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Update on Remdesivir in the Treatment of Novel Coronavirus Pneumonia

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Abstract: Worldwide epidemic prevention and control remain under significant stress due to the global novel coronavirus disease 2019 (COVID-19) pandemic and the ongoing emergence of variants like Omicron. The total confirmed COVID-19 cases

globally as of now topped 620 million, while the total number of fatalities exceeded 6.6 million. The screening, drug discovery, and clinical development of novel treatments are still the hottest subjects in the treatment of COVID-19, and scientists throughout the world are dedicated to identifying prospective therapeutic agents to treat COVID-19 patients, including the new uses of old medications. Remdesivir, a COVID-19 therapeutic medication developed by Gilead Sciences, exerts antiviral effects by suppressing the RNA-dependent RNA polymerase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Remdesivir has maintained high inhibitory activity against all existing SARS-CoV-2 variants, including the Omicron variant. We systematically retrieved Web of Science, CNKI, PubMed, and *Clinicaltrials.gov* to gather information related to Remdesivir on COVID-19 treatment. In this review, we summarized and reviewed the drug targets for COVID-19 management, especially the mechanism of action and research progress of Remdesivir. More importantly, the outcome of current clinical trials of Remdesivir alone and when combined with other drugs for COVID-19 management was analyzed, and the limitations and clinical significance of each clinical trial were evaluated. From this review, we can understand the development progress of Remdesivir for COVID-19 management, deepens the current understanding of Remdesivir research status, and gives us some inspiration for better drug use in COVID-19 management.

Keywords: COVID-19; SARS-CoV-2; Remdesivir; Clinical trials; RNA-dependent RNA polymerase

1. Introduction

With the global pandemic of novel coronavirus disease 2019 (COVID-19) epidemic and the continuous emergence of variants such as Omicron, global epidemic prevention and control remain challenging. Currently, the cumulative number of new COVID-19 cases worldwide is more than 620 million, and the fatality rate is more than 6.6 million [1, 2], and the numbers are still increasing. In addition, many reports have shown that the pandemic has severely impacted multiple countries worldwide, with India being one of the worst affected countries [3]. The exponential increase in COVID-19 infection cases and deaths in most countries results from a few waves attacking at different time points due to COVID-19 evolution. The fight against COVID-19 infection in Malaysia started in 2020, when the initial detected case involved three Chinese nationals in close contact with a COVID-19-positive patient [4]. Since then, the number of confirmed cases in Malaysia has increased exponentially to the current cases

at 5,122,568 and 37,165 fatalities (based on statistics shown by KKMNOW on 19 August 2023) [5]. Malaysia managed to swiftly control the spread of COVID-19 infection with strict healthcare guidelines, contact tracing, and the national vaccination program. One of the stringent measures implemented in Malaysia was the movement control order (MCO) [6]. It had a domino impact on both society and individual levels, ranging from economic to psychological dimensions [7]. Malaysia stepped into the transition of the COVID-19 pandemic to the endemic phase on 1 April 2023 [8].

Various control and prevention strategies such as vaccination, contact tracing, restricted traveling and boarder closure, physical distancing, wearing a face mask, practicing good hand hygiene, and other measures were employed by most countries to mitigate the risk of COVID-19 infection while ensuring the good health of people during the pandemic [3, 9-15]. The World Health Organization (WHO) introduced public health measures emphasizing self-care and health awareness [16, 17]. Hand hygiene was given great importance, and the public advocated using hand sanitizers. The use of face masks in public places increased significantly. People with multiple concurrent illnesses became more aware of their primary illnesses through improved diet and exercise regimens. People have become more open to receiving and acting on public health information. The pandemic lockdown reduced the spread of coronavirus transmission and indirectly reduced the rate of hospital admissions for community-acquired respiratory infections. There was an unprecedented global race in healthcare, innovation, and technology development. Artificial intelligence, including robots and drones, was rapidly developed and applied to healthcare, food, and delivery services to minimize physical contact between people [18].

In terms of the risk of getting severe COVID-19 infection, a study performed quantitative analysis of the top 50 countries affected with COVID-19 reported that countries with high numbers of older people aged 65 years old and above pose a significant risk of having high case fatality rate (CFR) from COVID-19. At the same time, there was no significant relationship between gender differences and smoking prevalence with COVID-19 CFR and mortality rate [19].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant is hallmarked by its rapid transmission, high virulence, and host immune evasion property [20-23]. There have been a total of five variants of concern (VOC) identified since the COVID-19 pandemic began: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) [24]. One of the prominent variants is the Delta variant (B.1.617.2), which was first discovered in India. It attracted worldwide attention

due to its faster spread than the original strain Alpha variant (B.1.1.1.7) [25]. The Omicron variant is the most infectious so far, which began to appear at the end of 2021 and spread twice as quickly as Delta variants [26].

BNT162b2 (Pfizer-BioNTech), Coronavacn (Sinovac), Covishield (AstraZeneca), mRNA-1273 (Moderna), Ad26.CoV2.S (Janssen) and Covaxin (Bharat Biotech) were among the vaccines granted emergency use by WHO. However, in the face of new variants, the protection rate of COVID-19 vaccines decreases, and the activity of antibody drugs decreases [27]. According to current research, the risk of relapse and severe side effects after vaccination is low. Most patients with autoimmune diseases show a good antibody response to vaccination, especially after the second dose of the vaccine [28]. In addition, most countries in Southeast Asia consider that the benefits of COVID-19 vaccination for pregnant women far outweigh the risks. The guidelines and recommendations for pregnant women are in place in countries including Malaysia and Singapore [29]. In addition, booster vaccination further improves vaccine efficacy and reduces the risk of infection, disease severity, hospitalization rates, and deaths [30].

Fever and respiratory symptoms are the most typical signs of COVID-19 infection. However, it can also affect the gastrointestinal system (GIT), causing symptoms including diarrhea, nausea, and/or vomiting, as well as abdominal discomfort [31]. This virus is airborne and transmitted from person to person, thus causing a fast spread worldwide [32]. The doubts on the vaccine efficacy are raised following the emergence and wide spreading of new variants. Neutralizing antibodies were shown to decrease against infection with BQ and XBB subvariants in comparison to infections caused by other variants. Fortunately, current evidence still demonstrates the efficacy against Omicron. Nonetheless, the treatment options available and the efficacy of vaccines against the latest circulating variant of SARS-CoV-2 should be periodically assessed to ensure the greatest protection to the public from this pandemic attack [33].

