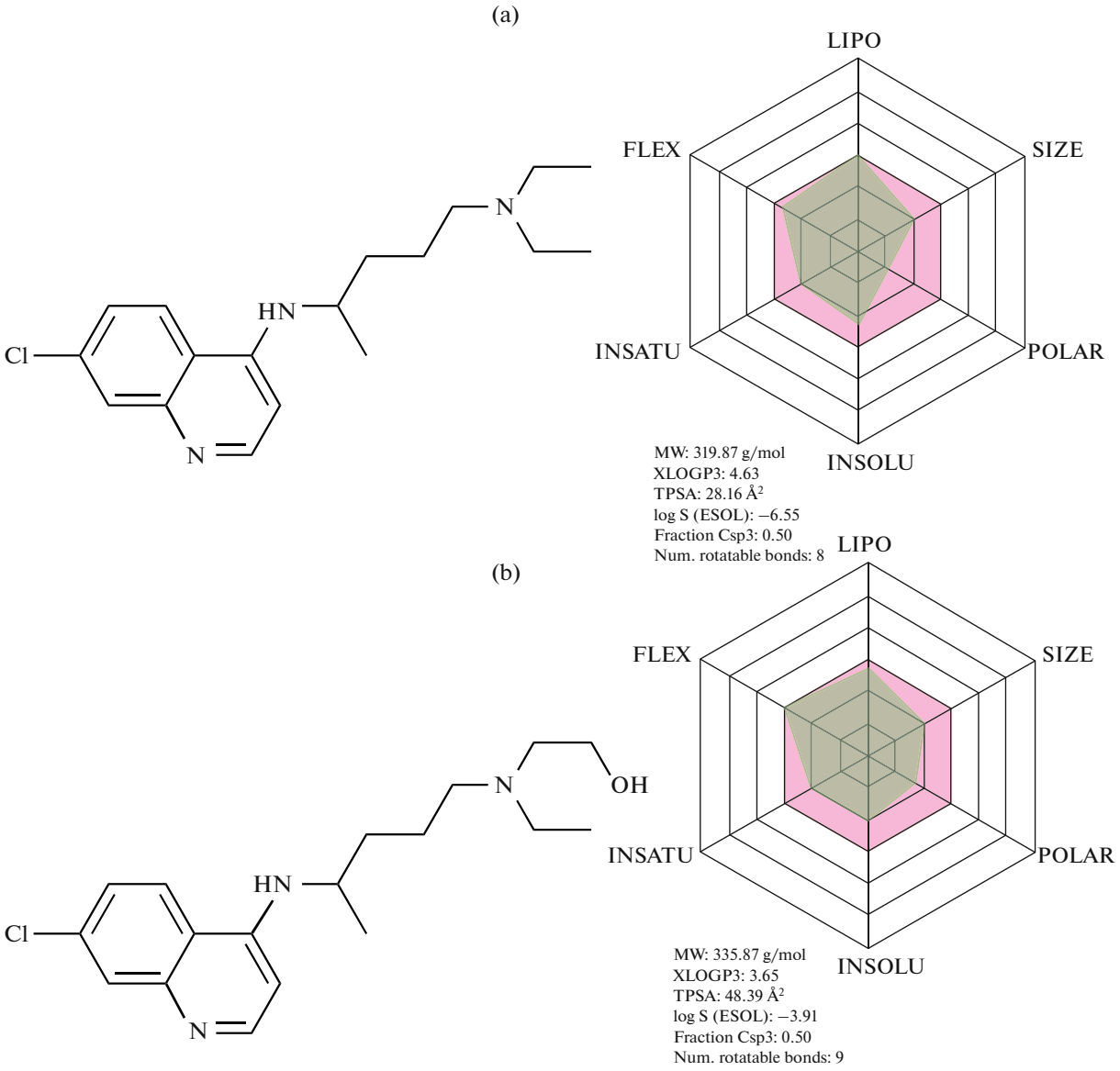


Fig. 5. Chemical structure of chloroquine (a) and hydroxychloroquine (b) ADME profile was achieved using the free web tool SwissADME. the red highlighted area represents the suitable physicochemical space for oral bioavailability, covering value intervals for the following: LIPO (lipophility): $-0.7 < \text{XLOGP3} < +5.0$, SIZE: $150 \text{ g/mol} < \text{MW} < 500 \text{ g/mol}$, POLAR (polarity): $20 \text{ Å}^2 < \text{TPSA} < 130 \text{ Å}^2$, INSOLU (insolubility): $0 < \text{Log S (ESOL)} < 6$, INSATU (insaturation): $0.25 < \text{Fraction Csp3} < 1$, FLEX (flexibility): $0 < \text{Num. rotatable bonds} < 9$, whereas the overlapped green highlighted area shows the calculated ADME profile for the molecule [23].

