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Biomedicine & Pharmacotherapy 146 (2022) 112517

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

RdRp inhibitors and COVID-19: Is molnupiravir a good option?

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ARTICLE INFO

Keywords:
SARS-CoV-2
Small molecule drug
RdRp inhibitors, Molnupiravir
Clinical trials

ABSTRACT

Rapid changes in the viral genome allow viruses to evade threats posed by the host immune response or antiviral drugs, and can lead to viral persistence in the host cells. RNA-dependent RNA polymerase (RdRp) is an essential enzyme in RNA viruses, which is involved in RNA synthesis through the formation of phosphodiester bonds. Therefore, in RNA viral infections such as SARS-CoV-2, RdRp could be a crucial therapeutic target. The present review discusses the promising application of RdRp inhibitors, previously approved or currently being tested in human clinical trials, in the treatment of RNA virus infections. Nucleoside inhibitors (NIs) bind to the active site of RdRp, while nonnucleoside inhibitors (NNIs) bind to allosteric sites. Given the absence of highly effective drugs for the treatment of COVID-19, the discovery of an efficient treatment for this pandemic is an urgent concern for researchers around the world. We review the evidence for molnupiravir (MK-4482, EIDD-2801), an antiviral drug originally designed for Alphavirus infections, as a potential preventive and therapeutic agent for the management of COVID-19. At the beginning of this pandemic, molnupiravir was in preclinical development for seasonal influenza. When COVID-19 spread dramatically, the timeline for development was accelerated to focus on the treatment of this pandemic. Real time consultation with regulators took place to expedite this program. We summarize the therapeutic potential of RdRp inhibitors, and highlight molnupiravir as a new small molecule drug for COVID-19 treatment.

1. Introduction

Three novel coronaviruses have emerged as human infectious pathogens during the last twenty years or so [1,2]. As evidenced by the emergence of SARS-CoV-2 and SARS-CoV, group 2b coronaviruses will continue to pose a health-threat in the future. The SARS-like CoV family from bats are zoonotic viruses able to grow in human airway cells, by recognizing angiotensin-converting enzyme 2 (ACE2) receptors, and show variations in vaccine gene sequence as well as therapeutic targets [3–7]. Therefore, to tackle the present COVID-19 global health emergency and to enhance preparedness for future pandemics, the discovery of drugs and vaccines that are more effective against high-risk RNA viruses, is required.

Small-molecule antiviral drugs can work via several pathways, such as interfering with a replication-related host factor, inhibiting the production of new viral particles, suppressing a virally encoded enzyme, or blocking viral entry into host cells [8]. Currently, many antiviral drugs are being evaluated in human clinical trials for the management of COVID-19, including ritonavir/lopinavir, remdesivir, and hydroxychloroquine [9–11].

When SARS-CoV-2 emerged as a global pandemic, molnupiravir was being investigated for seasonal influenza treatment under an IND application. Because of the evidence of activity in ferret influenza models [12–14], and favorable ADMET (absorption, distribution,

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https://doi.org/10.1016/j.biopha.2021.112517
Received 19 October 2021; Received in revised form 3 December 2021; Accepted 6 December 2021
Available online 9 December 2021

metabolism, excretion, and toxicity) results in lung tissue in several animal models, the path to drug development of molnupiravir was facilitated. Consultations with funding organizations, including NIAID (National Institute for Allergy and Infectious Disease) and DTRA (Defense Threat Reduction Agency) supported the development of molnupiravir (EIDD-2801). Development for the treatment and prophylaxis of aerosolized Venezuelan equine encephalitis virus (VEEV) was investigated in animal models. Existing in vivo and in vitro evidence suggested the effectiveness of EIDD-2801 (and its active metabolite EIDD-1931) against SARS, MERS and other human coronaviruses [15]. Therefore it was hypothesized that EIDD-2801 would also be useful for prophylaxis and treatment of infections caused by SAES-CoV-2. Herein, we summarize the therapeutic potential of RdRp inhibitors and highlight molnupiravir as a new small molecule drug for COVID-19 therapy.

2. Pathogenesis of COVID-19

To understand the pathogenic mechanisms and treatment targets of SARS-CoV-2, we need to review some aspects, such as the viral replication cycle, structure, and genome. The structure of a positive-stranded RNA CoV virus consists of an envelope and a nucleocapsid [16]. A SARS-CoV-2 virion possesses a 29.9-kb +ssRNA genome with a diameter of 50–200 nm [17]. It is the largest recognized RNA virus with a 3′-poly-A-tail and 5′-cap structure, having fourteen open reading frames (ORFs) encoding 27 separate proteins [18,19]. The structural proteins of the virion, include spike (S), envelope (E), nucleocapsid (N) and membrane (M). The RNA genome and the N protein are surrounded by the M, S and E proteins [20]. The virus-ACE2 receptor binding is facilitated by the S protein, which allows the virus to fuse with the host cell membrane [20]. SARS-CoV-2 utilizes the host transmembrane serine protease 2 (TMPRSS2) to modify the S protein in order to enter the target cells after binding to ACE2 [21] (Fig. 1). To carry out the virion-receptor binding leading to membrane fusion, the S protein of SARS-CoV-2 has two subunits; receptor-binding S1 and fusion protein S2. Cellular proteases cleave the spike protein at the cleavage site of S1-S2 to allow the attachment of the virus to the receptor and fusion with the cell membrane (Fig. 1). Analysis of the SARS-CoV-2 S protein showed a S1/S2 site insertion, which is absent in other strains of SARS-CoV [22]. It seems that, for effective spreading throughout the human host, as well as simple cell infection, this specific integration provides a gain-of-function alteration.

The viral RNA employs the host cell machinery to begin the synthesis of polypeptides and the replication of the viral genome, as well as creating the transcription-replication complex required to produce subgenomic RNAs and structural proteins (nucleocapsid, envelope) (Fig. 1). The envelope plays an essential role in the release, assembly and pathogenesis of the virus [23]. The precise roles of several small viral peptides have not yet been identified. Further studies are required to determine how the structural characteristics of SARS-CoV-2 affect the different pathogenic pathways. The symptoms of SARS-CoV-2 to some degree resemble those of the common cold, such as shortness of breath, coughing, and fever [24]; however, the infection may also result in SARS, multi-organ failure, and pneumonia, culminating in death in patients with co-existing conditions or advanced age (Fig. 2) [25]. In comparison with children and younger adults (6%), people aged over 60 years and those suffering from underlying conditions are more susceptible to the severe stage of COVID-19 (18.5%) [26]. The clinical information on deceased patients showed that the most frequent comorbidities of COVID-19 were diabetes mellitus (16.2–35%) and hypertension (24–75%) [24,27]. Of note, in COVID-19 patients treated with ACE inhibitors, more common comorbidities were reported [27,28]. The host cell-SARS-CoV-2 binding occurs via ACE2 receptor expressed on epithelial cells in the lungs, brain, kidney, intestines, and blood vessel endothelial cells [29]. ACE2 expression is significantly higher in hypertensive and diabetic patients treated with ACE inhibitors or angiotensin receptor blockers (ARBs) [29], thus increasing the overall severity of SARS-CoV-2.

The first pathological report on the severe form of COVID-19 showed that diffuse alveolar damage on both sides of the lungs led to the development of cellular fibromyxoid exudates [30]. The right lung showed hyaline membrane formation and lung cell shedding, suggesting ARDS (acute respiratory distress syndrome). The left lung revealed the formation of hyaline membrane as well as pulmonary edema, which implied early ARDS. In both lungs, interstitial mononuclear inflammatory infiltrates were also detected. Another investigation demonstrated that, during the progression of COVID-19, proteinuria and acute kidney injury could also occur. It was observed that ACE2 was higher in patients with COVID-19, and positive SARS-CoV nucleoprotein immunostaining was found in kidney tubules using a specific antibody [31]. In addition, limited interstitial mononuclear inflammatory infiltrates in the heart tissue were detected, indicating that cardiac impairment is not directly induced by this virus [30]. Aside from ARDS, during the infection process, inflammatory reactions were also triggered, leading to unrestrained inflammation in the lung. Because of cell damage and rapid viral replication, along with the virus-mediated downregulation of ACE2 and antibody-SARS-CoV-2 binding, these processes might result in excessive inflammatory responses [32]. The initial stages of rapid viral replication can cause endothelial and epithelial cell death, leading to the secretion of proinflammatory cytokines and chemokines (Fig. 3) [33]. Recently, an investigation evaluated the transcriptional responses caused by SARS-CoV-2 compared to other viral respiratory infections, to identify the transcriptional features responsible for the COVID-19 pathogenic effects [34]. They showed that SARS-CoV-2 affected the transcription of many genes. Despite viral replication, strong responses of IFN-I and IFN-III were not triggered by SARS-CoV-2, however the increased level of chemokines needed for recruitment of effector cells was detected. This inflammatory response was characterized by low levels of IFN-I and IFN-III in addition to increased chemokines and high levels of IL-6. Lowered innate antiviral defense plus increased inflammatory cytokine secretion is probably the driving force behind COVID-19 progression [34]. Furthermore, because the weakened immune reponse contributes to more replication of the virus, this can explain why the more severe forms of COVID-19 are commonly found in individuals suffering from comorbidities [35].

3. RdRp structure and function, and approved anti-RdRp drugs

A complex mechanism governs the replication of the viral genome involving multiple host and viral factors. When the virus has been introduced into the host cell, after uncoating, the virus begins to replicate, and subsequently to translate the viral proteins. Completion of these processes occurs in the cytoplasm for the majority of viruses via an RNA-dependent RNA polymerase (RdRp). There are some exceptions, one of the most important of which is the influenza virus. The RdRp is encoded as a multivalent enzyme by all members of the RNA virus family (except family Retroviridae), and acts as a nucleotidyl transferase (EC 2.7.7.48) [36]. RdRp produces nascent RNA strands by appending ribonucleotides to the 3'-hydroxyl end, so it synthesizes RNA molecules in a 5'-3' direction. Factors required for RdRp activity are one RNA template, two magnesium ions at the active site required for phosphodiester bond formation, ribonucleoside 5′-triphosphates (ATP, CTP, UTP and GTP) that are the constituents of nascent RNA. The RdRp structure contains two channels that connect with each other at the active site, including the primary channel to position the RNA template, and the secondary channel to position the input nucleoside triphosphate (NTP) [37–39].

Recently researchers have turned to studying RdRp as a promising therapeutic target against viral infections for multiple reasons(1) the critical function of this enzyme in replication of the majority of RNA viruses; (2) the enzyme has been conserved during the evolution of such viruses [40]; (3) lack of any homologous counterpart of this enzyme in mammalian cells; (4) availability of comprehensive information on the

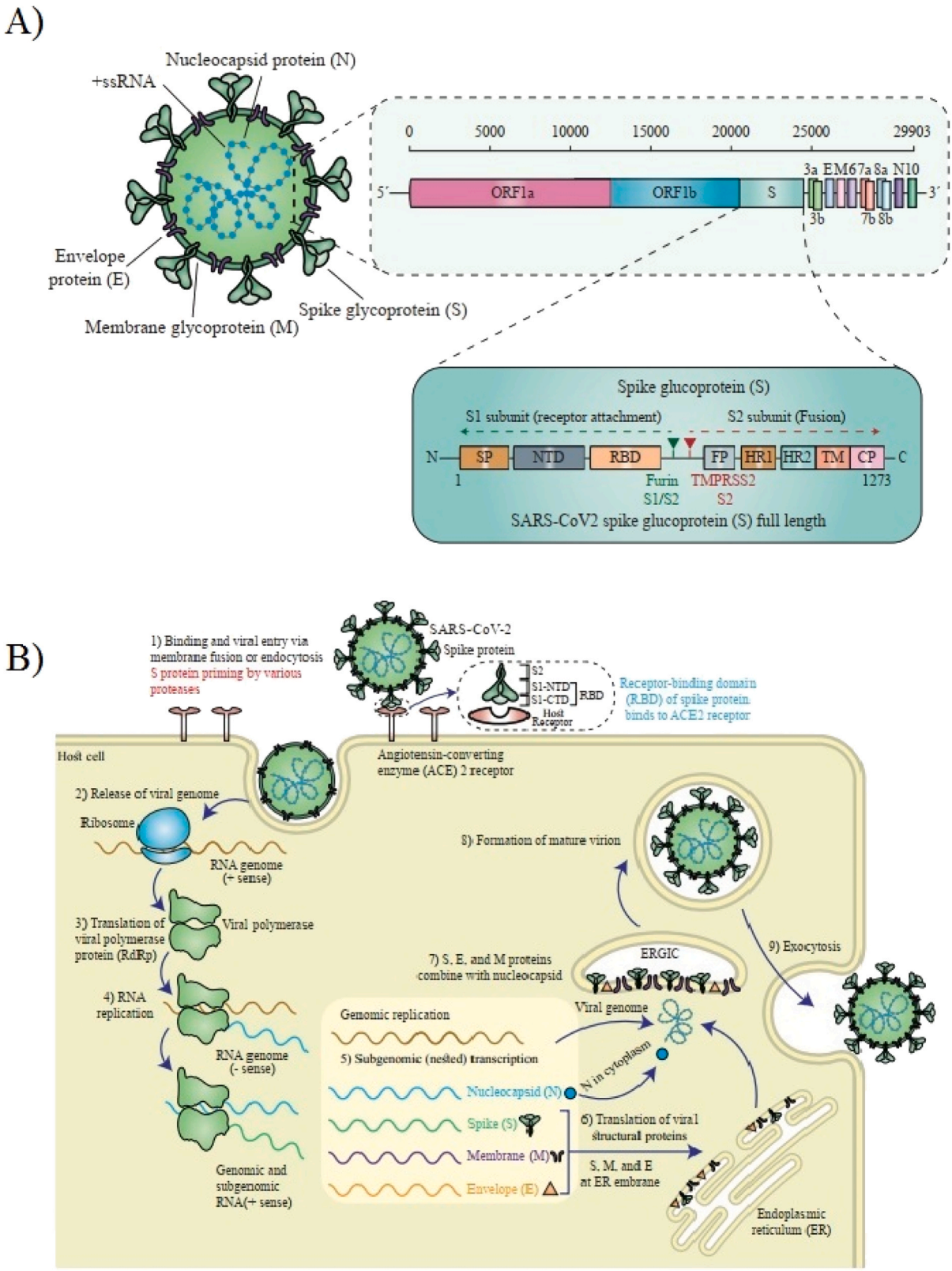

Fig. 1. Schematic representation of the structure and genome of coronavirus (A) and the replication cycle of SARS-CoV-2 (B). The structural proteins of the virus include proteins S, E, M, and N. Coronaviruses are approximately 100–160 nm in diameter, and enveloped with a lipid bilayer. This virus family has a large genome (positive-sense single-stranded RNA about 30 Kb length) that is bound to the nucleocapsid. The S proteins consist of subunits S1 and S2 and also TMPRSS2 and furin-related cleavage locations. S proteins are responsible for host cell-virus attachment following TMPRSS2-mediated activation. The S protein structure in the pre-fusion conformation, and genome plus C-terminal domain crystal structure of S protein combined with human ACE2 are shown in (A). The stages of coronavirus life cycle include (B) attachment and penetration (1), uncoating (2), gene expression (3 and 5–6) and replication (4), assembly (7−8), and release (9).