Extensive research has sought effective treatment with promising safety profiles for COVID-19. Repurposing drugs for COVID-19 infections is deemed to be an alternative to solve the urgency of current circumstances since it is time-consuming and challenging to develop a novel drug specifically for COVID-19. Recent research has shown that antiviral agents such as Molnupiravir and Remdesivir offer significant advantages in tackling COVID-19 infections. Also, immunomodulators can be particularly useful in treating COVID-19 infection by carefully examining the

mechanism of action of immunomodulators in hosts and their targeted immune system pathways. For example, anakinra and baricitinib, previously employed for rheumatoid arthritis treatment, can be repurposed to treat COVID-19 infection since these drugs can reduce inflammation in host cells [34]. Several biotherapeutics and chemotherapeutics, including Paxlovid (Nirmatrelvir & Ritonavir) fixed-dose combination, chloroquine and hydroxychloroquine, Nirmatrelvir and Ritonavir fixed-dose combination, Molnupiravir, Favipiravir, Remdesivir (Vekulary/Covifor) fixed-dose combination, methylprednisole, Ivermectin and Infliximab (Remsima®) fixed-dose have also been studied for their potential to be repurposed for the treatment of COVID-19 based on their anti-viral and anti-inflammation properties [35]. In battling long-term COVID-19 infection, a recent study showed that probiotics could be an adjunct therapy for COVID-19 treatment and its associated psychological symptoms. The possible anti-inflammatory effects are probable via a direct reduction in the plasma proinflammatory cytokine concentrations or indirectly through the restoration of gut permeability and inhibition within the kynurenine pathway [36].

Antiviral drugs that are particularly useful against various COVID-19 variants are urgently in need. Small-molecule antiviral drugs that target the key proteins in the viral cycle have become the main focus [37]. Four antiviral drugs have been approved for marketing or clinically marketed worldwide, consisting of Remdesivir (RDV), Molnupiravir (MOV), Paxlovid (Nirmatrelvir/Ritonavir, NMV/RTV, PF-07321332), and Ensitrelvir (S-217622). However, further investigation is necessary to investigate whether the above four drugs are effective against the SARS-CoV-2 virus. Previously screened COVID-19 antivirals such as Lopinavir/Ritonavir (LPV/RTV), hydroxychloroquine, and newly developed vaccines also have different clinical application characteristics. It should be noted that Remdesivir is the first drug approved by FDA for treating COVID-19 patients [38].

Several reports have been published in the New England Journal of Medicine (NEJM) on the 2019-nCoV cases. One study discussed how the first confirmed case in the United States was diagnosed and treated and highlighted that the patient experienced rapid remission after receiving investigational treatment with Remdesivir as a compassionate medication [39]. Relevant reports showed that on the second day of intravenous infusion of Remdesivir, oxygen saturation was also restored from 90% to 94% ~ 96% without oxygen inhalation. There are no symptoms other than a dry cough and runny nose [39, 40]. The paper also points out that large-scale clinical studies must confirm the drug's safety and effectiveness.

Even though Remdesivir was an investigational drug and had previously been primarily used to treat the Ebola virus [41], the data for SARS-CoV-2 was not available. Nevertheless, Remdesivir has gathered a lot of attention. According to Gilead Sciences, the efficacy of Remdesivir against other coronaviruses yields optimistic outcomes, despite the lack of antiviral evidence demonstrating its activity against SARS-CoV-2. In this review, we aimed to dissect the mechanism of action and research progress of Remdesivir in COVID-19 research, and also current clinical trials of Redemsivir alone or in combination with other drugs in the treatment of COVID-19 infections as well as the limitations and significance of each clinical trial. To achieve these objectives, we retrieved the data from various databases such as PubMed, Web of Science, CNKI, and *Clinicaltrials.gov* using a variety of specific search terms, including "Remdesivir" or "GS-5734" and "COVID-19" or "SARS-CoV-2" and "drugs for COVID-19" and as well as case reports and randomized controlled trials (RCTs) on Remdesivir's usage in treating COVID-19. We hope that this review can help elucidate the development of Remdesivir for COVID-19 management, enhance existing knowledge about current Remdesivir research status, and provide ideas for more effective pharmacological interventions in managing COVID-19.

2. Remdesivir

Remdesivir (GS-5734) is structurally characterized as a nucleoside monophosphate derivative with a molecular formula of C27H35N6O8P and a relative molecular mass of 602.58, CAS number 1809249-37-3. Its chemical structure is shown in Figure 1. Remdesivir is an RNA-dependent RNA polymerase (RdRp) inhibitor antiviral drug developed by Gilead Sciences. Veklury ® was launched in the US on 22 October 2020 and the injectable dosage form is currently the main dosage form. Both transcription and genome replication of RNA viruses are dominated by RdRp [27, 42]. Thus, the RdRp inhibitor class offers a broad spectrum of anti-RNA viral activity.

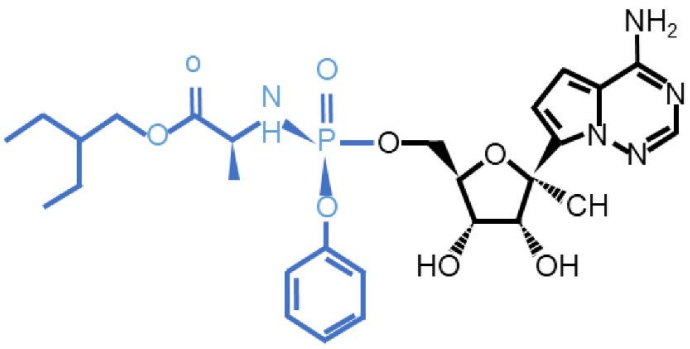

Figure 1. Structure of Remdesivir.

Remdesivir exhibits potent antiviral efficacy against several RNA virus families, such as filoviruses, paramyxoviruses, pneumonia viruses, and straight cortex viruses [43, 44]. Remdesivir, which was primarily indicated as an anti-Ebola virus (EBOV) agent [45], has entered phase III clinical trials to study its effect against EBOV (NCT03719586). It has been reported that Remdesivir treatment resulted in a higher mortality rate against the Ebola virus compared to monoclonal antibodies; hence, Remdesivir is replaced by monoclonal antibodies therapy [41]. Furthermore, Gilead's chief medical officer, Dr. Mersey Pardad, added that there is a lack of clinical evidence to support the application of Remdesivir as an emergency for Ebola virus infections [41]. In contrast, in animal experiments, intravenous injection of Remdesivir improved the pathological parameters, clinical symptoms, and signs of EBOV infection in non-human primates infected with EBOV without significant toxic side effects [43]. Its mechanism of inhibition chiefly by inhibiting RdRp activity[46]. With more exploration, researchers have found that the antiviral effect of Remdesivir is not limited to the Ebola virus but also possesses an inhibitory effect on various coronavirus viruses like MERS-CoV and SARS-CoV [47, 48]. This is one of the reasons why Remdesivir was chosen for clinical trials following the COVID-19 outbreak.

3. Remdesivir's action mechanism against SAR-CoV-2

SARS-CoV-2 is a member of the Coronavirus genus within the Coronavirus family of the order Nested Viruses and is a class of RNA viruses with envelopes and linear single-stranded positive-sense genomes. Notably, the host gets infected with SARS-CoV-2 by a process of viral multiplication that encompasses viral attachment, fusion, penetration, uncoating, transcription, translation, and virion release[34]. When a virus enters a host cell, its genome encodes non-structural proteins with the help of host cell mechanisms like helicase, papain-like protease (PLpro, nsp3), 3-chymotrypsin-like protease (3CLpro), and RdRp and structural proteins including spike protein and accessory protein for viral replication[49]. Various targets associated with the process of virus-infected hosts are the primary targets of antiviral drug mechanisms.