although the gaps in its safety profile are currently very broad and need to be filled by the forthcoming results from the ongoing clinical studies. On the basis of these factors, it is advised that physicians should be well informed of the significant number of factors/conditions during care (especially in the case of critically ill patients with comorbidities, diabetes, cardiovascular pathology, and elderly people) that could interact with this compound and lead to adverse events.

This medication is formulated in two pharmaceutical formulations (a solution, 5 mg/mL and a lyophilized formulation, 100 mg RDV powder) according to the review on compassionate use of RDV and is recommended for intravenous administration (30–120 min) after reconstitution in 0.9% saline or 5% glucose solutions, with the therapeutic dose being as follows: 200 mg on day 1 and 100 mg/day for the following 9 days. Lyophilized powder that must be reconstituted prior to use and administered intravenously, as indicated above, is the recommended formulation of RDV for compassionate use [24].

Table 1. Brief description of COVID-19 therapeutic options recommended by World Health Organization (WHO) guidelines [53–56]

Drug name	Pharmacological class	Clinical phase	EC_{50} (half maximal effective concentration)	Dose	Mechanism of action	Adverse effects
Remdesivir (RDV)	Nucleoside analogue	Severe	0.77 μM	200 mg—day 1. 100 mg/day—9 days	Inhibitor of the CoVs RNA-dependent RNA polymerase (RdRp)	• Incompletely characterized toxicological profile: phlebitis, constipation, headache, ecchymosis, nausea, pain in the extremities • Elevation of hepatic enzymes values
Chloroquine (CQ)	4-aminoquinoline	Mild-to-moderate and severe—depending on the guideline applied	23.90 μM (24 h) 5.47 μM (48 h)	CQ base (600 mg/diagnosis. 300 mg—12 h later and 300 mg up to 5 days) or CQ phosphate (1000 mg/diagnosis. 500 mg—12 h later and 300 mg up to 5 days)	Weak base able to elevate the pH of acidic intracellular organelles, such as endosomes and lysosomes	• Retinopathy • Hypotension • ECG changes • Irreversible cardiomyopathy—long-term users • Direct myocardial toxicity • Exacerbate the existent myocardial dysfunction • QT prolongation • Risk of Torsade de Pointes (TdP) even at therapeutic doses • Interaction with antiarrhythmics * in the case of HCQ, the adverse effects have a lower intensity, but are not absent
Hydroxychloroquine (HCQ)	4-aminoquinoline	Mild-to-moderate and severe—depending on the guideline applied	6.14 μM (24 h) 0.72 μM (48 h)	HCQ—400 mg at suspicion/diagnosis. 400 mg—12 h later and 200 mg—until day 5	Weak bases able to elevate the pH of acidic intracellular organelles, such as endosomes and lysosomes	
Liponavir/ritonavir (LPv/r)	Protease inhibitor	Mild-to-moderate	–	400/100 mg/day—14 days	Peptidomimetic inhibitor of HIV protease enzyme	• Hypercholesterolemia and increased serum triglycerides • Increased gamma-glutamyl transferase • Increased serum ALT • Upper respiratory tract infection • Diarrhea • Nausea • Headache • Skin rush • Neutropenia • Anxiety • QT prolongation