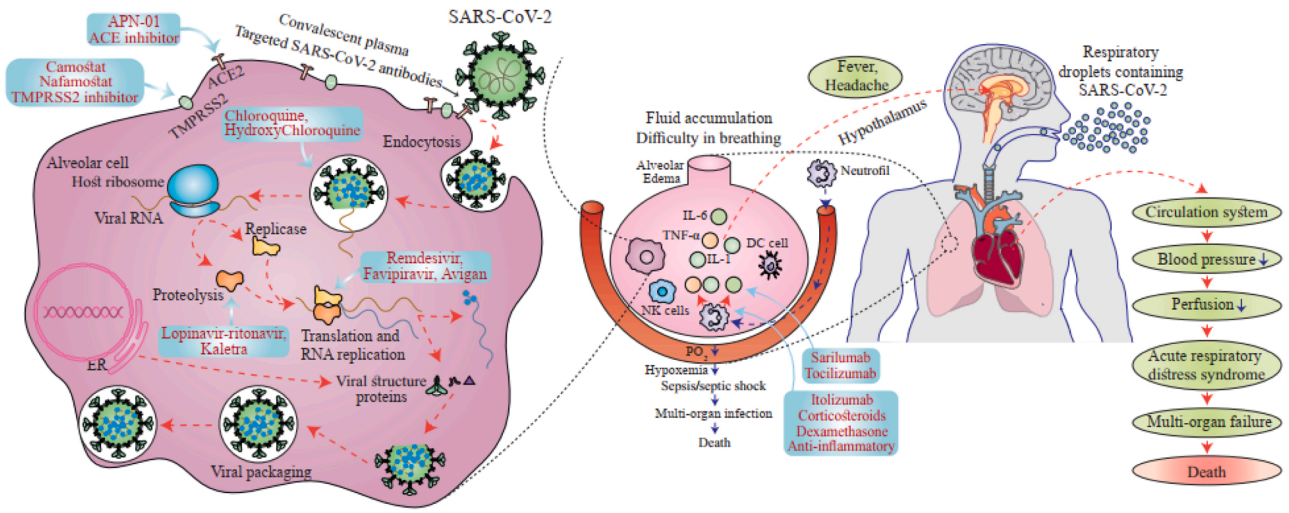

Fig. 2. Schematic view of SARS-CoV-2 replication and infection in host cells and possible therapeutic approaches through interfering with the replication cycle of SARS-CoV-2. This virus binds to the ACE2 receptor of host cells, followed by endocytosis, uncoating, replication by host cell machinery to form new viral components and eventually the release of virions via exocytosis. These processes could be impeded during any step through drug repurposing (highlighted in red). The virus triggers host immunity to express cytokines and inflammatory responses, and causes immune dysfunction by inducing or hindering different immune cells like neutrophils, macrophages, NK cells and dendritic cells, leading to multiple organ failure, septic shock, sepsis and even mortality. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

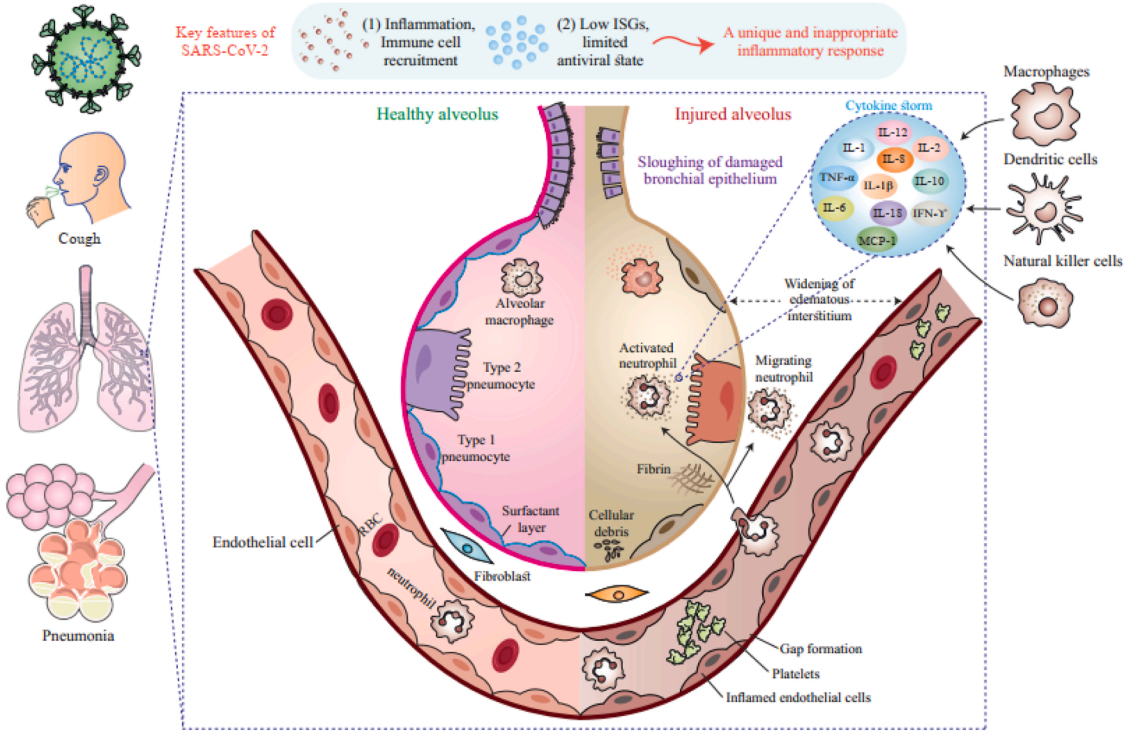

Fig. 3. Possible mechanism of cytokine storm development by SARS-CoV-2. There is an association between COVID-19 and elevated level of cytokines such as IL-6, TNF-α and IL-10. ISGs, IFN-triggered genes.

structure and function of this enzyme; (5) easy development and subsequent access to rapid biochemical screening using large libraries of compounds. On the other hand, there may be limitations to the use of RdRp inhibitors due to the emergence of drug-resistant variants of this enzyme, which highlights the potential need for other drugs to be used in combination approaches. Some successes in the field of RdRp inhibitors include, sofosbuvir, and remdesivir. Clinically approved sofosbuvir is prescribed to treat hepatitis C virus (HCV) infection. Remdesivir was first developed to treat Ebola virus infection, and was recently introduced as a treatment for hospitalized patients with severe COVID-19 [41]. Table 1 summarizes the investigational drugs in clinical trials, and antiviral drug approved by the US Food and Drug Administration (FDA), which target viral RdRP.

Table 1
FDA-approved anti-RdRp drugs.

Anti-RdRp drug	Approval Date or clinical status	Approved clinical used	Mechanism	Ref
Ribavirin	Approved in 1985	RSV, VHFs, HCV	Inhibits viral RNA polymerase and mRNA capping	[42]
Favipiravir	Approved in 2014 and randomized trial for SARS-CoV-2	Influenza A, Influenza B and Influenza C	Binds to catalytic site of viral RdRp and prevents the incorporation of NTs for viral genome replication	[43, 44]
Baloxavir	Approved in 2018	Influenza A and Influenza B	Binds to cap-dependent endonuclease in the PA subunit of the viral RdRp	[45]
Sofosbuvir	Approved in 2013	Genotype-2 or − 3 HCV	Inhibits HCV replication by binding to Mg2 + ions of viral RdRp	[46]
Remdesivir	Emergency use Authorization for SARS-CoV-2 in 2020	SARS-CoV-2	Competes with ATP and NTs for incorporation by viral RdRp	[47]
Dasabuvir	Approved in 2014 for use in combination with ritonavir/ ombitasvir/ paritaprevir/	Genotype-1 of HCV	Non-nucleoside RdRp inhibitor which binds to the palm domain of HCV RdRp and induces a conformational change	[48]

VHFs: Viral hemorrhagic fevers, **RSV**: Respiratory syncytial virus, **HCV**: hepatitis C virus,

4. Antiviral drugs for COVID-19 treatment

4.1. RdRp inhibitors

RNA-dependent RNA polymerase (RdRp) is a conserved enzymes in RNA viruses, with a crucial function in RNA virus replication [49–51]. Because of the conserved protein structure of RdRp, its inhibitors all show various degrees of antiviral activity [52–55]. When compared to coronaviruses, the RdRp protein of SARS-CoV-2 reveals an identical binding site with the same amino acid residues [39]. For instance, the structural similarity of RdRp in SARS-CoV-2 and SARS-CoV is 96%. Therefore, available potent compounds that inhibit RdRp have been extensively studied for the treatment of SARS-CoV-2.

4.2. Favipiravir

Favipiravir undergoes phosphoribosylation of the molecule within the tissue to produce the active form of the drug, favipiravir-RTP. The antiviral activity of favipiravir occurs by the following mechanisms. Firstly, favipiravir can serve as a RdRp substrate, because the enzyme recognizes it as a purine [56], therefore resulting in termination of protein synthesis in the virus (Figure 4). Secondly, favipiravir can be integrated into the viral RNA sequence thus preventing further replication [57]. These mechanisms of action, along with the conservation of the RdRp enzyme catalytic domain across different RNA viruses, explains the broad activity of this drug. Recently, favipiravir has been reported to trigger deadly mutagenesis during influenza virus replication in vitro, making it a virucidal agent [58]. Whether similar activity occurs against SARS-CoV-2 or not is unclear.

Yamada and colleagues investigated the ability of favipiravir to prevent SS-RNA virus replication under in vivo conditions [59]. In their study, favipiravir was used as a post-exposure prophylactic agent, and was orally administrated (for one week, beginning one hour after the inoculation of virus) in rabies virus-infected mice. Favipiravir considerably decreased the rate of virus positivity in the brain. In addition, in terms of post-exposure prophylactic efficacy, the agent showed similar efficacy to equine rabies virus immunoglobulin. It was concluded that, as a prophylaxis after exposure, favipiravir might be a suitable alternative to immunoglobulin [59]. The prophylactic potential of favipiravir before and after exposure needs more investigation in other viral diseases, including COVID-19. Initial human studies are crucial to develop effective therapies against COVID-19 [60]. The fast-track approval for marketing was issued by the Russian Ministry of Health for a favipiravir-derived agent in the treatment of COVID-19.

According to the results of a phase II/III clinical trial on sixty patients, the favipiravir-derived agent was tolerated and safe, and produced viral clearance in 62.5% of patients with COVID-19 after four days. On the fifth day, twice as many patients on the favipavir regimen were negative for SARS-CoV-2 by PCR, compared to the control patients ($p < 0.05$). After the interim findings of a phase II/III clinical trial, a conditional marketing approval was granted by the Russian Ministry of Health for favipiravir, making it the only approved oral treatment for moderately severe COVID- 19 [61]. The Food and Drug Administration (August 2020) approved an investigational new drug application (IND) for favipiravir as antiviral drug, produced by Appili Therapeutics [62]. This license allows the pharmaceutical industry to continue phase II clinical trials in the US, evaluating the effectiveness and safety of antiviral pills for COVID-19 pandemic control [62]. Currently, Appili is studying the use of favipiravir in a variety of clinical settings, with the goal of recruiting 760 patients in a phase II clinical trial in Canada and the United States [62]. Given the safety and mechanism of action, favipiravir is a promising candidate to treat COVID-19 [63]. Favipiravir has broad-spectrum activity against several SS-RNA viruses, is well tolerated in humans, and does not appear to cause resistance [64]. In terms of gastrointestinal complications, favipiravir has high safety compared to comparative drugs, including ritonavir/lopinavir, umifenovir, oseltamivir, and is comparable to placebo [65]. The antiviral activity of favipiravir at low doses is only mild-to-moderate. Therefore, relatively high doses of this drug are necessary to obtain significant antiviral activity [64]. Favipiravir can be associated with hyperuricemia, and could be teratogenic in pregnant females [65]. Thus, the administration of this drug should be under medical supervision. Further investigation of the preventative potential of favipiravir against viral infections, including COVID-19 is required. It could be useful to discover analogs and/or pro-drugs of favipiravir with better performance and higher safety margins [64]. Multiple clinical trials are being conducted for the evaluation of potential activity of favipiravir combined with other antiviral drugs to control the immune-induced pathology observed in COVID-19.