Remdesivir is a drug targeting RdRp. RdRp, necessary for viral RNA replication but absent in mature coronavirus particles, is translated from viral genomic RNA templates when coronavirus reaches host cells to express viral RdRp and complete viral RNA replication[50]. Remdesivir is a prodrug that does not possess any antiviral properties. Following ingestion by target cells in the body, Remdesivir is hydrolyzed by intracellular enzymes, and structural fragments of Remdesivir monophosphate (RMP) are produced after cleavage of phosphoramide and phosphoryl ester bonds. In vivo, RMP is sequentially phosphorylated and then metabolized to produce Remdesivir triphosphate (RTP; GS-443902) [50]. The in vivo transformation process of Remdesivir is shown in Figure 2. RTP is misrecognized by newly expressed viral RdRp, integrated

into newly synthesized viral RNA to block its replication process, and used to accomplish treatment goals since it shares structural similarities with adenine nucleoside triphosphate (ATP) [51, 52]. Figure 3 illustrates the mechanism action of in vivo SARS-CoV-2 inhibition of Remdesivir.

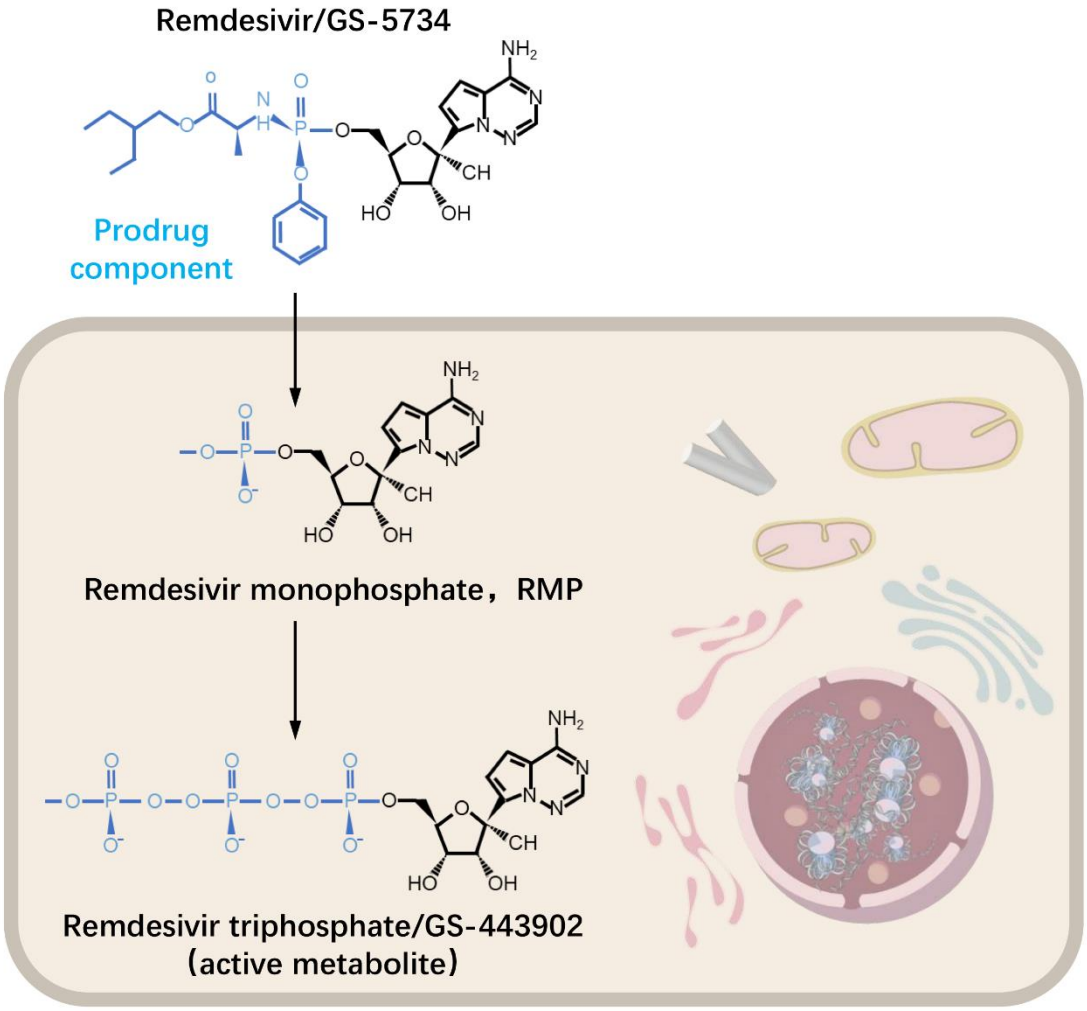

Figure 2. Intracellular activation of Remdesivir (GS-5734). Remdesivir is ingested by target cells and hydrolyzed by intracellular enzymes, and structural fragments of Remdesivir monophosphate (RMP) are released after cleavage of phosphoramide and phosphoryl ester bonds. In vivo, RMP is sequentially phosphorylated and then metabolized to produce Remdesivir triphosphate (RTP; GS-443902).

It has been suggested that GS-441524, a precursor compound phosphorylated to GS-443902, inhibits SARS-COV-2 both in vitro and in vivo and is a superior compound for treating COVID-19 [53, 54]. Brunotte and Schloer et al [55] found that GS-441524 and fluoxetine displayed good tolerance and antiviral effects against SARS-CoV-2 variants. It works by producing an active triphosphate phenotype of NTP that could suppress the RdRps of the SARS-COV-2, after being metabolized within the cell [56-58]. Moreover,

RNA replication terminated with Remdesivir's intermediate metabolites was significantly shielded from excision by the SARS-CoV-2 repair enzyme ExoN when pibrentasvir was present [58, 59]. In a COVID-19 mouse and ferret model, GS-621763 (the GS-441524 prodrug) treatment could lower viral load and enhance pulmonary functioning [60, 61].

Recently, the cryo-electron microscopy crystal structures of Remdesivir together with its target protein RdRp were discovered by Yin et al [62] and Bravo et al [63] which may be used to comprehend Remdesivir's antiviral mechanism better and instruct the rational design of improved antiviral medications. Furthermore, these electron microscopy structures reveal that template RNAs can be recognized by motif F and motif G in nsp12, and this strand is introduced into the core site to carry out the viral genome replication mechanism of chain extension [64].