4. CHLOROQUINE AND HYDROXYCHLOROQUINE

A 70-year-old antimalarial medication, currently one of the agents for amoebiasis and other protozoal diseases and antimalarials associated with irreversible retinal damage and life-threatening and fatal cardiomyopathy, chloroquine (CQ, Fig. 5a, see brief definition in Table 1), has been recently identified as a possible broad-spectrum antiviral drug [18, 28]. In the treatment of immune diseases such as systemic lupus erythematosus and rheumatoid arthritis, hydroxychloroquine (HCQ, Fig. 5b, see brief definition in Table 1) is a chloroquine analogue [29], one of the antimalarials and other anti-inflammatory and antirheumatic agents associated with ocular toxicity and cardiomyopathy [30]. For the last 30 years, HCQ has been used to treat Coxiella burnetii, the intracellular bacterium that causes Q fever, as the only effective agent that destroys intracellular pathogens. Another important therapeutic activity is against Tropheryma wippley [31], an intracellular bacterium. Both compounds are structurally 7-chloro-quinoline derivatives, with a fourth-position novaldiamine substituent where HCQ has an additional hydroxyl group grafted at the end of the chain. In terms of bioavailability, according to absorption, distribution, metabolism and excretion, the additional hydroxyl group (ADME) As predicted, the HCQ profile leads to improved hydrosolubility, versatility, and polarity, as well as a decrease in lipophilicity compared to CQ (Fig. 5). Because of the existence of the hydroxyl group, these variations in the ADME profiles of the two molecules can lead to different pharmacological actions, in terms of therapeutic effectiveness and outcome, but also in the incidence of toxic effects. It will also explore these pharmacokinetic aspects.

Several in vitro and in vivo studies have documented their therapeutic activity against several coronaviruses, such as human OC43, SARS-CoV, and MERS-CoV [32, 29], in order to reposition CQ and HCQ as antiviral candidates for COVID-19 therapy. The molecular mechanism of action has not yet been thoroughly elucidated for CQ and HCQ [29]. The mechanism of the antiviral activity of CQ against SARS-CoV has been investigated in previous studies. The authors concluded that an improvement in the endosomal pH value would be a potential mode of action of the drug in post-infection therapy due to the existence of three nitrogen atoms within the CQ molecule that give it its basic properties, leading to the abolition of virus-endosome fusion [33, 34]. These results also indicate that pre-infection therapy with CQ is responsible for under-glycosylated ACE2 cell surface expression, leading to a decrease in the affinity of the viral spike protein-cell receptor [33]. In line with these studies, a recent study also showed that within acidic intracellular organelles, such as early endosomes (EEs) and endolysosomes (ELs), CQ/HCQ induced pH elevation and also caused SARS-CoV-2 transport disruption between EE and EL [30], a stage that appears to be necessary in the release of the viral genome in SARS-like coronavirus infections [35]. At the same time, with regard to the molecular mechanism of action of CQ / HCQ, in-silico determinations were the focus of the possibility of discovering a possible target before experimental confirmation. Wu et al. screened two compound libraries against 19 SARS-CoV-2 protein targets (ZINC and a normal compound library of their own). Among the findings, the authors showed that chloroquine is capable of targeting nonstructural proteins such as Nsp3b, showing sufficient docking scores [36]. A number of mechanisms have been suggested for both CQ and HCQ in terms of anti-inflammatory and immunomodulatory activities, which include: decreased production of cytokines, suppression of immune effector cells and platelet function., Cell surface defense from external disorders, competitive binding to nucleic acid ligands or toll-like receptors (TLRs), lysosomal function interference, reduction of leakage of lysosomal enzymes, and endosomal NADPH oxidase (NOX) interference [37].

The potential mechanisms of action can be divided into two major groups, based on their activity against SARS-CoV-2: (1) inhibition of viral enzymes/processes (viral DNA and/or RNA polymerase), glycosylation of viral proteins, virus assemblage, new transport of viral particles and release of viruses and (2) inhibition of ACE2 cellular receptors, acidification of the cell membrane surface. Promising in vitro findings of CQ and HCQ against CoVs resulted in early clinical interest in the use of these two compounds for COVID-19 therapy and several clinical trials (over 50, most of which tested the effects of HCQ [38], were initiated [39]). Methodological deficiencies exist in the data collected from clinical trials (final results or preprint texts) [39] and are inconclusive:

(i) Better clinical results were observed in the HCQ-treated community but were not statistically relevant [40].

(ii) Co-administration of HCQ with azithromycin showed a decrease in viral load in patients with COVID-19 [41].

(iii) CQ inhibited exacerbation of pneumonia and shortened the course of infection (improved pulmonary imaging and increased viral clearance) [42].

(iv) Compared to CQ, HCQ proved to be stronger in terms of effectiveness [43, 44].