4.3. Remdesivir

Remdesivir is a RdRp inhibitor that has been tested against coronaviruses, which was initially introduced for the treatment of Ebola virus. According to one experimental study, early administration of remdesivir considerably decreased pulmonary damage and the viral load in SARS-CoV-2-infected monkeys [67–69].

Remdesivir interacts with the RdRp enzyme of the virus to induce delayed chain termination. It was shown to be active against several coronaviruses in vitro (e.g. MERS, SARS, bat-CoVs, contemporary human CoVs) [68]. Remdesivir is active against model β-coronavirus SARS, MERS, and murine hepatitis virus (MHV), suggesting a pan-CoV RdRp activity, even in the presence of proofreading exonuclease activity [70]. The delayed chain-termination is the main mechanism of action, based on biochemical findings using recombinant RdRp in respiratory syncytial virus [71–73]. Remdesivir suppresses viral replication (RSV and Ebola) in cellular experiments with an IC_{50} of 100 nM, while RNA polymerase II (Pol II) and mitochondrial RNAP in humans were not inhibited in the laboratory [71], showing about 500-fold

selectivity. The fact that nucleoside analogues are weak substrates for human polymerases, partly explains this selectivity [58]. In comparison with natural nucleotide pools, the triphosphate nucleotide analog, remdesivir was incorporated at high levels [74], probably explaining the potent antiviral performance by termination of premature RNA production.

After the findings of the NIAID and SIMPLE investigations, on May 1, 2020, the FDA approved remdesivir for use in hospitalized patients with severe COVID-19 under an Emergency Use Authorization (EUA). On August 28, 2020, the license was re-issued allowing the use of this drug in patients with non-severe COVID-19. On October 22, 2020, remdesivir became the first FDA-approved drug for management of the COVID-19 pandemic [75,76]. Findings from the Spinner et al. trial, SIMPLE, and NIAID all supported the final approval [77–79].

Shortly after the Chinese reports, the first COVID-19 patients appeared in the USA. One patient reported to urgent care in Snohomish County, Washington (January 20, 2020) with a 4-day history of cough and subjective fever, later to be established as the first positive COVID-19 patient in the USA [80]. On the seventh day of hospitalization and due to the worsening clinical condition, IV remdesivir was administered to the patient and no adverse effects were seen after infusion [80]. The next day, the clinical status improved, but any direct attribution to remdesivir was confounded by concurrent therapy, with supplemental oxygen, cefepime, vancomycin, guaifenesin, ibuprofen, and acetaminophen.

Of twelve cases diagnosed with definite SARS-CoV-2 infection, seven were hospitalized, and after worsening in COVID-19 severity, three were administered remdesivir. The duration of therapy was 4–10 days, the initial dose was 200 mg IV and the patients were given 100 mg by injection on each following day. All cases experienced gastrointestinal symptoms, including rectal bleeding, gastroparesis, vomiting, or nausea; however, treatment was maintained until respiratory symptoms improved, with all adverse effects showing resolution of signs [81]. Analysis of the safety or clinical efficacy of the treatment was precluded due to the absence of controlled randomized and the tiny sample size.

NIAID initiated a placebo-controlled, double-blind randomized phase III trial to assess the efficacy and safety of remdesivir compared to a placebo (NCT04280705) [82]. This investigation was developed on the basis of available Chinese trial evidence plus consultation with the World Health Organization (WHO) [83]. This study is still enrolling participants, assessing a primary outcome of disease severity on an eight-point ordinal scale, plus several secondary outcomes. Seventy-five clinical locations are predicted to take part in the trial, mainly in the US. Gilead Sciences conducted two comparative clinical trials to evaluate remdesivir versus standard care in patients with moderate or severe COVID-19 NCT04292899 [83]. The primary clinical outcomes including oxygen saturation and fever, as well as safety and efficiency of remdesivir (over five or ten days) compared to standard treatments, alone or combined, in the trial NCT04292730 [84].

After the FDA approval of remdesivir in the management of COVID-19, the WHO Solidarity trial detected no significant effect of remdesivir on death rates in patients with COVID-19 [85]. Furthermore, the study performed by Wang and colleagues showing no benefit after administration of remdesivir to patients with COVID-19 was not included during the process of remdesivir approval by FDA. Moreover, the occurrence of remdesivir-based adverse events has been reported in numerous hospitalized COVID-19 patients, thereby raising questions about the efficacy and safety of remdesivir in the management of COVID-19 [86].

4.4. Nitazoxanide

Nitazoxanide contains both a salicylamide and nitrothiazole moiety [87,88]. The properties of nitazoxanide could be explained by these moieties. For example, acetylbenzamide or salicylamide can function as an anti-infective against viruses, parasites, bacteria and fungi. It can also act as antipolymerase in hepatitis virus, and inhibit penetration of influenza virus, and the fusion with host cell membrane. It can act as an antioxidant, analgesic, affect interleukin generation, and modulate immune response [89]. The nitrothiazole moiety also shows anti-infective, anti-proliferative and anti-protozoal activity [90]. Nitrothiazole can inhibit oxidative stress [91] and impair redox reactions mediated by the pyruvate:ferredoxin oxidoreductase necessary for survival and energy metabolism in bacteria and anaerobic protozoa [87,88,92]. Moreover, nitazoxanide can potentiate host innate immunity and also inhibit different stages of the viral multiplication cycle [93,94]. In addition, nitazoxanide could boost the antiviral defense of host, with a low risk of antiviral resistance compared to drugs solely acting on viral proteins [89,95]. Several trials have tested nitazoxanide alone or combined with other antiviral drugs with promising results [94,96]. Nineteen COVID-19 clinical trials (ten trials using nitazoxanide alone and nine trials in combination with other antiviral drugs) have recently been registered in Brazil, Nigeria, Argentina, Mexico, Egypt, and US between April and August 2020 (https://clinicaltrials.gov/) (Nitazoxanide clinical trials, 2020). The dose of nitazoxanide is 600 mg two times per day, or even higher in most of the trials. Furthermore, nitazoxanide has been tested in combination with other potent drugs including ribavirin, ivermectin, and hydroxychloroquine. A recently performed *in silico* modelling study arrived at 73 combinations resulting from 32 potent drugs against SARS-CoV-2 and verified them in vitro investigations. The findings showed synergy between nitazoxanide combined with umifenovir, amodiaquine, or remdesivir, and strong antagonism in the combination of hydroxychloroquine and remdesivir [97]. Moreover, a combination therapy of nitazoxanide plus azithromycin [98] or hydroxychloroquine has been suggested [93].

4.5. Ribavirin

Ribavirin is a synthetic nucleoside guanosine analog, approved for the management of infections caused by RNA viruses, such as hantavirus, Lassa virus, hepatitis C virus (HCV), hepatitis E virus (HEV), and RSV. The combination of ribavirin and favipiravir has anti-coronavirus activity. The exonuclease enzyme is expressed by coronaviruses as a nonstructural protein 14 (nsp14-ExoN). The nsp14-ExoN has been shown to have RNA proofing functions [99]. Thus, coronaviruses are speculated to be resistant to nucleoside analogues. Experimental studies have revealed that ribavirin alone has poor anti-coronavirus activity, suggesting it must be combined with NIs against RNA viruses [100]. Synergistic effects of ribavirin combined with IFNα2b against MERS-CoV was seen in rhesus macaques, as well as in vitro, suggesting that IFN increases ribavirin activity at lower doses [101,102]. However, a combination of IFNα2b and ribavirin had no significant therapeutic benefit on clinical symptoms in five MERS-CoV-positive patients [103]. This combination therapy did increase the survival rate in twenty MERS patients on day 14 but not on day 28 [104]. In another study, the combination therapy of MERS patients with IFNβ1a or IFNα2a plus ribavirin provided no survival benefit [105]. Therefore, ribavirin does not provide clinical benefits for MERS-CoV or SARS-CoV patients. Although ribavirin therapy has been examined for the treatment of RSV and HCV in MERS and SARS patients, its side effects including anemia may be severe at high concentrations [106]. Based on the findings of a retrospective multicenter cohort investigation, there was no association between RBV/IFN-α treatment and the progression of non-severe COVID-19 to severe disease, or a reduction in the 30-day mortality rate [107]. It should be noted that the duration of hospitalization before discharge in COVID-19 patients might be extended following RBV/IFN-α treatment. Preclinical trials have confirmed the beneficial effects of RBV/IFN-α therapy for SARS and MERS [108,109], whereas this work did not observe any clinical benefits of RBV/IFN-α treatment (RBV and IFN-α alone or in combination) for COVID-19 patients [107]. Moreover, potential complications have been reported after ribavirin [110], which underscores the need for careful clinical investigation of the drug.

4.6. EIDD-1931

EIDD-1931 is a ribonucleoside analog which causes mutations in the RNA virus, and has recently been suggested to be effective for the management of COVID-19 [111,112]. EIDD-2801 is an isopropyl ester prodrug for EIDD-1931, which inhibits coronavirus replication in human and mouse airway epithelial cells [111,112]. Moreover, EIDD-1931 has been found to be useful for COVID-19 treatment [112]. It was also found to suppress remdesivir-resistant coronaviruses [112]. EIDD-1931 exists in two tautomeric forms [112]. One tautomer (EIDD-1931-t1) can mimic cytidine due to a single bonded N-OH group to carbon, whereas the other tautomer (EIDD-1931-t2) can mimic uridine because of an oxime group with a double bonded N-OH group to carbon (Fig. 4). Viral RdRp recognizes EIDD-1931-t1 as uridine instead of cytidine and thus places adenosine (instead of guanosine) in front of this base (Fig. 4) [111,112]. Based on a non-radioactive primer extension assay [102], EIDD-1931-triphosphate was incorporated as a U-analog at position + 4, G-analog at position + 3, and C-analogue at position +2 in the absence of any competing UTP or GTP [112]. According to recent evidence, the most stable base-pairing of EIDD-1931 occurs with G, and isoenergetic base pairs are formed between EIDD-2801 and G, U and A [113].

5. Molnupiravir structure and biological action

Molnupiravir (EIDD-2801/MK-4482) is a prodrug for the ribonucleoside analogue β-d-N4-hydroxycytidine (NHC; EIDD-1931), which has been shown to be useful in the treatment of RNA virus infections, such as influenza and pathogenic coronaviruses, as well as encephalitis alphaviruses (such as Eastern, Western and Venezuelan equine encephalitis viruses) [114–116]. In plasma, molnupiravir is rapidly cleaved to EIDD-1931, and after it distributes into different tissues, it is transformed into the 5′-triphosphate (Fig. 5) [114]. EIDD-1931 5′-triphosphate is a substrate for virally encoded RdRp and causes a catastrophic error in replication after integration into the emerging RNA chain [114,117]. When the rate of mutations in the virus goes beyond a tolerable threshold, the virus is extinguished.

Molnupiravir is well absorbed, and the plasma concentration of EIDD-1931 shows dose-dependent, linear pharmacokinetics after administration of 50–1600-mg doses [118]. The absorption rate is slower when taken with food, but the absorption extent (as evaluated by AUC_{inf}) is similar for both fasted and fed states [118]. Thus, concurrent use of molnupiravir with food does not provide synergistic therapeutic effects. The capacity-restricted uptake seen in pharmacokinetic investigations performed in animals, has not been seen in humans [114]. A multiple-ascending-dose study, with administration doses of 50–800 mg (BID), could be predicted from the exposure in a single-ascending-dose investigation [118]. EIDD-1931 has a half-life of 0.907–7.08 h, and is notably dose dependent. However, the use of BID dosage in the multiple-ascending-dose investigation was based on the *half-life* of the active antiviral compound, EIDD-1931 5′-triphosphate, measured both in vitro and in vivo [114,119]. In these studies, the intracellular EIDD-1931 5′-triphosphate *half life* ranged from 3 h in Huh-7 cells to 6.6 h in murine lung tissue. Molnupiravir was tolerated at a single dose up to 1600 mg, and 50–800 mg BID for 5.5 days [118]. In the single-ascending-dose study, headache was the most common adverse effect, with diarrhea in the multiple-ascending-dose study. In the single-ascending-dose study, numerous placebo-treated patients reported headaches (18.8% placebo, 12.5% molnupiravir), and in the multiple-ascending-dose investigation (7.1%), the same number of placebo-treated patients reported diarrhea, as did molnupiravir-administered patients. In this study one patient discontinued treatment due to a rash; however, no other patients reported significant adverse effects [118]. The absence of any dose-dependent changes in clinical laboratory findings, electrocardiography, vital signs, along with the tolerability data, showed the safety of molnupiravir at the duration and dose assessed in the investigation. Recruitment limitations (e.g. variation in body mass index) and possible metabolic differences in patients, such as gastrointestinal disease or diabetes may have led to variability in pharmacokinetic parameters. Although most patients were Caucasian and male due to the inclusion criteria as well as the geographic constraints of the study location, there were no identified race- or sex-based metabolic concerns. These findings supported the advancement of molnupiravir into phase II clinical trial in patients with high-risk RNA-viral infections, such as COVID-19 [118].