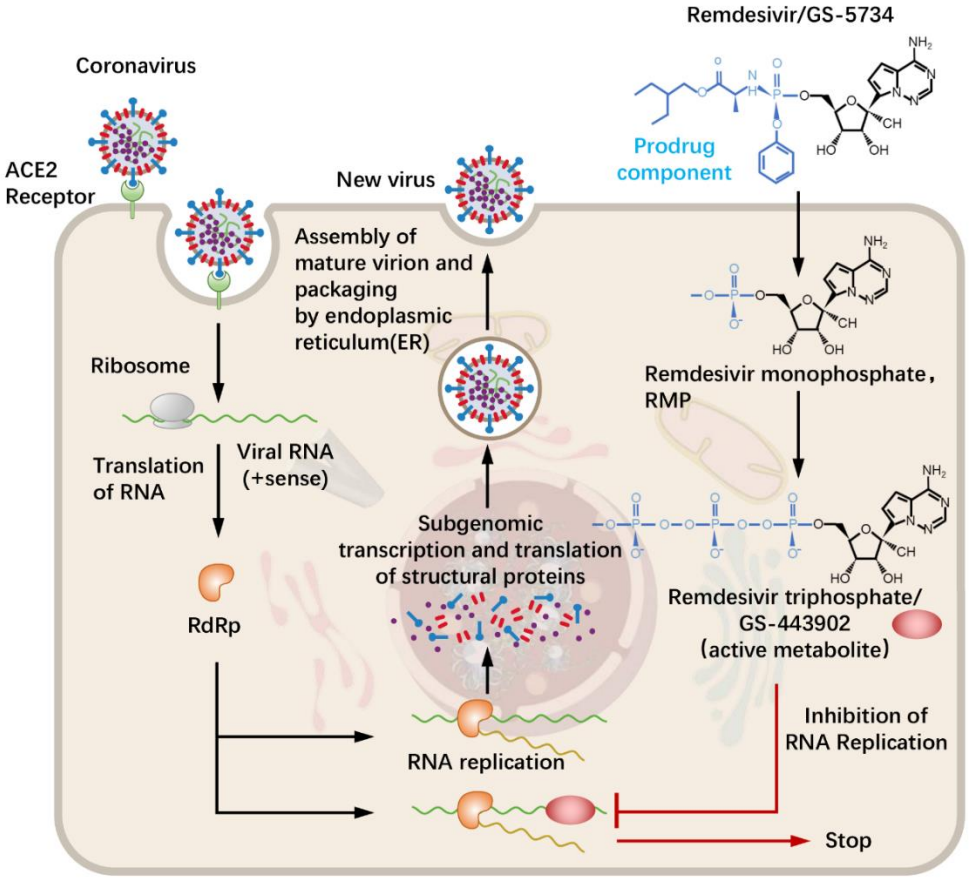

Figure 3. The mechanism via which Remdesivir suppresses SARS-COV-2 replication. GS-5734 was quickly transformed into Remdesivir monophosphate (RMP) intracellularly. Then, RMP undergoes further phosphorylation steps to become the active triphosphate metabolite (GS-443902) that could effectively inhibit viral RNA replication. RdRp effectively incorporates the active triphosphate form of RDV (GS-443902) with RNA to prevent SARS-COV-2 RNA from replicating.

4. Treatment of COVID-19 patients with Remdesivir and other trial drugs

From a clinical virological point of view, the primary methods that can effectively be used to control, prevent, and treat SARS-CoV-2 transmission and infection include vaccines, monoclonal antibodies, interferon therapy, and small molecule antiviral drugs, including oligonucleotides and peptides [65]. Drug repurposing and new drug screening, discovery, and clinical development of new treatments are still the hottest topics in treating COVID-19 infections. Scientists worldwide are committed to finding potential drugs to treat patients infected with COVID-19. Understanding the structure, virological characteristics, and survival mode of SARS-CoV-2 is still helpful in the process of developing drugs, SARS-CoV-2, similar to SARS-CoV, a severe acute respiratory syndrome coronavirus, and MERS-CoV is an enveloped sense single-stranded RNA virus [66]. At present, the complete sequencing of the viral genome has been completed. At the whole genome level, SARS-CoV-2 is up to 96.2% identical to coronavirus in Chrysanthemum sinensis head bats, implying that it is a novel coronavirus that could be derived from bats [67]. It has also been reported that the intermediate host of novel coronavirus may be pangolin, but the source of novel coronavirus has not been determined so far [68].

Through endocytosis, SARS-CoV-2 infects the host after attaching to specific host cell receptors (ACE2 receptors). Notably, the spike protein (S protein) of novel coronaviruses also necessitates the use of type II transmembrane serine proteases of host cells, like TMPRSS2, which helps the S protein of novel SARS-CoV-2 enter the host cell by cleaving the S protein of novel SARS-CoV-2, before mediating the fusion of the virus with the host cell membrane. If ACE2 is compared to a "doorknob", TMPRSS2 is "lubricating oil". With the help of TMPRSS2 and ACE2, SARS-CoV-2 successfully invades human cells. After that, a variety of mechanisms for virus proliferation take place, including uncoating, transcription, translation, extracellular release, etc. Its proliferation process mainly uses proteases such as 3CLpro, Nsp3, RdRp, spike proteins, and accessory proteins for viral replication, followed by key processes such as assembly and extracellular release [49] (Figure 4).

The main purpose of antiviral drugs is to block the infection and transmission of viruses by inhibiting or interfering with their infection or replication process for the above different stages. Therefore, antiviral drugs can be divided into direct anti-SARS-CoV-2 drugs against viral proteins and indirect anti-SARS-CoV-2 drugs that target host cell proteins according to different drug targets (Table 2).

4.1. Direct-acting antiviral drugs

4.1.1. 3CLpro Inhibitors

3CLpro, a cysteine protease that can be regarded as the primary SARS-CoV-2 protease, hydrolyzes polyproteins pp1a and pp1ab to ensure the generation of nsp4 ~ 16, a key non-structural protein for viral transcriptional replication, which includes RdRp, helicase, and 3CLpro itself. The effect of 3CLpro inhibitors is to produce immature or weakly virulent viruses by affecting the activity of 3CLpro. Representative medications of 3CLpro inhibitors include Paxlovid (nirmatrelvir/Ritonavir) [69], Kaletra (Lopinavir/Ritonavir) [70, 71], and Darunavir/cobicistat [72, 73].

4.1.2. RdRp Inhibitors

RdRp uses viral mRNA as a template and nucleosides as substrates to synthesize complementary RNA strands, but RdRp cannot distinguish nucleosides from nucleoside analogs. RdRp inhibitors are antiviral drugs designed based on this principle, and nucleoside spatial binding is blocked by the competitive binding of RdRp inhibitors to RdRp, affecting viral RNA synthesis. Representative medications of RdRp inhibitors include Remdesivir, Ribavirin [74], Favipiravir [75-78], Molnupiravir [79], and VV116 [80-83].