(v) HCQ apparently did not provide defense against SARS-CoV-2 infection (results of a broad Israeli healthcare database analysis) [45].

The relationship between HCQ and azithromycin for the treatment of patients with COVID-19 was based on several premises: azithromycin demonstrated

in vitro activity against Ebola and Zika viruses and protective effects against serious infections of the respiratory tract in patients with viral infection [41], but further studies confirmed the efficacy of HCQ and azithromycin combination [46]. In three comprehensive clinical trials, CQ and HCQ are also evaluated, that is, the WHO-funded SOLIDARITY trial evaluating these compounds as a possible therapy against SARS-CoV-2 infection, the HERO-HCQ, a study sponsored by the National Institutes of Health (NIH) evaluating their preventive potential, and the INSERM-launched Discovery trial (French Institut National de la Santé Et de la Recherche Médicale) [44, 45]. Although the two compounds share similar chemical structures, it has been stated that HCQ has some therapeutic advantages, such as lower toxicity in animals, compared with CQ [30]. It is important to note that both CQ and HCQ interact with the isoenzymes and drug transporters of cytochrome P450: CYP2C8, CYP2D6, CYP3A4, P-gp that are primarily metabolized by CYP2C8 and CYP3A4, and recognized drug transporter P-glycoprotein inhibitors.(P-gp), thus describing the interactions with related antiviral drugs (increasing/decreasing). Both CQ and HCQ exhibit favorable pharmacokinetic properties: effective oral absorption and tissue distribution patterns, resulting in high levels of CQ and bone marrow, liver, kidney, lungs, adrenal gland, and pituitary gland for HCQ in the liver, spleen, kidney, and lungs. It should be noted that the cells containing melanin strongly bind to the process of chloroquine, explaining the retinal toxicity of the two compounds [29, 37].

5. JAPAN FLU DRUG

Favipiravir

Favipiravir (Scheme 1), a derivative of pyrazinecarboxamide marketed under the brand name Avigan, is an antiviral drug used in Japan for the treatment of influenza, in addition to treating many other viral infections [47]. Toyama Chemical (Fujifilm group) is being produced and manufactured and was approved for medical use in Japan in 2014 [48]. The active pharmaceutical ingredient for the flu medication Avigan was licensed to Zhejiang Hisun Pharmaceuticals co. of China in 2016 by Tokyo-based Fujifim [49]. It is suspected that the mechanism of its action is related to the selective inhibition of viral RNA-dependent RNA polymerase [50]. Favipiravir was studied in China in February 2020 for the experimental treatment of emerging COVID-19 [51] trials in Japan are also expected [42]. Favipiravir was first synthesized from 2-aminopyrazine [42], an affordable and commercially available starting source. Over the past few months, clinical studies have been performed all over the world to assess the efficacy of favipiravir in the management of COVID-19.

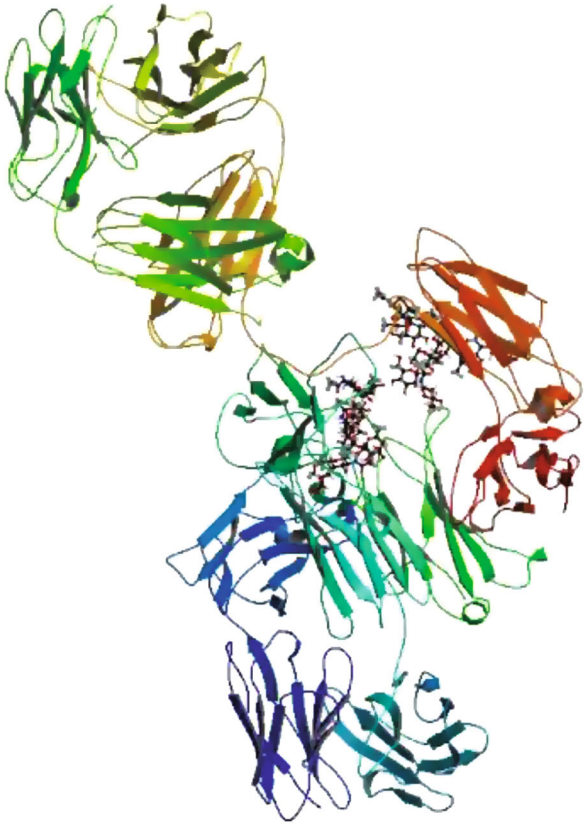
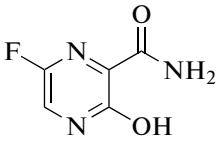


Fig. 6. Protein chemical formula of tocilizumab.