Molnupiravir is now being assessed in a phase III clinical trial for the treatment of COVID-19 [118]. The drug is bioavailable in oral form and could be administered to outpatients with early stages of COVID-19 to decrease the risk of hospitalization. *In vitro* findings showed that transition mutations of G-to-A and C-to-U were dose-dependently increased

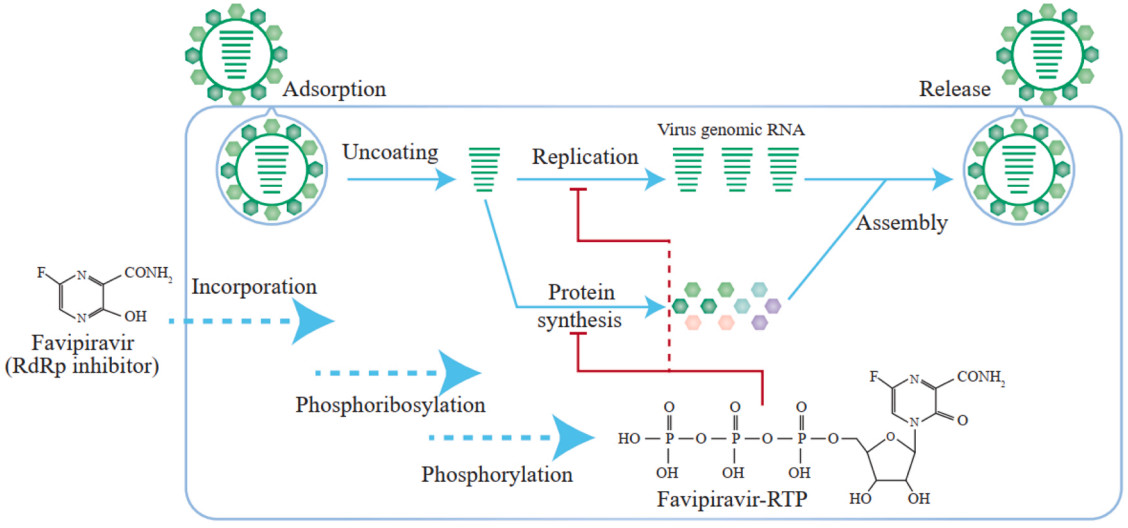

Fig. 4. Mechanism of action of antiviral effects of favipiravir (T-705). After incorporation into the cell, the drug is converted to favipiravir ribofuranosyl-5′-triphosphate (T-705-RTP) in the host cells. Favipiravir enters the purine nucleotide salvage pathways via purine phosphoribosyltransferase, and is then converted to favipiravir-triphosphate after phosphorylation by viral RNA-dependent RNA polymerase (RdRp). Hypoxanthine guanine phosphoribosyltransferase plays a role in favipiravir phosphorylation. T-705-RTP competes with purine nucleosides to be integrated into the virus RNA, and thus interferes with virus replication, by inhibiting the RdRp present in the RNA virus [66].

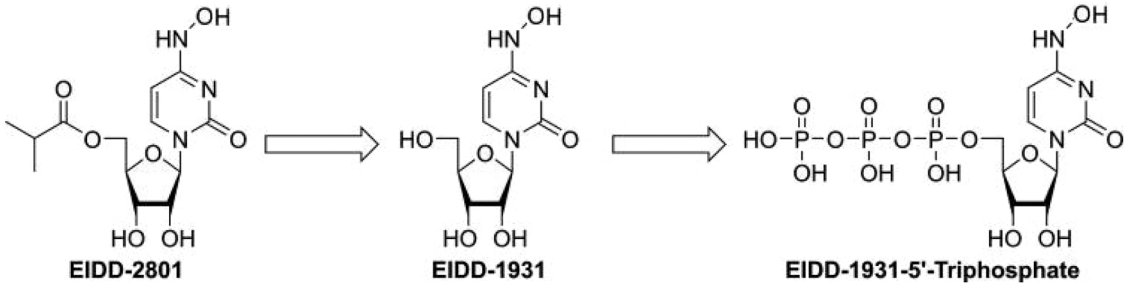

Fig. 5. Mulnopiravir is transformed to EIDD-1931 (NHC) rapidly in plasma, and then to active antiviral agent of EIDD-1931 5′-triphosphate following dispersion in different tissues through host kinases.

along with the antiviral activity against coronaviruses [116,117]. Thus, molnupiravir can be categorized as a mutagenic nucleotide analog. Fig. 6 shows the mechanism of the complex between molnupiravir and RdRp in SARS-CoV-2, highlighting the effect on RNA synthesis fidelity and efficiency.

6. Molnupiravir and COVID-19

NHC can suppress SARS-CoV-2, MERS-CoV and SARS-CoV with submicromolar EC_{50}, depending upon the cell line [116]. Also, molnupiravir could inhibit SARS-CoV-2 replication in humanized mice [116,120].

Sheahan and colleagues have reported that the NHC possesses a broad range of antiviral activity against SARS-CoV, SARS-CoV-2, MERS-CoV, and related zoonotic 2b/2c Bat-CoVs. It has good activity against a coronavirus with a resistance mutation to the nucleoside analog inhibitor remdesivir [116]. Both therapeutic and prophylactic use of EIDD-2801 prevented body weight loss and decreased viral load, and improved pulmonary performance in mice with SARS-CoV or MERS-CoV infections. The reduced replication of MERS-CoV under in vivo and in vitro conditions was related to an increased frequency of transition mutation in the viral cell RNA, but not in the host cell RNA, supporting a lethal mutagenesis activity in CoVs. The oral bioavailability and potency of NHC/EIDD-2801 against several coronaviruses suggest its beneficial use as an efficient drug against SARS-CoV-2 and other zoonotic coronaviruses [116].

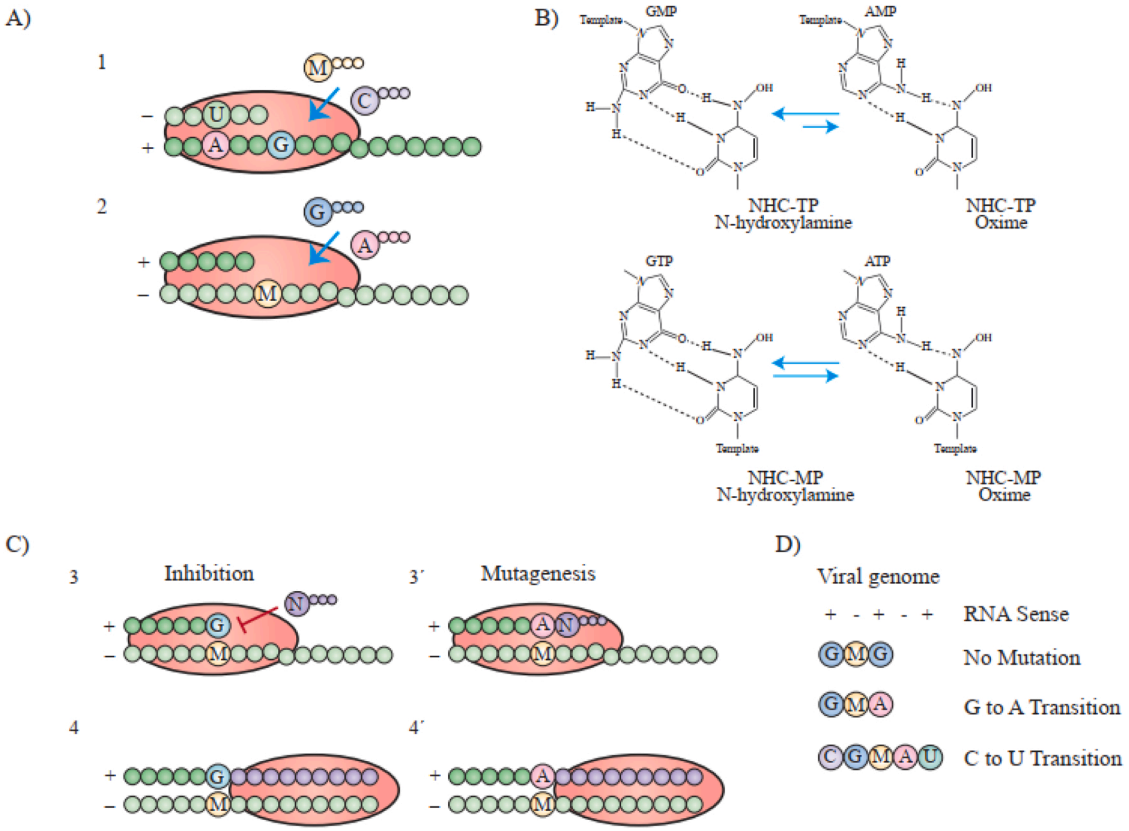

Fig. 6. NHC model of mutagenesis versus SARS-CoV-2; *(A)* Schematic incorporation of nucleotide into RNA primer (*gray circles*) or template (*white circles*) mediated by RNA-dependent RNA polymerase (*oval*) of SARS-CoV-2; minus and plus marks indicate RNA sense; U, G, C and A letters are natural nucleotide bases and M letter is molnupiravir; NTP triphosphate moiety is three *small circles*; (B) Tautomerization accounts for alternative base-pairing of NHC base moiety. N-hydroxylamine is predominant tautomer in the presence of NHC-TP substrate, but oxime and N-hydroxylamine forms are both found in the presence of template-embedded NHC-MP.; (C) Mechanism of template-embedded NHC-MP action for viral mutagenesis and inhibition. Incorporation of NTP into template NHC-MP is shown as *blue circles*.; (D) Mutagenic and inhibitory effects of NHC on viral replication. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

A recent study utilized a platform based on 'human lung-only' (LoM) mice to allow effective replication of human coronaviruses, such as MERS-CoV, SARS-CoV, SARS-CoV-2, and two pre-pandemic SARS-like bat coronaviruses in vivo [120]. The replication occurred in the bona fide human lung tissue within the mice, and needed no modification of host or virus. It was shown that bats harbor endogenous coronaviruses able to be directly transmitted to humans. Further evaluation of SARS-CoV-2 infection in human lung tissue revealed predominant infection of epithelial cells, such as ciliated airway cells and type II pneumocytes. Acute infection was cytopathic and mediated robust type I interferon and inflammatory responses. Moreover, both prophylactic and therapeutic administration of EIDD-2801 inhibited SARS-CoV-2 replication, and was promising for COVID-19 prevention and treatment [120].

Molnupiravir/EIDD-2801 received an IND for influenza in the U.K. and the U.S. as a basis for preliminary data on activity versus strongly pathogenic coronaviruses. Pre-IND sessions and coronavirus IND revisions (cross-referral to influenza IND) were accelerated by the FDA. The data on coronavirus activity combined with the influenza IND were the basis for package submission in the U.K. The U.K set up an Expert Working Group regarding COVID-19 studies. A guidance was published by the Medicines and Healthcare Products Regulatory Agency (MHRA) and also the Commission on Human Medicines (CHM) on the Clinical Trial Applications (CTAs) for COVID-19 studies (https://www.gov.uk/guidance/clinical-trials-applications-for-coronavirus-covid-19) to identify routes to provide prompt scientific advice, review, and possible approval for COVID-19 treatments. According to the MHRA, all routine elements such as Investigational Medicinal Product Dossier (IMPD), Study Protocol and Investigator's Brochure should be included in the CTA, and the final draft documents should undergo rolling review. The MHRA provided real-time review comments and authorized the research team to make the requested alterations before formally submitting the CTA. According to the MHRA recommendation, the Research Ethics Committee (REC) should not be convened in a routine way that involves the sequential review of rules and ethics in a single application, but rather Director of the Approvals Service for the Health Research Authority (HRA) should make a request for expedited review. According to the MHRA proposal, the single ascending dose (SAD) should be used entirely for the initial submission, and later elements such as cohorts of multiple ascending doses (MAD) can be added as placeholders to be modified on the next date. The REC and the MHRA both agreed an identical expedited review for the protocol amendment.

Multiple and single doses of molnupravir were assessed in a phase I clinical trial in healthy subjects, which included examination of food effects on pharmacokinetics [118]. After molnupiravir administration, EIDD-1931 was rapidly detected in plasma, with a median time to the peak of 1.00–1.75 h, and thereafter decreased with a geometric $t_{1/2}$ of about 1 h, along with a significantly slower removal phase after higher single or multiple doses [121]. The mean maximum detected concentration, as well as area under the time-concentration curve increased in a dose-dependent manner, and no further accumulation was found after multiple doses. When given along with food, a reduction was found in the absorption rate, but not in total exposure. Molnupiravir is generally well tolerated. Less than 50% of participants experienced any complication, and the incidence of adverse events was actually greater in the placebo group. About 93% of reported adverse effects were mild [121]. Although no severe adverse effects or significant changes in electrocardiography, vital signs or clinical laboratory findings were reported, one patient did not complete the study because of a rash. According to the results in animal models, plasma concentration exceeded the anticipated effective dose; thus before the maximal tolerated dose was reached, the dose escalation was discontinued [121]. Khoo and co-workers examined the safety and optimal dose of molnupiravir in patients with early symptomatic infection [122]. After screening and enrollment of 18 patients, they received oral doses of 300, 600 and 800 mg molnupiravir (BID, for five days) or a placebo. A dose was considered unsafe when the likelihood of 30% or higher dose-limiting toxicity (as primary outcome) compared to controls was 25% or more. Safety, virological response, pharmacokinetics, and clinical progression were the secondary outcomes. Molnupiravir was well tolerated at all three doses without any serious adverse effects. Of note, 4 out of 4, 4 out of 4, and 1 out of 4 of patients receiving 300, 600 or 800 mg of molnupiravir, respectively, as well as 5 out of 6 control subjects, reported at most one complication, and all of them were mild (equal to or lower than grade II). The probability of more than 30% excess toxicity over control subjects at 800 mg was predicted to be 0.9%. Because molnupiravir was safe and well-tolerated; 800 mg BID for five days was proposed for the Phase II trial [122].