4.1.3. Drugs targeting stinging glycoproteins

As one of the four structural proteins of coronavirus, spike glycoprotein (S protein) is responsible for the receptor recognition and binding of coronavirus and host cells and the entry of the virus into host cells. Notably, angiotensin-converting enzyme II (ACE2) on the host cell surface can be specifically bound by the S protein, which can then lysed into two subunits, S1 and S2, in response to proteases from the host cell acting on the protein. While S2 facilitates the fusion of the virus and host membranes, S1 is involved in recognizing the cell receptor ACE2. Thus, coronavirus infection and transmission may be prevented and treated by targeting the S protein.

Arbidol is a non-nucleoside antiviral compound with a broad-spectrum antiviral activity that affects a variety of viral infections by interfering with the fusion of viral lipid membranes and host lipid membranes [84-87]. In one study, the abidol treatment group did not exhibit superior clinical effectiveness in contrast with the combined lopinavir/ritonavir treatment group in enhancing viral removal and improving clinical symptoms. Therefore, additional investigations are warranted to validate the therapeutic effectiveness of this medication for SARS-CoV2 [88].

Bebtelovimab is a neutralizing antibody that acts against the spike protein N-terminal domain (NTD) or receptor-binding domain (RBD) of the viral S protein. On 11 February 2022, the US FDA urgently approved bebtelovimab, a new monoclonal antibody drug of Eli Lilly and Company, to treat common SARS-CoV2 caused by Omicron strain in adults and adolescents aged over 12 years (minimum weight of 40 kg, approximately 88 pounds). Recently, scientists evaluated six neutralizing antibodies approved for marketing in the United States, Imdevimab and Casirivimab of Regeneron, Tixagevimab, and Cilgavimab of AstraZeneca, Sotrovimab of Vir Biotechnology, and Bebtelovimab of Eli Lilly, through in vitro live virus neutralization experiments. Ultimately, only Eli Lilly's bebtelovimab showed similar efficacy against multiple variants to those of ancestral strain [89]. However, Lilly's phase III human clinical trial of bebtelovimab is still ongoing, and its effect on humans remains to be further validated.

4.2. Host-specific therapeutic agents

Earlier this year, the Omicron BA.2 variant replaced the Delta strain; although the Omicron BA.2 mutant is far less harmful than the Delta strain, it has stronger infectivity, which leads to the Omicron BA.2 variant being more dangerous. The coronavirus is not moving in an increasingly weak direction. Today, the BA.4/BA.5 mutant, which swept the world, has broken this fantasy. At present, Omicron BA.4/5 has a more significant impact on human health than that of the original BA.2. Virus is prone to gene mutation under the natural replication process and the external environmental pressure imposed by drugs, so anti-coronavirus drugs targeting viral proteins are challenging in terms of antiviral resistance. Therefore, host targeting strategies have become an important development direction for anti-coronavirus drug research [63, 78]. Current therapeutic agents against the host mainly regulate immune and inflammatory responses or affect the fusion of cell membranes and viral envelopes to affect the invasion of the virus to exert antiviral effects.

4.2.1. Interferon (IFN)

Interferons act with relevant receptors on surrounding uninfected cells upon secretion by virus-infected host cells and promote the synthesis of antiviral proteins by these cells to prevent further infection, thereby inhibiting the virus [90]. Interferons are the mainstay of antiviral therapy in clinical practice [91]. Current clinical phase II trials of interferon Beta-1a have ended (NCT04385095), and results suggest that unlike patients receiving a placebo, those receiving interferon Beta-1a have a higher likelihood

of improving and recovering quicker from SARS-CoV-2 infection, providing strong clinical evidence for further trial studies [92].

4.2.2. Chloroquine and Hydroxychloroquine

Research has demonstrated that chloroquine and hydroxychloroquine have favourable immunomodulating effects, broad-spectrum antiviral activity, and their antimalarial properties [93, 94]. The antiviral mechanism of the drug may be through increasing endosomal pH, which suppresses pH-dependent virus-endosome fusion. At the beginning of the outbreak, researchers found that both drugs could effectively suppress SARS-CoV-2 at the cellular level [43, 95]. However, later clinical research discovered that treatment with chloroquine or hydroxychloroquine had no remarkable impact on COVID-19 patients' mortality rates, clinical recovery times, or disease cure [96]. The results of Hoffmann and Ou et al confirm this conclusion [97, 98] and explain the paradoxical phenomenon. Hoffmann et al found that the viral inhibitory activity of chloroquine is cell-type dependent; that is, chloroquine and hydroxychloroquine can efficiently inhibit viral entry into Vero cells with loss of transmembrane serine protease 2 (TMPRSS2) expression but are ineffective in Vero and Calu-3 cells with relatively high expression of TMPRSS2 protein. In addition, Ou et al. found that compared to SARS-CoV-1, SARS-CoV-2 was more dependent on the TMPRSS2 pathway, and combining hydroxychloroquine and TMPRSS2 inhibitors could successfully suppress the entry of SARS-CoV-2 into host cells.

4.2.3. Nafamostat and Camostat Mesylate

TMPRSS2 is distinct from the host determinant of ACE2 and effectively activates the SARS-CoV S protein [99], a serine protease on the surface of human cells that facilitates SARS-CoV-2 viral cell entrance. By suppressing TMPRSS2, the serine protease inhibitors nafamostat and camostat suppress the SARS-CoV-2 envelope from fusing with the surface membranes of host cells [99-101].

4.2.4. Other Drugs Acting on the Host

It was found that, like SARS-CoV, cathepsin B, and L (CatB/L) are required for cell invasion, and Aloxistatin (E64D), a CatB/L inhibitor, is an irreversible membrane-permeable cysteine protease inhibitor. Cathepsin L is required for SARS-CoV-2 viral invasion, while Aloxistatin treatment can effectively reduce cell invasion of 92.3% of SARS-CoV-2 viral particles [102]. During the 2003 SARS-CoV epidemic, glucocorticoids were widely used to treat critically ill patients, and a retrospective study

showed that glucocorticoids reduced patient mortality and length of hospital stay[103]. In addition, some immunomodulators, such as nitazoxanide (NTZ), can inhibit the release of proinflammatory cytokines, generates the production of interferons α and β, and induce the host innate immune response, performing a good inhibitory function against a variety of viruses [104, 105].

4.3. Natural Medicines

Baicalin is one of the main bioactive components of Scutellaria baicalensis Georgi. It has been reported that baicalin has an antiviral effect by inhibiting 3Clpro. The inhibitory effect of baicalin on SARS-CoV-2 3Clpro protease is IC50 = 0.94 ± 0.20 μmol/L. Additionally, Baicalein's antiviral replication activity in Vero E6 cells infected with SARS-CoV-2 is EC50 = 2.94 ± 1.19 μmol/L, while its cytotoxicity is CC50 > 200 μmol/L [106]. Glycyrrhizic acid is a triterpene isolated from the rhizome of Glycyrrhiza uralensis and is an antiviral agent with a broad spectrum of activity [107]. SARS-CoV entry and replication are remarkably inhibited by glycyrrhizic acid [108]. Glycyrrhizic acid and its derivatives are expected to be developed as drugs against SARS-CoV-2. Recently, researchers screened targeted COVID-19 3CLpro, a major protease inhibitor, and found that shikonin could inhibit the Mpro of new coronavirus in vitro, but the specific SARS-CoV-2 effect still needed further experimental verification.