Scheme 1.

The Major Clinical Studies Are Summarized Here

China. A prospective, open-label, multi-center study in China was performed by Chen et al. [52] to compare two treatment arms in the management of clinically verified COVID-19 (maximum time of initiation of symptoms before randomization: 12 days). Conventional therapy with umifenovir (Arbidol) (200 mg three times a day) or with favipiravir (1600 mg twice a day followed by 600 mg twice a day) for 7 (extendable to 10 days) days. The study included 240 patients in both groups with a 1 : 1 randomization. The authors found that there was no substantial difference between the two groups in the clinical rate of recovery at day 7 (61.21% for favipiravir vs. 51.67% for umifenovir, 95% CI: –0.0305 to 0.2213, *p* 1/4 0.1396).

Post hoc analysis found that, among those with moderate COVID-19 (71.43% vs. 55.86%, 95% CI: 0.0271 to 0.2843, p 1/4 0.0199) and earlier resolution of fever and cough ($p < 0.0001$), favipiravir-treated patients showed a trend towards clinical improvement at day 7. In terms of the occurrence of auxiliary oxygen therapy or noninvasive mechanical ventilation, there were no major variations between the two classes. In terms of all-cause death, dys-pnea after taking medicine, and respiratory failure, the two classes were comparable. These have all been considered moderate side effects. When adequate knowledge about the effectiveness of this medication was uncertain, the most significant downside was the use of umifenovir as the control arm. The sample size was estimated on the premise that the time to clinical recovery with umifenovir was shortened by 50%, without evidence supporting this hypothesis. The effect of favipiravir (day 1: 1600 mg twice daily, day 2–14: 600 mg twice daily) vs. lopinavir/ritonavir (day 1–14: 400/100 twice daily) on the treatment of COVID-19 was compared in another open-label, nonrandomized study [53] from China. Via nasal inhalation, both groups received interferon-alpha (5 million units twice a day). Those aged 16–74 years, SARS-CoV-2 positive, onset of symptoms over the past 7 days and mild-moderate disease were recruited.

Fifty-six patients with laboratory-confirmed COVID 19 were screened from January 30 to February 14 and 35 patients were positive for favipiravir. From January 24 to January 30, 91 COVID-19 laboratory-confirmed patients already undergoing treatment with lopinavir/ritonavir were screened for eligibility, of which 45 were eligible for the control arm. There were no statistically significant variations in the baseline characteristics of both weapons. However, relative to the lopinavir/ritonavir arm, patients in the favipiravir arm reported a statistically significant shorter median period to viral clearance (4 days vs. 11 days, $p < 0.001$), an increase in chest CT findings after randomization at day 14 (91.4% vs. 62.2%, p 1/4 0.004), and a lower rate of adverse reactions (11.43% vs. 55.56% $p <$ 0.001). Multivariate research showed that favipiravir was independently linked to faster viral clearance and improvement of the chest CT scan. A potential selection bias may have confused the findings with the drawbacks of non-randomized analysis and the absence of blinding.

Japan. In order to assess the safety and efficacy of favipiravir, a Japanese observational research group reported details of hospitalized COVID-19 patients in Japan [54]. A total of 2158 cases from 407 hospitals were reported from February to May 2020. Favipiravir was administered at a dosage of 1800 mg orally on day 1 in more than 90% of cases, followed by 800 mg twice daily on the following days. The median therapy period was 11 days. At 7 and 14 days, clinical progress rates were 73.8 and 87.8, 66.6 and 84.5%, respectively, and 40.1 and 60.3% for mild, moderate, and serious diseases. Thus, the vast majority of mild and moderate disease patients recovered from the disease, although the findings were not encouraging in those with serious disease. The mortality rates for mild, moderate, and serious diseases at the time of the survey were 5.1, 12.7 and 31.7%, respectively. It should be emphasized that there was no control arm in this study that prevented direct comparison of the clinical course with those who did not receive the agent. In a small case series consisting of 11 severe COVID-19 patients in Japan, Favipiravir in combination with nafomostat (trans-membrane protease serine 2 inhibitor, previously used successfully in MERS-CoV-2 infection, acute pancreatitis and DIC) was found to be useful.