In a double-blind and randomized phase III trial (MOVe-OUT), the safety and efficacy of molnupiravir were evaluated in non-hospitalized adult COVID-19 patients aged $\geq$ 18 years (n = 1850; NCT04575597, MK-4482-002) [123]. According to the interim analysis (n = 775) for this trial, the risk of hospitalization or death was significantly decreased up to 50% ($p = 0.0012$) on the 29th day. Based on the findings, 7.3% (28 of 385 patients receiving molnopiravir) were either hospitalized or deceased, compared with 14.1% (53 of 377) placebo patients, and there were no deaths in the molnopiravir-treated patients on the 29th day compared to 8 deaths in the placebo group. In addition, the time between the onset of illness, the specific variant of SARS-CoV-2 (delta, gamma, or mu), and the presence of underlying conditions had no influence on the molnupiravir efficacy. Possible adverse events (35% for molnupiravir versus 40% for placebo) and drug-induced adverse events (12% for molnupiravir versus 11% for placebo) were almost the same in both groups. Treatment discontinuation was lower in the molnupiravir group (1.3%) versus the placebo group (3.4%) [124,125]. Another double-blind randomized phase III trial (MOVe-IN, NCT04575584) evaluated the safety and efficacy of molnupiravir in hospitalized adult COVID-19 patients aged $\geq$ 18 years (n = 304; MK-4482–001), but it was terminated because the data from the interim analysis suggested that the clinical benefits of this drug were unlikely to be significant in hospitalized patients [123,126]. At the present time, a randomized, double-blind, placebo-controlled multicenter phase III trial (NCT04939428) with the large sample size of 1332 patients is underway (MOVe-AHEAD) to evaluate the safety and efficacy of molnupiravir to prevent the incidence of COVID-19 in non-infected adults living with an infected person. The trial hypothesized that molnopiravir would be effective in preventing definitive COVID-19 transmission compared to placebo until the 14th day [127]. Various pharmaceutical companies in India have recently reported limited findings from the interim analysis of phase III trials of molnupiravir among Indian COVID-19 patients aged 18–60 years suffering from mild symptoms (upper respiratory tract signs and/or fever with no hypoxia or dyspnea) or moderate symptoms (pneumonia without severe signs but with hypoxia and/or dyspnea, respiratory rate of $\geq$24 breaths per minute, cough with SpO_2 of $\leq$ 93% within the range of 90–93% on room air, or fever). In an open-label, multicenter randomized clinical trial (CTRI/2021/05/033739) carried out by Hetero Labs Limited of Hyderabad (India), the interim analysis was published on July 9, 2021 including patients with mild COVID-19 (n = 741). They evaluated the safety and efficacy of 800-mg molnupiravir (4 × 200 mg) twice a day (every 12 h) for five days in combination with SOC, versus SOC alone (as control) for five days after the onset of symptoms. Their interim findings were as follows: [1] clinically earlier improvement (2-fold reduction on WHO Clinical Progression Scale) in molnupiravir (63.4%) compared to SOC (22.3%) at the 5th day ($p < 0.0001$), molnupiravir (79.0%) compared to SOC (49.5%) at the 10th day ($p < 0.0001$), and molnupiravir (81.6%) compared to SOC (73.2%) at the 14th day ($p = 0.02$); [2] short-term improvement ($p = 0.0001$) in molnupiravir (median time = 8 days) compared to SOC (median time = 12 days); [3] more negative RT-PCR tests ($p < 0.0001$) in molnupiravir (77.4%) compared to SOC (26.1%) at the 5th day, in molnupiravir (94.0%) compared to SOC (57.2%) at the 10th day and in molnupiravir (97.0%) relative to SOC (85.2%) at 14th day; [4]

significant decrease in the duration of hospitalization ($p = 0.003$) in molnupiravir (1.9%) compared to SOC (6.2%) within 14 days. Neither group showed any mortality. The most prevalent complications were mild in severity, diarrhea, headache and nausea. All subjects completed the trial [128]. Overall, the interim findings from the ongoing Indian phase III trial indicated that there was a significant reduction in the duration of hospitalization for mild COVID-19 patients treated with molnupiravir compared to those treated with SOC alone; and there were no distinct drug-mediated adverse events, although the two groups exhibited no difference in mortality rate.

In another phase III trial examining the efficacy of molnupiravir in Indian patients with mild COVID-19 carried out by Optimus pharma (CTRI/2021/06/033992), the interim findings were reported on July 21, 2021. In a first report on 353 patients, the molnupiravir group (78.3%) exhibited more negative RT-PCR tests compared to the SOC arm (48.4%) at the 5th day [129]. According to a personal communication from Optimus Pharma, there was a significant increase in negative RT-PCR tests among the molnupiravir group (77.4%) compared to the SOC group (51.5%) at the 5th day ($p < 0.0001$), and in the molnupiravir group (99.5%) compared to the SOC group (69.5%) at the 10th day ($p < 0.0001$). It should be noted that there was no difference ($p = 0.62$) at the 14th day (99.5% for molnupiravir group versus 98.5% for SOC group) in the second interim analysis on 403 patients. There were earlier clinical improvements (minimal 1-fold improvement compared to the baseline on the WHO ordinal scale) in the molnupiravir group (79.0%) relative to the SOC group (51.3%) at the 5th day ($p < 0.0001$), and in the molnupiravir group (97.8%) relative to the SOC group (82.3%) at the 10th day 10 ($p < 0.0001$). It should be noted that there was no difference at 14th day. The number of hospitalizations was one case for the molnupiravir group and three cases for the SOC group, while the rate of adverse events was 6.5% for the molnupiravir group and 8.9% for the SOC group. Only one patient experienced a serious adverse event in the molnupiravir group and three patients in the SOC group. Overall, the interim findings from this ongoing Indian phase III trial suggested that there was an earlier clinical improvement (based on the negativity of RT-PCR) in the COVID-19 patients treated with molnupiravir than for those treated with SOC alone, and there were no distinct drug-mediated adverse events. Multiple other ongoing investigations on molnupiravir in patients with mild COVID-19 are being conducted by other Indian pharmaceutical companies, which have not yet reported their results [130,131].

The medicine regulatory authority of the UK has recently authorized the administration of the antiviral mulnopiravir to manage mild-to-moderate COVID-19 infections in adult patients with at least one risk factor for severe disease. According to a press release by the manufacturer of the drug (MSD), the interim findings from the phase III trial suggested that the administration of molnupiravir could decrease the risk of hospitalization or mortality up to approximately 50% among non-hospitalized adult patients suffering from mild to moderate COVID-19, who were at risk of poor outcomes [132]. Moreover, 28 (7.3%) patients (out of 385 participants) treated with molnupiravir and 53 (14.1%) patients (out of 377 participants) treated with placebo were hospitalized or died up to the 29th day post randomization. There were no deaths at the 29th day in the molnupiravir group, but there were 8 deaths in the placebo group. The independent data monitoring committee stopped the trial recruitment early owing to the positive results [132]. Table 2 lists various studies on molnupiravir in different models, ranging from in vitro to humans.

Table 2
Pre-clinical and clinical studies on Molnupiravir.

Model	Number of patients or animals (F/M)	Intervention	Follow up	Phase	Ref
In vivo: hamsters	SG hamsters (F)	Molnupiravir	4 days	–	[133]
In vitro: VeroE6 Huh7 HtAEC HsAEC		Remdesivir EIDD-1931 AT-511 GS-441524 IFN (β1and λ1)			[134]
In vitro: A549-hACE2		Molnupiravir Ribavirin Favipiravir			[135]
In vivo: Immunodeficient mice implanted with human lung tissue		Molnupiravir	2 days		[120]
Humans	103	Molnupiravir	28–30 days	Phase I	[122]
In vitro		Pibrentasvir Ombitasvir Sofosbuvir Remdesivir Favipiravir Molnupiravir AT-527			[136]
Humans	64 (53 M/ 11 F)	Molnupiravir	14 days	Phase 1	[118]
Humans	202 (98 M/ 104 F)	Molnupiravir	28 days	Phase 2a	[137]
In vivo: Syrian hamsters	12	Molnupiravir	4 days		[138]
In vivo: Ferrets		Molnupiravir	4 & 10 days		[139]
In vivo: Mice		Molnupiravir	5 days		[116]
In vitro: Human airway epithelial cell		Molnupiravir			

7. Conclusions

RdRp is an essential viral protein of RNA viruses, and has been found to be an important target for the development of antiviral drugs. Regarding the similarity of important drug-binding sites between SARS-CoV, MERS-CoV and SARS-CoV-2 RdRps, the repurposing of established RdRp inhibitors for SARS-CoV-2 treatment is a promising approach. Molnupiravir (formerly called EIDD-2801) can act as a RdRP inhibitor and as a prodrug for beta-D-N4-hydroxycytidine (EIDD-1931), thereby acquiring the ability to control SARS-CoV-2 infections. A ferret model demonstrated the prophylactic ability of this agent to prevent infection. According to two phase I clinical trials (NCT04746183 and NCT04392219), the oral administration of molnupiravir at therapeutic doses was well-tolerated and safe. In two phase II clinical trials (NCT04405570 and NCT04405739), five-days of oral administration of molnupiravir resulted in acceptable efficacy, shown by removal of nasopharyngeal virus in patients suffering from early and mild COVID-19. There are ongoing clinical trials at phases II/III, including NCT04575584 with a sample size of 304 and NCT04575597 with a sample size of 1850. Based on a recent trial (NCT04575597), molnupiravir produced a significant decrease in the risk of hospitalization or mortality among adult patients suffering from mild-to-moderate COVID-19. For the benefit of individual and general health, molnopiravir may be used clinically to rapidly treat COVID-19 patients and to prevent the transmission of SARS-CoV-2. Molnupiravir could effectively decrease the viral load in the nasopharynx, and displayed good tolerability and safety among COVID-19 patients treated with a short-term (five-day) regimen. The medicine regulators of the UK have recently authorized the administration of the antiviral mulnopiravir to manage the mild-to-moderate COVID-19 in adult patients with at least one risk factor for severe disease [132]. Mulnopiravir should be evaluated for the optima

ltiming and dosage, and for any interference with other agents prescribed to control COVID-19. The safety of molnopiravir is an important issue that needs to be clarified with large-scale epidemiological data obtained in the post-marketing phase. Mulnopiravir is the first oral antiviral drug that is directly effective in attenuating viral RNA and SARS-CoV-2 in the nasopharynx, which is well tolerated and with good safety. Oral antiviral drugs (such as molnupiravir) have a major advantage over injectable drugs (remdesivir) against COVID-19. The promising results of the initial trials to control COVID-19 give us hope for more successful clinical trials in the future.

Funding

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

HM involved in conception, design, statistical analysis and drafting of the manuscript. SMRH, MHP, MRH, and MKSH contributed in data collection and manuscript drafting. All authors approved the final version for submission.

CRediT authorship contribution statement

Hamed Mirzaei involved in conception, design, statistical analysis and drafting of the manuscript. Seyed Mohammad Reza Hashemian, Mohammad Hossein Pourhanifeh, Michael R Hamblin, and Mohammad Karim Shahrzad contributed in data collection and manuscript drafting. All authors approved the final version for submission.

Conflict of interest statement

Authors declare no conflicts of interest.

Data availability

Not applicable.

Acknowledgements

We thankful to the Alborz Darou Pharmaceutical Co. (Qazvin, Iran) for their supports.