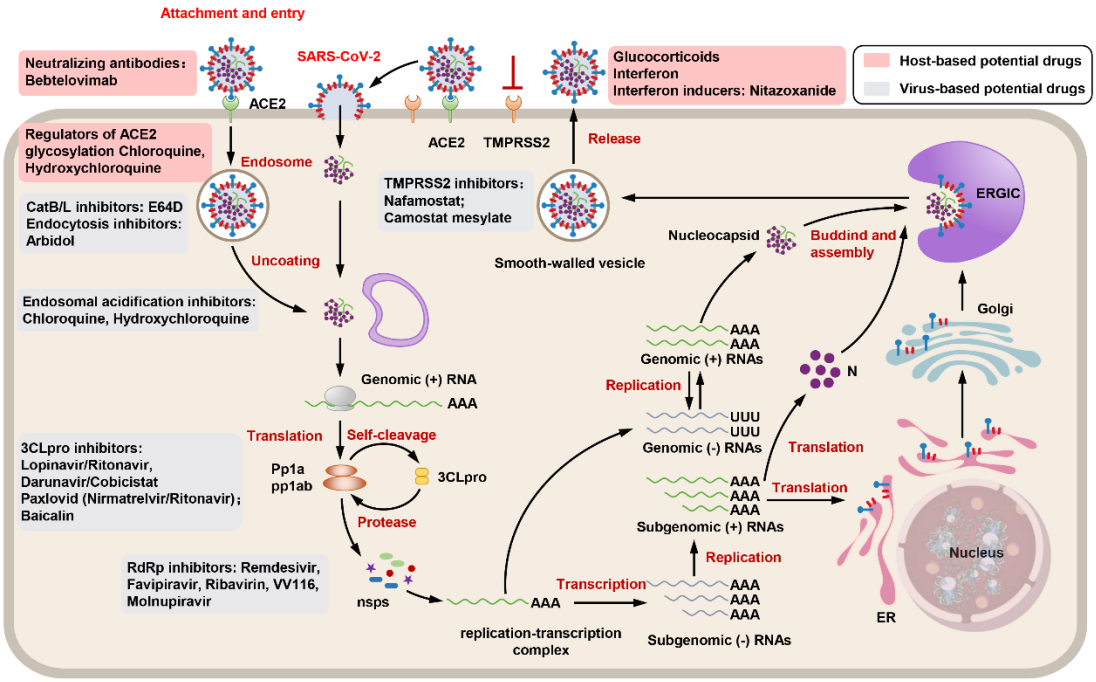

Figure 4. Replication cycle of SARS-CoV-2 and virus/host-based candidate drugs for treating COVID-19.

Table 1. Information about Remdesivir and other drugs for COVID-19 treatment.

Serial number	Classification of drugs	Drug name	Reported mechanism of action	Developer	Original indication
1	Direct antiviral drugs	Remdesivir	RdRp inhibitor	Gilead	Ebola
2		Paxlovid(Nirmatrelvir/Ritonavir)	3CLpro inhibitor	Pfizer	HIV/AID
3		Kaletra(Lopinavir/ritonavir)	3CLpro inhibitor	King Abdullah International Med Res Cent	HIV/AID
4		Darunavir/cobicistat	3CLpro inhibitor	Janssen	HIV/AID
5		VV116	RdRp inhibitor	Shanghai Junshi Biosciences	-
6		Ribavirin	RdRp inhibitor	ICN Pharmaceuticals	RSV
7		Favipiravir	RdRp inhibitor	Toyama Chemical	Influenza
8		Molnupiravir	RdRp inhibitor	Merck and Ridgeback	-
9		Bebtelovimab	Neutralizing antibodies	Eli Lilly and Company	-
10		Arbidol	Blocking virus entry by interfering with clathrin	Moscow-based Masterlek™	Influenza
11		Interferon	Interferon response		HBV and HCV

12	Host-specific therapeutic agents	Chloroquine & Hydroxychloroquine	Interference with the transport and fusion of viruses	Bayer & Sanofi-aventis	Malaria
13		Nafamostat	TMPRSS2 inhibitor	Ono Pharmaceutical	Anti-coagulant
14		Camostat mesylate	TMPRSS2 inhibitor	Ono Pharmaceutical	Chronic pancreatitis
15		Aloxistatin(E64D)	CatB/L inhibitor	-	Inhibits platelet aggregation
16		Glucocorticoid	Regulate immune response	-	Rheumatic arthritis
17		Nitazoxanide	Interferon response	Romark Laboratories	Antiparasitic
18	Natural Medicines	Baicalin	3CLpro inhibitor and the regulator of inflammatory	-	Chronic hepatitis
19		Glycyrrhizic acid	Regulator of inflammation and immunity	-	Chronic hepatitis
20		Diammonium glycyrrhizinate	Regulator of inflammation and immunity	Chiatai Tianqing	Chronic hepatitis
21		Shikonin	3CLpro inhibitor and the regulator of inflammatory	-	-

Note: - indicates no data available

5. Progress in the clinical use of Remdesivir alone in COVID-19 management

Remdesivir, as a new SARS-CoV-2 of global concern, was queried in *ClinicalTrials. gov* for the key terms Remdesivir and COVID-19 (as of October 2022). A total of 138 registered clinical trials were retrieved. Key searches such as Remdesivir, COVID-19, and Clinical Trials were queried in Pubmed and a total of 57 relevant results were found. The authors collated the important clinical trial-related information, as shown in Table 2.

COVID-19's first confirmed case in the US was described in detail in an article published in the NEJM on 31 January 2020. According to the article, the 35-year-old patient was treated experimentally with Remdesivir as a compassionate drug and experienced rapid remission. Relevant reports showed that on the second day of intravenous infusion of Remdesivir, oxygen saturation was also restored from 90% to 94% ~ 96% without oxygen inhalation. There have been no other symptoms except for a dry cough and runny nose [39], and this is the first report of good results using Remdesivir. In March 2020, within 36 hours after the SARS-CoV-2 infection, Angela Haczku et al. gave Remdesivir to an American female patient aged 40 years and after 10 days of therapy, the patient's health condition remarkably improved, and she was discharged two weeks later [109]. Following this, a large-scale clinical trial of Remdesivir began the dawn of COVID-19 management.

Remdesivir's effectiveness in treating Chinese patients with severe COVID-19 was examined in a randomized, double-blind, placebo-controlled research. The findings were published in The Lancet on 19 April, 2020. The study (NCT04257656) was conducted in 10 hospitals in Hubei province, where 237 patients were treated between 06 February 2020 and 12 March 2020. Remdesivir (200 mg initial dose administered intravenously on Day 1 and 100 mg daily for the remaining 9 treatment days) or a placebo was given to patients in a 2:1 randomization process. Patients were allowed to use ritonavir/lopinavir, interferon, and corticosteroids during this period. Time to clinical improvement (TTC1) was the primary endpoint. Remdesivir failed to provide a statistically remarkable therapeutic advantage in this research of adult critically ill inpatients with COVID-19, according to the analysis of the data [64]. Nevertheless, Gilead believed the findings were inconclusive due to the early termination of the study caused by insufficient patient enrolments.