Median age, time from onset of symptoms to admission to ICU, and PaO2/FiO2 admission ratio were 68 years (IQR 60–69), 8 days (IQR 7–11), and 131 days (IQR 114–198). Eight patients (73%) needed intrusive mechanical ventilation, and three patients (27%) needed extracorporeal membrane oxygenation (ECMO). All patients required oxygen therapy. Out of 11 patients, 7 were successfully weaned from artificial ventilation and 1 patient with a DNR order died. The ICU and the hospital discharged nine and seven patients, respectively. At the time the paper was written, one patient was weaned from ventilation was still in the hospital. A prospective clinical trial (jRCTs031200026) is scheduled to start soon in Japan with this combination [55]. Randomized with a 1 : 1 : 1 high-dose ratio of favipiravir (1800 mg twice daily on day 1, followed by 800 mg twice daily for the next 13 days) versus low-dose favipiravir (1600 mg twice daily on day 1, followed by 600 mg twice daily for the next 13 days) versus standard of care (SOC). With no demonstrable side-effects, favipiravir was very effective. In 68% of patients on favipiravir, fever returned to normal within 3 days, compared with 6 days in the control group. Sixty-five percent of the 40 patients taking favipiravir tested negative for the virus within the first 4 days of treatment, twice as many as in the normal therapy community. 35 of the 40 (87.5%) patients tested negative for the virus at the end of day 10. The dose of favipiravir will be selected in the pivotal step of the trial based on the results of the pilot study and will be compared with the SOC as previously stated. The objective of the study is to examine the rate of viral elimination by day 10, the time to viral elimination within 28 days and the time to clinical improvement [56].

Side Effects/Adverse Effects

The previously mentioned Japanese study [57] found that adverse reactions were seen in approximately 20% of patients who received favipiravir (at a

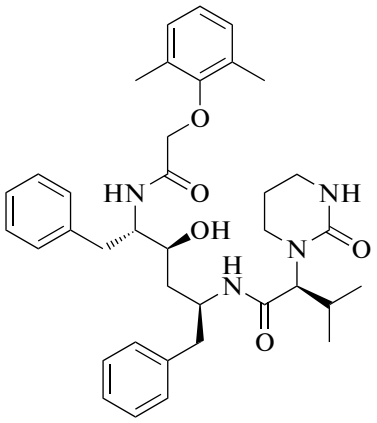
lower dose than COVID-19 approved) (Table 2). The relatively mild adverse effects included hyperuricemia and diarrhea in 5% of the participants and decreased neutrophil count and transaminitis in 2% of the participants.

The presence of psychological symptoms associated with favipiravir was demonstrated in one study. The effect of favipiravir on QTc prolongation remains unclear, with some pharmacodynamic studies indicating a positive association [58], but a Japanese study suggesting otherwise [59].

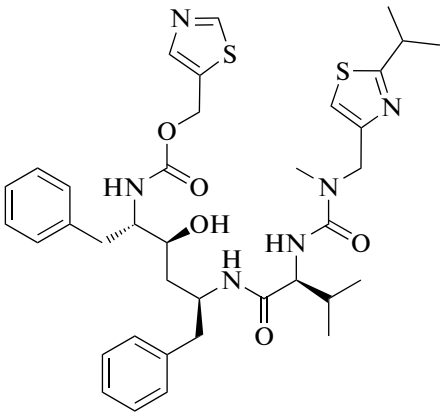
Overall, as was confirmed by a broad systematic analysis, favipiravir has a strong safety profile [60]. We offer a brief description of the adverse effect profile of this drug in the following sections [61].

6. AN HIV DRUG COMBINATION

Lopinavir/ritonavir (LPV/r) (Scheme 2), sold under the brand name Kaletra is a fixed dose combination medication for the treatment and prevention of HIV/AIDS [49].



Lopinavir



Ritonavir

Scheme 2.