References

[1] C.I. Paules, H.D. Marston, A.S. Fauci, Coronavirus infections-more than just the common cold, JAMA 323 (8) (2020) 707–708.
[2] H.D. Marston, G.K. Folkers, D.M. Morens, A.S. Fauci, Emerging viral diseases: confronting threats with new technologies, Sci. Transl. Med 6 (253) (2014), 253ps10.
[3] A.J. Brown, J.J. Won, R.L. Graham, K.H. Dinnon 3rd, A.C. Sims, J.Y. Feng, T. Cihlar, M.R. Denison, R.S. Baric, T.P. Sheahan, Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase, Antivir. Res. 169 (2019), 104541.
[4] V.D. Menachery, Jr Yount BL Jr., K. Debbink, S. Agnihothram, L.E. Gralinski, J. A. Plante, R.L. Graham, T. Scobey, X.Y. Ge, E.F. Donaldson, S.H. Randell, A. Lanzavecchia, W.A. Marasco, Z.L. Shi, R.S. Baric, A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence, Nat. Med. 21 (12) (2015) 1508–1513.
[5] M. Mohammadi, M. Shayestehpour, H. Mirzaei, The impact of spike mutated variants of SARS-CoV2 [Alpha, Beta, Gamma, Delta, and Lambda] on the efficacy of subunit recombinant vaccines, Braz. J. Infect. Dis. 25 (4) (2021), 101606.
[6] T. Donyavi, F. Bokharaei-Salim, H.B. Baghi, K. Khanaliha, M. Alaei Janat-Makan, B. Karimi, J. Sadri Nahand, H. Mirzaei, A. Khatami, S. Garshasbi, M. Khoshmirsafa, S. Jalal Kiani, Acute and post-acute phase of COVID-19: analyzing expression patterns of miRNA-29a-3p, 146a-3p, 155-5p, and let-7b-3p in PBMC, Int. Immunopharmacol. 97 (2021), 107641.
[7] S.A. Hosseini, F. Zahedipour, H. Mirzaei, R. Kazemi Oskuee, Potential SARS-CoV-2 vaccines: concept, progress, and challenges, Int. Immunopharmacol. 97 (2021), 107622.
[8] A. Zumla, J.F. Chan, E.I. Azhar, D.S. Hui, K.Y. Yuen, Coronaviruses - drug discovery and therapeutic options, Nat. Rev. Drug Disco 15 (5) (2016) 327–347.
[9] B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, H. Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, J. Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, C. Wang, A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19, N. Engl. J. Med. 382 (19) (2020) 1787–1799.
[10] F.X. Lescure, L. Bouadma, D. Nguyen, M. Parisey, P.H. Wicky, S. Behillil, A. Gaymard, M. Bouscambert-Duchamp, F. Donati, Q. Le Hingrat, V. Enouf, N. Houhou-Fidouh, M. Valette, A. Mailles, J.C. Lucet, F. Mentre, X. Duval, D. Descamps, D. Malvy, J.F. Timsit, B. Lina, S. van-der-Werf, Y. Yazdanpanah, Clinical and virological data of the first cases of COVID-19 in Europe: a case series, Lancet Infect. Dis. 20 (6) (2020) 697–706.
[11] A. Cortegiani, G. Ingoglia, M. Ippolito, A. Giarratano, S. Einav, A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19, J. Crit. Care 57 (2020) 279–283.
[12] J.-J. Yoon, M. Toots, S. Lee, M.-E. Lee, B. Ludeke, J.M. Luczo, K. Ganti, R.M. Cox, Z.M. Sticher, V. Edpuganti, D.G. Mitchell, M.A. Lockwood, A.A. Kolykhalov, A. L. Greninger, M.L. Moore, G.R. Painter, A.C. Lowen, S.M. Tompkins, R. Fearns, M. G. Natchus, R.K. Plemper, Orally efficacious broad-spectrum ribonucleoside analog inhibitor of influenza and respiratory syncytial viruses, Antimicrob. Agents Chemother. 62 (8) (2018) e00766-18.
[13] M. Toots, J.-J. Yoon, R.M. Cox, M. Hart, Z.M. Sticher, N. Makhsous, R. Plesker, A. H. Barrena, P.G. Reddy, D.G. Mitchell, R.C. Shean, G.R. Bluemling, A. A. Kolykhalov, A.L. Greninger, M.G. Natchus, G.R. Painter, R.K. Plemper, Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia, Sci. Transl. Med 11 (515) (2019) eaax5866.
[14] M. Toots, J.-J. Yoon, M. Hart, M.G. Natchus, G.R. Painter, R.K. Plemper, Quantitative efficacy paradigms of the influenza clinical drug candidate EIDD-2801 in the ferret model, Transl. Res 218 (2020) 16–28.
[15] T.P. Sheahan, A.C. Sims, S. Zhou, R.L. Graham, A.J. Pruijssers, M.L. Agostini, S. R. Leist, A. Schäfer, K.H. Dinnon, L.J. Stevens, J.D. Chappell, X. Lu, T.M. Hughes, A.S. George, C.S. Hill, S.A. Montgomery, A.J. Brown, G.R. Bluemling, M. G. Natchus, M. Saindane, A.A. Kolykhalov, G. Painter, J. Harcourt, A. Tamin, N. J. Thornburg, R. Swanstrom, M.R. Denison, R.S. Baric, An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice, Sci. Transl. Med 12 (541) (2020) eabb5883.
[16] A.R. Fehr, S. Perlman, Coronaviruses: an overview of their replication and pathogenesis, Methods Mol. Biol. 1282 (2015) 1–23.
[17] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.
[18] A. Wu, Y. Peng, B. Huang, X. Ding, X. Wang, P. Niu, J. Meng, Z. Zhu, Z. Zhang, J. Wang, J. Sheng, L. Quan, Z. Xia, W. Tan, G. Cheng, T. Jiang, Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China, Cell Host Microbe 27 (3) (2020) 325–328.
[19] D. Licastro, S. Rajasekharan, S. Dal Monego, L. Segat, P. D'Agaro, A. Marcello, Isolation and full-length genome characterization of SARS-CoV-2 from COVID-19 cases in northern Italy, J. Virol. 94 (11) (2020) e00543–20.
[20] C. Wu, Y. Liu, Y. Yang, P. Zhang, W. Zhong, Y. Wang, Q. Wang, Y. Xu, M. Li, X. Li, M. Zheng, L. Chen, H. Li, Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods, Acta Pharm. Sin. B 10 (5) (2020) 766–788.
[21] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pöhlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280, e8.
[22] J.A. Jaimes, J.K. Millet, G.R. Whittaker, Proteolytic cleavage of the SARS-CoV-2 spike protein and the role of the novel S1/S2 site, iScience 23 (6) (2020), 101212.
[23] D. Schoeman, B.C. Fielding, Coronavirus envelope protein: current knowledge, Virol. J. 16 (1) (2019) 69.
[24] M. Kumar, S. Al Khodor, Pathophysiology and treatment strategies for COVID-19, J. Transl. Med. 18 (1) (2020) 353.
[25] J.-L. Vincent, F.S. Taccone, Understanding pathways to death in patients with COVID-19, Lancet Respir. Med. 8 (5) (2020) 430–432.
[26] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138

hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069.
[27] L. Fang, G. Karakiulakis, M. Roth, Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir. Med 8 (4) (2020) e21-e.
[28] W.-J. Guan, N.-S. Zhong, Clinical characteristics of Covid-19 in China. Reply, N. Engl. J. Med. (2020) 382.
[29] Y. Wan, J. Shang, R. Graham, R.S. Baric, F. Li, Receptor recognition by the novel coronavirus from wuhan: an analysis based on decade-long structural studies of SARS coronavirus, J. Virol. 94 (7) (2020) e00127–20.
[30] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med 8 (4) (2020) 420–422.
[31] H. Su, M. Yang, C. Wan, L.X. Yi, F. Tang, H.Y. Zhu, F. Yi, H.C. Yang, A.B. Fogo, X. Nie, C. Zhang, Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China, Kidney Int. 98 (1) (2020) 219–227.
[32] Y. Fu, Y. Cheng, Y. Wu, Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools, Virol. Sin. 35 (3) (2020) 266–271.
[33] Y. Zhu, J. Li, Z. Pang, Recent insights for the emerging COVID-19: drug discovery, therapeutic options and vaccine development, Asian J. Pharm. Sci. 16 (1) (2021) 4–23.
[34] D. Blanco-Melo, B.E. Nilsson-Payant, W.C. Liu, S. Uhl, D. Hoagland, R. Møller, T. X. Jordan, K. Oishi, M. Panis, D. Sachs, T.T. Wang, R.E. Schwartz, J.K. Lim, R. A. Albrecht, B.R. tenOever, Imbalanced host response to SARS-CoV-2 drives development of COVID-19, Cell 181 (5) (2020) 1036–1045, e9.
[35] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, T. China Novel Coronavirus Investigating and Research, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.
[36] J. Černý, B. Černá Bolfíková, J.J. Valdes, L. Grubhoffer, D. Růžek, Evolution of tertiary structure of viral RNA dependent polymerases, PloS One 9 (5) (2014), e96070.
[37] Y. Zhao, T.S. Soh, J. Zheng, K.W. Chan, W.W. Phoo, C.C. Lee, M.Y. Tay, K. Swaminathan, T.C. Cornvik, S.P. Lim, P.Y. Shi, J. Lescar, S.G. Vasudevan, D. Luo, A crystal structure of the dengue virus NS5 protein reveals a novel inter-domain interface essential for protein flexibility and virus replication, PLoS Pathog. 11 (3) (2015), e1004682.
[38] H. Malet, N. Massé, B. Selisko, J.-L. Romette, K. Alvarez, J.C. Guillemot, H. Tolou, T.L. Yap, S. Vasudevan, J. Lescar, B. Canard, The flavivirus polymerase as a target for drug discovery, Antivir. Res. 80 (1) (2008) 23–35.
[39] Y. Gao, L. Yan, Y. Huang, F. Liu, Y. Zhao, L. Cao, T. Wang, Q. Sun, Z. Ming, L. Zhang, J. Ge, L. Zheng, Y. Zhang, H. Wang, Y. Zhu, C. Zhu, T. Hu, T. Hua, B. Zhang, X. Yang, J. Li, H. Yang, Z. Liu, W. Xu, L.W. Guddat, Q. Wang, Z. Lou, Z. Rao, Structure of the RNA-dependent RNA polymerase from COVID-19 virus, Science 368 (6492) (2020) 779–782.
[40] S.T. de Farias, A.P. dos Santos Junior, T.G. Rêgo, M.V. José, Origin and evolution of RNA-dependent RNA polymerase, Front. Genet. 8 (2017) 125.
[41] F. Picarazzi, I. Vicenti, F. Saladini, M. Zazzi, M. Mori, Targeting the RdRp of emerging RNA viruses: the structure-based drug design challenge, Molecules 25 (23) (2020) 5695.
[42] J.D. Graci, C.E. Cameron, Mechanisms of action of ribavirin against distinct viruses, Rev. Med. Virol. 16 (1) (2006) 37–48.
[43] Y. Furuta, T. Komeno, T. Nakamura, Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase, Proc. Jpn. Acad. Ser B 93 (7) (2017) 449–463.
[44] Y. Furuta, K. Takahashi, M. Kuno-Maekawa, H. Sangawa, S. Uehara, K. Kozaki, N. Nomura, H. Egawa, K. Shiraki, Mechanism of action of T-705 against influenza virus, Antimicrob. Agents Chemother. 49 (3) (2005) 981–986.
[45] T. Noshi, M. Kitano, K. Taniguchi, A. Yamamoto, S. Omoto, K. Baba, T. Hashimoto, K. Ishida, Y. Kushima, K. Hattori, M. Kawai, R. Yoshida, M. Kobayashi, T. Yoshinaga, A. Sato, M. Okamatsu, Y. Sakoda, H. Kida, T. Shishido, A. Naito, In vitro characterization of baloxavir acid, a first-in-class cap-dependent endonuclease inhibitor of the influenza virus polymerase PA subunit, Antivir. Res. 160 (2018) 109–117.
[46] E. De Clercq, G. Li, Approved antiviral drugs over the past 50 years, Clin. Microbiol. Rev. 29 (3) (2016) 695–747.
[47] D.S. Aschenbrenner, Remdesivir approved to treat COVID-19 amid controversy, Am. J. Nurs. 121 (1) (2021) 22–24.
[48] A.A. Eltahla, F. Luciani, P.A. White, A.R. Lloyd, R.A. Bull, Inhibitors of the hepatitis C virus polymerase; mode of action and resistance, Viruses 7 (10) (2015) 5206–5224.
[49] X. Xu, Y. Liu, S. Weiss, E. Arnold, S.G. Sarafianos, J. Ding, Molecular model of SARS coronavirus polymerase: implications for biochemical functions and drug design, Nucleic Acids Res. 31 (24) (2003) 7117–7130.
[50] A.J. Te Velthuis, J.J. Arnold, C.E. Cameron, S.H. Van Den Worm, E.J. Snijder, The RNA polymerase activity of SARS-coronavirus nsp12 is primer dependent, Nucleic Acids Res. 38 (1) (2010) 203–214.
[51] D.-G. Ahn, J.-K. Choi, D.R. Taylor, J.-W. Oh, Biochemical characterization of a recombinant SARS coronavirus nsp12 RNA-dependent RNA polymerase capable of copying viral RNA templates, Arch. Virol. 157 (11) (2012) 2095–2104.
[52] J.F. Drexler, F. Gloza-Rausch, J. Glende, V.M. Corman, D. Muth, M. Goettsche, A. Seebens, M. Niedrig, S. Pfefferle, S. Yordanov, L. Zhelyazkov, U. Hermanns, P. Vallo, A. Lukashev, M.A. Müller, H. Deng, G. Herrler, C. Drosten, Genomic characterization of severe acute respiratory syndrome-related coronavirus in European bats and classification of coronaviruses based on partial RNA-dependent RNA polymerase gene sequences, J. Virol. 84 (21) (2010) 11336–11349.
[53] I. Imbert, J.C. Guillemot, J.M. Bourhis, C. Bussetta, B. Coutard, M.P. Egloff, F. Ferron, A.E. Gorbalenya, B. Canard, A second, non-canonical RNA-dependent RNA polymerase in SARS Coronavirus, EMBO J. 25 (20) (2006) 4933–4942.
[54] J.S. Rest, D.P. Mindell, SARS associated coronavirus has a recombinant polymerase and coronaviruses have a history of host-shifting, Infect. Genet. Evol. 3 (3) (2003) 219–225.
[55] C.J. Gordon, E.P. Tchesnokov, J.Y. Feng, D.P. Porter, M. Götte, The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus, J. Biol. Chem. 295 (15) (2020) 4773–4779.
[56] Y. Furuta, B.B. Gowen, K. Takahashi, K. Shiraki, D.F. Smee, D.L. Barnard, Favipiravir (T-705), a novel viral RNA polymerase inhibitor, Antivir. Res 100 (2) (2013) 446–454.
[57] Z. Jin, L.K. Smith, V.K. Rajwanshi, B. Kim, J. Deval, The ambiguous base-pairing and high substrate efficiency of T-705 (Favipiravir) Ribofuranosyl 5'-triphosphate towards influenza a virus polymerase, PLoS One 8 (7) (2013), e68347.
[58] T. Baranovich, S.S. Wong, J. Armstrong, H. Marjuki, R.J. Webby, R.G. Webster, E. A. Govorkova, T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro, J. Virol. 87 (7) (2013) 3741–3751.
[59] K. Yamada, K. Noguchi, T. Komeno, Y. Furuta, A. Nishizono, Efficacy of favipiravir (T-705) in rabies postexposure prophylaxis, J. Infect. Dis. 213 (8) (2016) 1253–1261.
[60] S.M. Hashemian, T. Farhadi, A.A. Velayati, A review on remdesivir: a possible promising agent for the treatment of COVID-19, Drug Des. Dev. Ther. 14 (2020) 3215–3222.
[61] Ivashchenko A.A., Dmitriev K.A., Vostokova N.V., Azarova V.N, Blinow A.A, Egorova A.N., et al. AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. medRxiv. 2020.
[62] S.M. Hashemian, T. Farhadi, A.A. Velayati, A review on favipiravir: the properties, function, and usefulness to treat COVID-19, Expert Rev. Anti Infect. Ther. 19 (8) (2021) 1029–1037.
[63] Y.X. Du, X.P. Chen, Favipiravir: pharmacokinetics and concerns about clinical trials for 2019–nCoV infection, Clin. Pharmacol. Ther. 108 (2) (2020) 242–247.
[64] L. Delang, R. Abdelnabi, J. Neyts, Favipiravir as a potential countermeasure against neglected and emerging RNA viruses, Antivir. Res. 153 (2018) 85–94.
[65] V. Pilkington, T. Pepperrell, A. Hill, A review of the safety of favipiravir–a potential treatment in the COVID-19 pandemic? J. Virus Erad. 6 (2) (2020) 45–51.
[66] K. Shiraki, T. Daikoku, Favipiravir, an anti-influenza drug against life-threatening RNA virus infections, Pharmacol. Ther. 209 (2020), 107512.
[67] B.N. Williamson, F. Feldmann, B. Schwarz, K. Meade-White, D.P. Porter, J. Schulz, N. van Doremalen, I. Leighton, C.K. Yinda, L. Pérez-Pérez, A. Okumura, J. Lovaglio, P.W. Hanley, G. Saturday, C.M. Bosio, S. Anzick, K. Barbian, T. Cihlar, C. Martens, D.P. Scott, V.J. Munster, E. de Wit, Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2, Nature 585 (7824) (2020) 273–276.
[68] T.P. Sheahan, A.C. Sims, R.L. Graham, V.D. Menachery, L.E. Gralinski, J.B. Case, S.R. Leist, K. Pyrc, J.Y. Feng, I. Trantcheva, R. Bannister, Y. Park, D. Babusis, M. O. Clarke, R.L. Mackman, J.E. Spahn, C.A. Palmiotti, D. Siegel, A.S. Ray, T. Cihlar, R. Jordan, M.R. Denison, R.S. Baric, Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses, Sci. Transl. Med 9 (2017) 396.
[69] E.S. Amirian, J.K. Levy, Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses, One Health 9 (2020), 100128.
[70] N. Green, R.D. Ott, R.J. Isaacs, H. Fang, Cell-based assays to identify inhibitors of viral disease, Expert Opin. Drug Discov. 3 (6) (2008) 671–676.
[71] T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva, D. Siegel, M. Perron, R. Bannister, H.C. Hui, N. Larson, R. Strickley, J. Wells, K.S. Stuthman, S.A. Van Tongeren, N.L. Garza, G. Donnelly, A.C. Shurtleff, C.J. Retterer, D. Gharaibeh, R. Zamani, T. Kenny, B.P. Eaton, E. Grimes, L.S. Welch, L. Gomba, C.L. Wilhelmsen, D.K. Nichols, J.E. Nuss, E.R. Nagle, J.R. Kugelman, G. Palacios, E. Doerffler, S. Neville, E. Carra, M.O. Clarke, L. Zhang, W. Lew, B. Ross, Q. Wang, K. Chun, L. Wolfe, D. Babusis, Y. Park, K.M. Stray, I. Trancheva, J.Y. Feng, O. Barauskas, Y. Xu, P. Wong, M.R. Braun, M. Flint, L.K. McMullan, S.S. Chen, R. Fearns, S. Swaminathan, D.L. Mayers, C.F. Spiropoulou, W.A. Lee, S.T. Nichol, T. Cihlar, S. Bavari, Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys, Nature 531 (7594) (2016) 381–385.
[72] E.P. Tchesnokov, J.Y. Feng, D.P. Porter, M. Götte, Mechanism of inhibition of ebola virus RNA-dependent RNA polymerase by Remdesivir, Viruses 11 (2019) 4.
[73] P.C. Jordan, C. Liu, P. Raynaud, M.K. Lo, C.F. Spiropoulou, J.A. Symons, L. Beigelman, J. Deval, Initiation, extension, and termination of RNA synthesis by a paramyxovirus polymerase, PLoS Pathog. 14 (2) (2018), e1006889.
[74] C.J. Gordon, E.P. Tchesnokov, J.Y. Feng, D.P. Porter, M. Götte, The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus, J. Biol. Chem. 295 (15) (2020) 4773–4779.
[75] Food U., Administration D. FDA approves first treatment for COVID-19. 2020. 2020.
[76] Food U., Administration D. COVID-19 update: FDA broadens emergency use authorization for Veklury (remdesivir) to include all hospitalized patients for treatment of COVID-19. 2020. 2020.
[77] C.D. Spinner, R.L. Gottlieb, G.J. Criner, J.R. Arribas López, A.M. Cattelan, A. Soriano Viladomiu, O. Ogbuagu, P. Malhotra, K.M. Mullane, A. Castagna, L.Y.