Gilead also revealed promising outcomes from a clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) that compared

Remdesivir at a 10-day dosage to placebo for COVID-19 (ACTT-1, NCT04280705) on 29 April 2020. The clinical trial, which began on 21 February, involved 1063 patients. The trial used a double-blind method. Both patients and doctors did not know who received the drug rather than the placebo, which means that unconscious bias would not affect the results, and the main purpose of the trial was to see how long the patient's condition took to improve. Time to clinical recovery, measured in 29 days, was the study's primary endpoint. An independent data analysis and safety monitoring board (DSMB) in the United States reviewed and analyzed the outcomes of the test data on 27 April and concluded that patients receiving the Remdesivir drug recovered 31% faster, the midline recovery time (ability to be discharged to maintain a normal life) was 11 days for patients using the drug, relative to 15 days for those not using the drug. There was also a reduction in mortality (11.6% to 8%) [110].

Why do the conclusions of the Chinese and American clinical trials of Remdesivir appear diametrically opposite? Expert analysis suggests that the US NIH and China published in the Lancet studies and designs are double-blind placebo-controlled clinical trials (RCTs) with the same regimen. However, the main difference is the difference in study endpoints. The study endpoint indicators of NIH in the United States are loose. Still, the sample size in the US is larger, and the number of study enrollments in China is significantly reduced compared with the preset number of enrollments. In any case, trials with larger sample sizes and better study endpoint designs are required for COVID-19 management with Remdesivir.

Gilead Sciences' first SIMPLE trial (NCT04292899) assessed the safety and efficacy of a 5-day and 10-day course of intravenous Remdesivir in critically ill hospitalized patients with COVID-19. In total, 397 subjects were allocated at random (1:1) to start receiving either 5 or 10 days of Remdesivir and standard treatment in the first stage of the research. The NEJM released the complete results on 27 May 2020. The extension phase of this trial involved 5600 additional patients, and the outcomes demonstrated that the 5- and 10-day courses of Remdesivir were similarly effective in treating hospitalized patients with severe COVID-19, however, the extent of benefit could not be determined because there was no placebo control [111].

Gilead Sciences Spinner et al enrolled 596 patients with moderate COVID-19 in a randomized and open-label phase III clinical trial of Remdesivir in a second SIMPLE trial (NCT04292730). Three groups were established at random from all patients: Remdesivir was administered to 197 patients for a 10-day course, 199 patients for a 5-day course, and 200 patients just received standard therapy. Remdesivir was

given via intravenous injection on Day 1 in a dosage of 200 mg, then 100 mg every day for the duration of the entire course. Preliminary results showed a better distribution of clinical status in the group given a 5-day course of Remdesivir in contrast with the standard treatment group [112].

Based on this, Remdesivir, an antiviral medication from Gilead Sciences, received approval from the US FDA on 22 October 2020, to treat inpatients with novel coronavirus, becoming the first officially approved new coronavirus treatment in the United States [113]. However, the solidarity trial (NCT04315948) trial, organized by the World Health Organization (WHO), questions Remdesivir's efficacy. With 11,266 inpatients with COVID-19 from 30 different countries, this clinical study is presently the largest one to examine COVID-19 management. In the study, 2750 people were treated with Remdesivir, 1411 with ritonavir/lopinavir, 954 with hydroxychloroquine, 651 with interferon + lopinavir, 1412 with interferon alone, and 4088 as a standard of care control. On 15 October 2020, WHO published study results showing that Remdesivir with ritonavir/lopinavir, hydroxychloroquine, and interferon regimens showed little impact on 28-day mortality among hospitalized with COVID-19 [114].

The main limitations of the study were the unknown time from symptom onset to treatment initiation, the ungrouping of low versus high flow oxygen therapy patients, and the enrollment of patients mainly from countries with limited medical care. Gilead immediately issued a statement questioning the WHO's findings. Gilead believes there are no strict enrollment criteria for this multicenter open-label clinical trial, but it pursues to give patients the most investigational drug, so the design lacks rigor.

On 22 December 2021, Gilead Sciences announced data from the latest phase III clinical trial of Remdesivir (PINETREE trial, NCT04501952). This randomized, double-blind, placebo-controlled experiment aimed to assess how well Remdesivir treated high-risk COVID-19 patients within 7 days of the onset of symptoms. In particular, the trial involved 562 subjects with high-risk factors (– for example, age 60 years and above, obesity, certain underlying conditions) who experienced new coronary pneumonia symptoms within 7 days; patients were not immunized and were randomly classified into two groups. Remdesivir was administered by intravenous injection to the experimental group (n = 279) at doses of 200 mg on Day 1 and 100 mg on Days 2 and 3; the control group (n = 283) received a placebo (intravenously). Hospitalization or all-cause mortality linked to novel coronary pneumonia was the primary endpoint. Two patients in the Remdesivir group were hospitalized for COVID-19 versus 15 patients in the placebo group (hazard ratio 0.13 for hospitalization/death; P value = 0.008). Within

28 days, four Remdesivir-treated patients and 21 placebo-treated patients were admitted to the hospital again (hazard ratio 0.19 for disease progression). No deaths within 28 days were recorded [115].

According to the findings of this study, on 22 January 2022, the US FDA expanded the scope of application of Gilead Sciences' antiviral drug Remdesivir for high-risk adults and pediatric (aged > 12 with a minimum of 40 kg) non-hospitalized patients exhibiting mild to moderate symptoms [116]. At the same time, the FDA has increased pediatric emergency use authorization (EUA) to extend the target population to include pediatric (at least 3.5 kg) hospitalized or high-risk non-hospitalized patients with a weight range of 3.5 to 40 kg or less or aged < 12 years [117].

The National Institutes of Health's official website released an update to the Guidelines for the Treatment of Novel Corona Virus Pneumonia on 01 April 2022 (91): ①For patients with mild disease, Pfizer's nirmatrelvir tablet/ritonavir tablet combination package (trade name: Paxlovid) and Gilead Sciences' s Remdesivir are preferentially recommended; Lilly's Bebtelovimab or Merck's Molupniravir can be used when the above two drugs are inaccessible; ②For critically ill patients, Remdesivir is preferentially recommended, followed by Eli Lilly's JAK inhibitor baricitinib. The clinical dose of Remdesivir was also specified: ①For mild patients, 200 mg of Remdesivir was intravenously injected on day 1, and 100 mg was intravenously injected on days 2 and 3; ②For critically ill hospitalized adult patients, Remdesivir was intravenously given in doses of 200 mg on day 1 and 100 mg every day for the next four days, or until discharge.