Table 2. Depicting adverse effects of favipiravir

Diseases	≥1%	0.5–1%	<0.5%
Hypersensitivity		Rash	Eczema, pruritus
Hepatic	AST(GOT) increased ALT(GPT) increased γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea	Nausea Vomiting Abdominal Pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic	Neutrophil count decreased, white blood cell count decreased	Glucose, urine present	White blood increased cell count reticulocyte count decreased, monocytes increased
Metabolic disorders	Blood uric acid increased (4.79%) Blood triglycerides increased	–	Blood potassium increased
Respiratory	–	–	Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others	–	–	CPK increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo

Table 3. Interventional trials investigating the efficacy of lopinavir/ritonavir in COVID-19 [76]

Study title	ClinicalTrials.gov Identifier	Interventions (LPV/r vs. or LPV/r Plus.)	Locations
Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	NCT04307693	-Hydroxychloroquine	Korea
OUTpatient Treatment of COVID-19 in Patients with risk factor for Poor Outcome (OUTCOV)	NCT04365582	-Azithromycin -Hydroxychloroquine	France
Trial of Early Therapies During Non-Hospitalized Outpatient Window for COVID-19 (TREAT-NOW)	NCT04372628	-Hydroxychloroquine	USA
Treatments for COVID-19: Canadian Arm of the sOLIDARITY Trial (CATCO)	NCT04330690	-Remdesivir -Hydroxychloroquine	Canada
Clinical Trial to Evaluate ecacy of Three Types of Treatment in Patients With Pneumonia by COVID-19 (Covid-19HUF)	NCT04346147	-Imanitib -Baricitinib -Hydroxychloroquine	Spain
Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers (COVIDAXIS)	NCT04328285	-Placebo -Hydroxychloroquine	France
COVID MED Trial: Comparison of Therapeutics for Hospitalized Patients Infected With SARS-CoV-2 (COVIDMED)	NCT04328012	-Placebo -Hydroxychloroquine -Losartan	USA
Safety and Ecacy of Hydroxychloroquine + Favipiravir Drug Regimen in Comparison with Hydroxychloroquine + Kaletra on the Need for Intensive Care Unit Treatment in Patients with COVID-19	NCT04376814	-Favipiravir -Hydroxychloroquine	Iran
Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia	NCT04359095	-Azithromycin -Hydroxychloroquine -Standard treatment	Colombia
Ecacy and Safety of Umifenovir as an Adjuvant Therapy Compared to the Control Therapeutic regiment of Interferon Beta 1a, Lopinavir/Ritonavir, and a Single Dose of Hydroxychloroquine in Moderate to Severe COVID-19: A Randomized, double-Blind, Placebo-Controlled, Clinical Trial	NCT04350684	-Umifenovir -Interferon-β 1a -Hydroxychloroquine -Standards of Care	Iran
A Prospective/Retrospective, Randomized controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia	NCT04255017	-Abidol hydrochloride -Oseltamivir	China
COVID-19 Ring-Based Prevention Trial with Lopinavir/Ritonavir (CORIPREV-LR)	NCT04321174	None	Canada
Ecacy of Pragmatic Same-day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland (COPEP)	NCT04364022	-Hydroxychloroquine	Switzerland
Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	NCT04321993	-Baricitinib -Hydroxychloroquine	Canada
Interferon Beta 1a in Hospitalized COVID-19 Patients (IB1aIC)-Interferon Beta-1A	NCT04350671	-Hydroxychloroquine	Iran

Table 3. (Contd.)

Study title	ClinicalTrials.gov Identifier	Interventions (LPV/r vs. or LPV/r Plus.)	Locations
Evaluation of Ecacy of Levamisole and Formoterol+Budesonide in Treatment of COVID-19	NCT04331470	-Levamisole + -Budesonide + -Formoterol inhaler -Hydroxychloroquine	Iran
Evaluating and Comparing the Safety and Eciency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection	NCT04261907	-ASC09/ritonavir	China
Austrian Corona Virus Adaptive Clinical Trial (COVID-19) (ACOVACT)	NCT04351724	-Hydroxychloroquine -Candesartan -Clazakizumab -Placebo -Other treatments	Austria
Antiviral Therapy and baricitinib for the treatment of Patients with moderate or severe COVID-19	NCT04373044	-Baricitinib -Hydroxychloroquine -Remdesivir	USA
Trial of treatments for COVID-19 in hospitalized adults (DisCoVeRy)	NCT04315948	-Remdesivir -Interferon Beta-1A Hydroxychloroquine -Standard of care	France
Low Dose Anti-Inflammatory Radiotherapy for the treatment of Pneumonia by COVID-19	NCT04380818	-Low-dose radiotherapy -Hydroxychloroquine -Tocilizumab -Azithromycin -Corticosteroid -LMWH	Spain
Lopinavir/Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	NCT04276688	-Ribavirin -Interferon Beta-1B	China
Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID-19: A Randomized Control	NCT04303299	-Darunavir -Oseltamivir -Favipiravir	Thailand
Trial (THDMS-COVID-19)		-Hydroxychloroquine	
Randomised Evaluation of COVID-19 therapy (RECOVERY)	NCT04381936	-Corticosteroid -Hydroxychloroquine -Azithromycin -Convalescent plasma -Tocilizumab	United Kingdom