A. Chai, M. Roestenberg, O.T.Y. Tsang, E. Bernasconi, P. Le Turnier, S.C. Chang, D. SenGupta, R.H. Hyland, A.O. Osinusi, H. Cao, C. Blair, H. Wang, A. Gaggar, D. M. Brainard, M.J. McPhail, S. Bhagani, M.Y. Ahn, A.J. Sanyal, G. Huhn, F. M. Marty, Effect of Remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial, JAMA 324 (11) (2020) 1048–1057.

[78] J.D. Goldman, D.C.B. Lye, D.S. Hui, K.M. Marks, R. Bruno, R. Montejano, C. D. Spinner, M. Galli, M.Y. Ahn, R.G. Nahass, Y.S. Chen, D. SenGupta, R. H. Hyland, A.O. Osinusi, H. Cao, C. Blair, X. Wei, A. Gaggar, D.M. Brainard, W. J. Towner, J. Muñoz, K.M. Mullane, F.M. Marty, K.T. Tashima, G. Diaz, A. Subramanian, I. GS-US–, Remdesivir for 5 or 10 days in patients with severe Covid-19, N. Engl. J. Med 383 (19) (2020) 1827–1837.

[79] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R. W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D. A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M.D. Oh, G. M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C. B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, M. ACTT-Study Group, Remdesivir for the treatment of Covid-19 - final report, N. Engl. J. Med 383 (19) (2020) 1813–1826.

[80] M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, C. Spitters, K. Ericson, S. Wilkerson, A. Tural, G. Diaz, A. Cohn, L. Fox, A. Patel, S. I. Gerber, L. Kim, S. Tong, X. Lu, S. Lindstrom, M.A. Pallansch, W.C. Weldon, H. M. Biggs, T.M. Uyeki, S.K. Pillai, T. Washington State -nCoV Case Investigation, First case of 2019 novel coronavirus in the United States, N. Engl. J. Med 382 (10) (2020) 929–936.

[81] The C-IT, S.A. Kujawski, K.K. Wong, J.P. Collins, L. Epstein, M.E. Killerby, et al., First 12 patients with coronavirus disease 2019 (COVID-19) in the United States, medRxiv (2020), 2020.03.09.20032896.

[82] COVID A. Treatment Trial (ACTT)-Full Text View-ClinicalTrials. gov ⟨https://clinicaltrials.gov/ct2/show⟩. NCT04280705.

[83] R.T. Eastman, J.S. Roth, K.R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik, M. D. Hall, Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19, ACS Cent. Sci. 6 (5) (2020) 672–683.

[84] R.T. Eastman, J.S. Roth, K.R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik, M. D. Hall, Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19, ACS Cent. Sci. 6 (5) (2020) 672–683.

[85] C. WHO Solidarity Trial, H. Pan, R. Peto, A.M. Henao-Restrepo, M.P. Preziosi, V. Sathiyamoorthy, Q. Abdool Karim, M.M. Alejandria, C. Hernández García, M. P. Kieny, R. Malekzadeh, S. Murthy, K.S. Reddy, M. Roses Periago, P. Abi Hanna, F. Ader, A.M. Al-Bader, A. Alhasawi, E. Allum, A. Alotaibi, C.A. Alvarez-Moreno, S. Appadoo, A. Asiri, P. Aukrust, A. Barratt-Due, S. Bellani, M. Branca, H. Cappel-Porter, N. Cerrato, T.S. Chow, N. Como, J. Eustace, P.J. García, S. Godbole, E. Gotuzzo, L. Griskevicius, R. Hamra, M. Hassan, M. Hassany, D. Hutton, I. Irmansyah, L. Jancoriene, J. Kirwan, S. Kumar, P. Lennon, G. Lopardo, P. Lydon, N. Magrini, T. Maguire, S. Manevska, O. Manuel, S. McGinty, M. T. Medina, M.L. Mesa Rubio, M.C. Miranda-Montoya, J. Nel, E.P. Nunes, M. Perola, A. Portolés, M.R. Rasmin, A. Raza, H. Rees, P. Reges, C.A. Rogers, K. Salami, M.I. Salvadori, N. Sinani, J. Sterne, M. Stevanovikj, E. Tacconelli, K. Tikkinen, S. Trelle, H. Zaid, J.A. Røttingen, S. Swaminathan, Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results, N. Engl. J. Med 384 (6) (2021) 497–511.

[86] Y. Wang, D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Y. Hu, G. Luo, K. Wang, Y. Lu, H. Li, S. Wang, S. Ruan, C. Yang, C. Mei, Y. Wang, D. Ding, F. Wu, X. Tang, X. Ye, Y. Ye, B. Liu, J. Yang, W. Yin, A. Wang, G. Fan, F. Zhou, Z. Liu, X. Gu, J. Xu, L. Shang, Y. Zhang, L. Cao, T. Guo, Y. Wan, H. Qin, Y. Jiang, T. Jaki, F.G. Hayden, P.W. Horby, B. Cao, C. Wang, Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial, Lancet 395 (10236) (2020) 1569–1578.

[87] J.F. Rossignol, Nitazoxanide: a first-in-class broad-spectrum antiviral agent, Antivir. Res. 110 (2014) 94–103.

[88] A. Hemphill, J. Mueller, M. Esposito, Nitazoxanide, a broad-spectrum thiazolide anti-infective agent for the treatment of gastrointestinal infections, Expert Opin. Pharm. 7 (7) (2006) 953–964.

[89] M. Krátký, J. Vinšová, Antiviral activity of substituted salicylanilides–a review, Mini Rev. Med Chem. 11 (11) (2011) 956–967.

[90] B. Colín-Lozano, I. León-Rivera, M.J. Chan-Bacab, B.O. Ortega-Morales, R. Moo-Puc, V. López-Guerrero, E. Hernández-Núñez, R. Argüello-Garcia, T. Scior, E. Barbosa-Cabrera, G. Navarrete-Vázquez, Synthesis, in vitro and in vivo giardicidal activity of nitrothiazole-NSAID chimeras displaying broad antiprotozoal spectrum, Bioorg. Med Chem. Lett. 27 (15) (2017) 3490–3494.

[91] S.I. El-Kowrany, A.E.A. El Ghaffar, Z.S. Shoheib, R.F. Mady, G.A.M. Gamea, Evaluation of nitazoxanide as a novel drug for the treatment of acute and chronic toxoplasmosis, Acta Trop. 195 (2019) 145–154.

[92] M. Kumar, S. Adhikari, J.G. Hurdle, Action of nitroheterocyclic drugs against Clostridium difficile, Int J. Antimicrob. Agents 44 (4) (2014) 314–319.

[93] Padmanabhan S. Potential dual therapeutic approach against SARS-CoV-2/COVID-19 with Nitazoxanide and Hydroxychloroquine 2020.

[94] P.R. Martins-Filho, J.A. Barreto-Alves, R. Fakhouri, Potential role for nitazoxanide in treating SARS-CoV-2 infection, Am. J. Physiol. Lung Cell. Mol. Physiol. 319 (1) (2020) L35–L36.

[95] D. Tilmanis, P. Koszalka, I.G. Barr, J.F. Rossignol, E. Mifsud, A.C. Hurt, Host-targeted nitazoxanide has a high barrier to resistance but does not reduce the emergence or proliferation of oseltamivir-resistant influenza viruses in vitro or in vivo when used in combination with oseltamivir, Antivir. Res. 180 (2020), 104851.

[96] D.B. Mahmoud, Z. Shitu, A. Mostafa, Drug repurposing of nitazoxanide: can it be an effective therapy for COVID-19? J. Genet Eng. Biotechnol. 18 (1) (2020) 35.

[97] T. Bobrowski, L. Chen, R.T. Eastman, Z. Itkin, P. Shinn, C.Z. Chen, H. Guo, W. Zheng, S. Michael, A. Simeonov, M.D. Hall, A.V. Zakharov, E.N. Muratov, Synergistic and antagonistic drug combinations against SARS-CoV-2, Mol. Ther. 29 (2) (2021) 873–885.

[98] M.T. Kelleni, Nitazoxanide/azithromycin combination for COVID-19: A suggested new protocol for early management, Pharm. Res. 157 (2020), 104874.

[99] E. Minskaia, T. Hertzig, A.E. Gorbalenya, V. Campanacci, C. Cambillau, B. Canard, J. Ziebuhr, Discovery of an RNA virus 3'->5' exoribonuclease that is critically involved in coronavirus RNA synthesis, Proc. Natl. Acad. Sci. USA 103 (13) (2006) 5108–5113.

[100] E.C. Smith, H. Blanc, M.C. Surdel, M. Vignuzzi, M.R. Denison, Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics, PLoS Pathog. 9 (8) (2013), e1003565.

[101] D. Falzarano, E. de Wit, A.L. Rasmussen, F. Feldmann, A. Okumura, D.P. Scott, D. Brining, T. Bushmaker, C. Martellaro, L. Baseler, A.G. Benecke, M.G. Katze, V. J. Munster, H. Feldmann, Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques, Nat. Med. 19 (10) (2013) 1313–1317.

[102] D. Falzarano, E. de Wit, C. Martellaro, J. Callison, V.J. Munster, H. Feldmann, Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin, Sci. Rep. 3 (2013) 1686.

[103] J.A. Al-Tawfiq, H. Momattin, J. Dib, Z.A. Memish, Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study, Int J. Infect. Dis. 20 (2014) 42–46.

[104] A.S. Omrani, M.M. Saad, K. Baig, A. Bahloul, M. Abdul-Matin, A.Y. Alaidaroos, G. A. Almakhlafi, M.M. Albarrak, Z.A. Memish, A.M. Albarrak, Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study, Lancet Infect. Dis. 14 (11) (2014) 1090–1095.

[105] S. Shalhoub, F. Farahat, A. Al-Jiffri, R. Simhairi, O. Shamma, N. Siddiqi, A. Mushtaq, IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study, J. Antimicrob. Chemother. 70 (7) (2015) 2129–2132.

[106] A. Zumla, J.F.W. Chan, E.I. Azhar, D.S.C. Hui, K.-Y. Yuen, Coronaviruses - drug discovery and therapeutic options, Nat. Rev. Drug Discov. 15 (5) (2016) 327–347.

[107] H. Li, N. Xiong, C. Li, Y. Gong, L. Liu, H. Yang, X. Tan, N. Jiang, Q. Zong, J. Wang, Z. Lu, X. Yin, Efficacy of ribavirin and interferon-α therapy for hospitalized patients with COVID-19: a multicenter, retrospective cohort study, Int. J. Infect. Dis. 104 (2021) 641–648.

[108] D. Falzarano, E. De Wit, A.L. Rasmussen, F. Feldmann, A. Okumura, D.P. Scott, D. Brining, T. Bushmaker, C. Martellaro, L. Baseler, A.G. Benecke, M.G. Katze, V. J. Munster, H. Feldmann, Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV–infected rhesus macaques, Nat. Med. 19 (10) (2013) 1313–1317.

[109] F. Chen, K.H. Chan, Y. Jiang, R.Y. Kao, H.T. Lu, K.W. Fan, V.C. Cheng, W.H. Tsui, I.F. Hung, T.S. Lee, Y. Guan, J.S. Peiris, K.Y. Yuen, In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds, J. Clin. Virol. 31 (1) (2004) 69–75.

[110] M.P. Muller, L. Dresser, J. Raboud, A. McGeer, E. Rea, S.E. Richardson, T. Mazzulli, M. Loeb, M. Louie, N. Canadian SARS Research, Adverse events associated with high-dose Ribavirin: evidence from the Toronto outbreak of severe acute respiratory syndrome, Pharmacother. J. Hum. Pharmacol. Drug Ther. 27 (4) (2007) 494–503.

[111] Z.M. Sticher, G. Lu, D.G. Mitchell, J. Marlow, L. Moellering, G.R. Bluemling, D. B. Guthrie, M.G. Natchus, G.R. Painter, A.A. Kolykhalov, Analysis of the potential for N 4-hydroxycytidine to inhibit mitochondrial replication and function, Antimicrob. Agents Chemother. 64 (2) (2020) e01719-e01719.

[112] T.P. Sheahan, A.C. Sims, S. Zhou, R.L. Graham, A.J. Pruijssers, M.L. Agostini, S. R. Leist, A. Schäfer, K.H. Dinnon, L.J. Stevens, J.D. Chappell, X. Lu, T.M. Hughes, A.S. George, C.S. Hill, S.A. Montgomery, A.J. Brown, G.R. Bluemling, M. G. Natchus, M. Saindane, A.A. Kolykhalov, G. Painter, J. Harcourt, A. Tamin, N. J. Thornburg, R. Swanstrom, M.R. Denison, R.S. Baric, An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice, Sci. Transl. Med 12 (2020) 541.

[113] N. Jena, Role of different tautomers in the base-pairing abilities of some of the vital antiviral drugs used against COVID-19, Phys. Chem. Chem. Phys. 22 (48) (2020) 28115–28122.

[114] G.R. Painter, R.A. Bowen, G.R. Bluemling, J. DeBergh, V. Edpuganti, P. R. Gruddanti, D.B. Guthrie, M. Hager, D.L. Kuiper, M.A. Lockwood, D.G. Mitchell, M.G. Natchus, Z.M. Sticher, A.A. Kolykhalov, The prophylactic and therapeutic activity of a broadly active ribonucleoside analog in a murine model of intranasal venezuelan equine encephalitis virus infection, Antivir. Res. 171 (2019), 104597.

[115] M. Toots, J.J. Yoon, R.M. Cox, M. Hart, Z.M. Sticher, N. Makhsous, R. Plesker, A. H. Barrena, P.G. Reddy, D.G. Mitchell, R.C. Shean, G.R. Bluemling, A. A. Kolykhalov, A.L. Greninger, M.G. Natchus, G.R. Painter, R.K. Plemper, Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia, Sci. Transl. Med. 11 (2019) 515.

[116] T.P. Sheahan, A.C. Sims, S. Zhou, R.L. Graham, A.J. Pruijssers, M.L. Agostini, S. R. Leist, A. Schäfer, K.H. Dinnon, L.J. Stevens, J.D. Chappell, X. Lu, T.M. Hughes, A.S. George, C.S. Hill, S.A. Montgomery, A.J. Brown, G.R. Bluemling, M.

G. Natchus, M. Saindane, A.A. Kolykhalov, G. Painter, J. Harcourt, A. Tamin, N. J. Thornburg, R. Swanstrom, M.R. Denison, R.S. Baric, An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice, Sci. Transl. Med. 12 (2020) 541.

[117] M.L. Agostini, A.J. Pruijssers, J.D. Chappell, J. Gribble, X. Lu, E.L. Andres, G. R. Bluemling, M.A. Lockwood, T.P. Sheahan, A.C. Sims, M.G. Natchus, M. Saindane, A.A. Kolykhalov, G.R. Painter, R.S. Baric, M.R. Denison, Small-molecule antiviral β-d-N (4)-hydroxycytidine inhibits a proofreading-intact coronavirus with a high genetic barrier to resistance, J. Virol. 93 (2019) 24.

[118] W.P. Painter, W. Holman, J.A. Bush, F. Almazedi, H. Malik, N. Eraut, M.J. Morin, L.J. Szewczyk, G.R. Painter, Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2, Antimicrob. Agents Chemother. 65 (2021) 5.

[119] B.I. Hernandez-Santiago, T. Beltran, L. Stuyver, C.K. Chu, R.F. Schinazi, Metabolism of the anti-hepatitis C virus nucleoside beta-D-N4-hydroxycytidine in different liver cells, Antimicrob. Agents Chemother. 48 (12) (2004) 4636–4642.

[120] A. Wahl, L.E. Gralinski, C.E. Johnson, W. Yao, M. Kovarova, K.H. Dinnon, H. Liu, V.J. Madden, H.M. Krzystek, C. De, K.K. White, K. Gully, A. Schäfer, T. Zaman, S. R. Leist, P.O. Grant, G.R. Bluemling, A.A. Kolykhalov, M.G. Natchus, F.B. Askin, G. Painter, E.P. Browne, C.D. Jones, R.J. Pickles, R.S. Baric, J.V. Garcia 3rd, SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801, Nature 591 (7850) (2021) 451–457.

[121] G.R. Painter, M.G. Natchus, O. Cohen, W. Holman, W.P. Painter, Developing a direct acting, orally available antiviral agent in a pandemic: the evolution of molnupiravir as a potential treatment for COVID-19, Curr. Opin. Virol. 50 (2021) 17–22.

[122] S.H. Khoo, R. Fitzgerald, T. Fletcher, S. Ewings, T. Jaki, R. Lyon, N. Downs, L. Walker, O. Tansley-Hancock, W. Greenhalf, C. Woods, H. Reynolds, E. Marwood, P. Mozgunov, E. Adams, K. Bullock, W. Holman, M.D. Bula, J. L. Gibney, G. Saunders, A. Corkhill, C. Hale, K. Thorne, J. Chiong, S. Condie, H. Pertinez, W. Painter, E. Wrixon, L. Johnson, S. Yeats, K. Mallard, M. Radford, K. Fines, V. Shaw, A. Owen, D.G. Lalloo, M. Jacobs, G. Griffiths, Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose-escalating, randomized controlled study. The, J. Antimicrob. Chemother. 76 (2021) 3286–3295.

[123] Sharp M. Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482–002). 2020.

[124] Ridgeback's Ma. Merck and Ridgeback's investigational oral antiviral molnupiravir reduced the risk of hospitalization or death by approximately 50 percent compared to placebo for patients with mild or moderate COVID-19 in positive interim analysis of phase 3 study. Accessed 20 Oct 2021.

[125] E. Mahase, Covid-19: Molnupiravir reduces risk of hospital admission or death by 50% in patients at risk, British Medical Journal Publishing Group, 2021 (MSD reports).

[126] Ridgeback's Ma. Merck and Ridgeback biotherapeutics provide update on progress of clinical development program for molnupiravir, an investigational oral therapeutic for the treatment of mild-to-moderate COVID-19 - Merck.com. Last accessed on October 20, 2021.

[127] Sharp M. Study of MK-4482 for Prevention of Coronavirus Disease 2019 (COVID-19) in Adults (MK-4482–013). 2021.

[128] India H. Hetero Announces Interim Clinical Results from Phase III Clinical Trials of Molnupiravir conducted in India. 9th July 2021.

[129] India. Optimus announces interim clinical results from phase III clinical trials of molnupiravir conducted in India. 21 July, 2021.

[130] Search result, clinical trials registry - India (CTRI). CTRI Last accessed on October 20, 2021.

[131] A.K. Singh, A. Singh, R. Singh, A. Misra, Molnupiravir in COVID-19: a systematic review of literature, Diabetes Metab. Syndr. Clin. Res. Rev. 15 (2021), 102329.

[132] E. Mahase, Covid-19: UK becomes first country to authorise antiviral molnupiravir, Br. Med. J. Publ. Group (2021) n2697.

[133] R. Abdelnabi, C.S. Foo, S. De Jonghe, P. Maes, B. Weynand, J. Neyts, Molnupiravir inhibits the replication of the emerging SARS-CoV-2 variants of concern (VoCs) in a hamster infection model, J. Infect. Dis. 224 (2021) 749–753.

[134] T.N.D. Do, K. Donckers, L. Vangeel, A.K. Chatterjee, P.A. Gallay, M.D. Bobardt, J. P. Bilello, T. Cihlar, S. De Jonghe, J. Neyts, D. Jochmans, A robust SARS-CoV-2 replication model in primary human epithelial cells at the air liquid interface to assess antiviral agents, Antivir. Res. 192 (2021), 105122.

[135] S. Zhou, C.S. Hill, S. Sarkar, L.V. Tse, B.M.D. Woodburn, R.F. Schinazi, T. P. Sheahan, R.S. Baric, M.T. Heise, R. Swanstrom, β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells, J. Infect. Dis. 224 (3) (2021) 415–419.

[136] X. Wang, C.Q. Sacramento, S. Jockusch, O.A. Chaves, C. Tao, N. Fintelman-Rodrigues, M. Chien, J.R. Temerozo, X. Li, S. Kumar, W. Xie, D.J. Patel, C. Meyer, A. Garzia, T. Tuschl, P.T. Bozza, J.J. Russo, T. Souza, J. Ju, Combination of antiviral drugs to inhibit SARS-CoV-2 polymerase and exonuclease as potential COVID-19 therapeutics, bioRxiv Prepr. Serv. Biol. (2021).

[137] Fischer W., Eron JJ, Holman W., Cohen MS, Fang L., Szewczyk LJ, et al. Molnupiravir, an Oral Antiviral Treatment for COVID-19. medRxiv: the preprint server for health sciences. 2021.

[138] K. Rosenke, F. Hansen, B. Schwarz, F. Feldmann, E. Haddock, R. Rosenke, K. Barbian, K. Meade-White, A. Okumura, S. Leventhal, D.W. Hawman, E. Ricotta, C.M. Bosio, C. Martens, G. Saturday, H. Feldmann, M.A. Jarvis, Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model, Nat. Commun. 12 (1) (2021) 2295.

[139] R.M. Cox, J.D. Wolf, R.K. Plemper, Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets, Nat. Microbiol. 6 (1) (2021) 11–18.