Lopinavir and ritonavir were originally developed as an inhibitor of HIV protease, one of a family of pseudo-C2-symmetric small molecule inhibitor [49]. In 2020 lopinavir/ritonavir was found not to work in severe COVID-19 (Table 3). In the trial the medication was started within about two weeks after the start of symptoms [49].

Synthesis of ritonavir and lopinavir, a short synthesis of hydroxyethylene dipeptide isostere, a core unit of the HIV-protease inhibitors ritonavir and lopinavir, its C-3 epimer and C2 symmetric diaminodiol is described. The crucial aspects of the synthesis are self-cross metathesis and exploitation of C2-symmetric of the metathesis product to obtain the required skeleton [62].

7. AN IMMUNOSUPPRESSANT AND AN ARTHRITIS DRUG

Tocilizumab

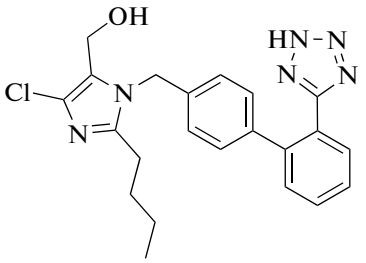
Tocilizumab (Fig. 6), also known as atlizumab, is an immunosuppressive drug, mainly for the treatment of rheumatoid arthritis and systemic juvenile idio-

pathic arthritis, a severe form of arthritis in children [63]. It was developed by Hoffmann–La Roche and Chugai. It is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer [64]. Tocilizumab permitted to treat coronavirus disease 2019 (COVID-19) of inflammation in patients in China, but there is no evidence whether this treatment is effective. In Australia (ASCIA) considered tocilizumab drug to be as an off-label medecine with COVID-19 related acute respiratory distress syndrome [49].

8. A BLOOD PRESSURE DRUG

Losartan

Losartan (Scheme 3), sold under the trade name Cozaar, is a medication mainly used to treat high blood pressure [65]. It is also used for diabetic kidney disease, heart failure, and left ventricular enlargement [66]. Losartan is a selective, competitive angiotensin II receptor type 1 (AT1) antagonist, reducing the end organ responses to angiotensin II. All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin–angiotensin system [57]. A hypothesis emerged in an opinion commentary published in March 2020, that AT1R blockers such as losartan may work to mitigate the symptoms of COVID-19 (SARS-CoV-2) infection [68].



Scheme 3.

The preparation of losartan and its potassium salt, which comprises reacting 4'-bromomethyl-2-biphenylcarbonitrile with 2-butyl-4-chloro-5-formylimidazole in the presence of a base and a phase transfer catalyst to produce a cyano aldehyde. Reacting the formed cyano aldehyde with sodium azide in the presence of tributyl tin chloride to produce aldehyde tetrazole. reducing the formed aldehyde tetrazole with sodium borohydride to produce Losartan [49].

CONCLUSION

Coronavirus disease (COVID-19) drug development researches are still under trials of process. These drugs are included vaccine or therapeutic prescription drug. To date there is no approved specific drug to cure patients infected by SARS-CoV-2. A large number of local and international special scientific research centers are working hard to test vaccine candidates and potential drugs for COVID-19 disease in various stages of preclinical or clinical research. We have believe and hope in science.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human participants performed by any of the authors and doesnot contain any studies involving animals performed by any of the author.

Conflict of Interests

The authors report no conflicts of interest.

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