On the other hand, a prospective observational study that included consecutive COVID-19 outpatients with at least one risk factor for disease progression receiving nirmatrelvir/ritonavir, Molnupiravir, or 3-day Remdesivir was conducted. Overall, the study showed that hospitalization or death due to COVID-19 occurred more often in patients treated with Remdesivir (n = 10/196, 5.1%) compared with those who received nirmatrelvir/ritonavir (n = 2/252, 0.8%) or Molnupiravir (n = 2/114, 1.8%). However, the incidence of adverse events was rare in patients treated with Remdesivir, mainly involving asymptomatic bradycardia[118]. In another study, 70% of pediatric patients aged 2m to 17y treated with Remdesivir had clinical improvement. Nevertheless, the study is still ongoing and the safety and efficacy of Remdesivir in pediatric populations remain to be concluded[119]. One single-center retrospective study also demonstrated that Remdesivir alone reduces the risk of severe COVID-19 up to 7% (95%CI = 3-11%) [120].

6. Remdesivir's Effectiveness In COVID-19 When Combined with Other Drugs

Researchers and medical professionals are still actively searching for innovative treatments due to the uncertainties regarding Remdesivir's efficacy and the pandemic of novel COVID-19, causing an increasing number of infections and even fatalities. The clinical application of Remdesivir when combined with other drugs to treat COVID-19 is summarized below (Table 2).

In March 2021, the NEJM reported the findings of Kalil et al's clinical trial of the Janus kinase inhibitor baricitinib plus Remdesivir for COVID-19 management (NCT04330690). This was a randomized, double-blind, placebo clinical trial that enrolled 1033 patients (a random assignment was used to classify 518 patients into the control group and 515 in the combination treatment group) and showed that baricitinib + Remdesivir showed greater effectiveness relative to Remdesivir monotherapy in decreasing the time required for recovery and accelerating improvement in clinical status among patients with Covid-19, especially among patients undergoing noninvasive or high-flow oxygen ventilation. Less severe adverse outcomes were linked to the combination [121].

In March 2021, Gilead Sciences announced that a phase III clinical trial of the combination of Remdesivir in treating severe new coronary artery disease failed. The results of this clinical trial (NCT04409262) showed that in patients with comorbid severe coronary artery disease and COVID-19, the combination of tocilizumab + Remdesivir was not effective at reducing the time to hospitalization for pneumonia or discharge by day 28 in contrast with placebo + Remdesivir [122]. The combination of tocilizumab + and Remdesivir was not as good as Remdesivir monotherapy in treating COVID-19 patients with severe new coronary artery disease. On the other hand, a combination of tocilizumab + Remdesivir treatment in a prospective randomized cohort study encompassing 108 adult patients with systemic hyperinflammation state and PCR positive for COVID-19 significantly reduced C-reactive protein (CRP) level while improving PaO2/FiO2 (P/F) ratio post-treatment. Nonetheless, this combination treatment comes with some complications including secondary bacterial infections (42.3%), myocarditis (15.4%), and pulmonary embolism (7.7%). The authors also concluded that although tocilizumab + Remdesivir treatment improves severe COVID-19 infection, the increased need for mechanical ventilation or ICU contributed to the appearance of thrombotic and cardiac events[123]. In addition, another multicentre study also reported that the combination of Remdesivir–tocilizumab resulted in a better mortality rate and clinical and pulmonary outcomes compared to the dexamethasone

therapy for severe COVID-19 treatment. However, a significant survival benefit was not demonstrated[124]. Additionally, it has been shown that among hospitalized patients with COVID-19 pneumonia, Interferon beta-1a + Remdesivir was not more effective than Remdesivir monotherapy. In contrast with patients who received a placebo, those who needed high-flow oxygen at baseline had poorer results (NCT04492475)[125].

A randomized, double-blind, placebo clinical trial (NCT04501978) was reported in the NEJM in March 2021 to examine the impact of the neutralizing monoclonal antibody LY-CoV555 on COVID-19. Specifically, the trial enrolled 314 patients (163 in the LY-CoV555 group and 151 in the placebo group), all of whom received Remdesivir, based on which LY-CoV555 and placebo were administered. When provided in conjunction with Remdesivir, LY-CoV555, a neutralizing monoclonal antibody that has been linked to a reduction in viral load and the frequency of hospitalizations or ER visits in non-hospitalized COVID-19 patients, was not effective in inpatients with COVID-19 without end-organ failure[126].

Drugs with immunomodulatory functions, Baricitinib (92) and dexamethasone (96) have demonstrated improved therapeutic results among COVID-19 patients. On this basis, Wolfe et al performed a randomized, double-blind, double-placebo clinical trial (NCT04640168) to examine the effect of baricitinib and Remdesivir and a combination of dexamethasone and Remdesivir in preventing further disease development in hospitalized COVID-19 patients requiring oxygen. In this clinical study, 1010 participants were enrolled, of which 516 (51%) were given baricitinib + Remdesivir + placebo, and 494 (49%) received dexamethasone + Remdesivir + placebo. All patients were given Remdesivir (≤10 days), along with either dexamethasone (or a comparable intravenous placebo), for at most 10 days, or baricitinib (or matching oral placebo), for at most 14 days. The variation in mechanical ventilation-free survival between the two groups by day 29 in the modified intention-to-treat population served as the primary endpoint. By day 29, mechanical ventilation-free survival was similar between baricitinib + Remdesivir and dexamethasone + Remdesivir; however, dexamethasone was linked to remarkably more adverse events [127].

Whether administering Ensovibep enhances treatment outcomes in COVID-19 patients based on administering Remdesivir was examined in a randomized, double-blind, placebo-controlled clinical trial (NCT04501978). Ensovibep (n = 247) or a placebo (n = 238) was given as an infusion to 485 randomly chosen patients. The primary outcome measure was the 90-day sustained recovery, determined as 14

consecutive days at home or place of usual residence after hospital discharge. Ensovibep was ineffective in enhancing the therapeutic outcomes for hospitalized patients with COVID-19 given conventional therapy, like Remdesivir, compared to placebo, according to trial findings. In addition, no safety issues were found [128].

Table 2. Information about Completed and Ongoing Major Clinical Trials of Remdesivir.

Trial Number	Study design	Intervention	Control	Amount	Test contents	Study Start Date	Study Completion Date	Primary endpoint	Conclusion
NCT04257656	A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Trial	Remdesivir	The same volume of placebo infusions	237 patients (158 participants received Remdesivir, whereas 78 received a placebo)	To assess Remdesivir's effectiveness and safety among hospitalized adult patients with severe COVID-19	February 2020	April 2020	Time to clinical improvement up to day 28 (6-point ordinal scale)	The variation in time to clinical improvement was not affected by Remdesivir. (21 days vs 23 days, P=0.24, not statistically significant)
NCT04280705	Multicenter, Adaptive, Randomized, Blinded, Controlled Trial	Remdesivir	The same volume of placebo infusions	1062 patients (522 received a placebo, compared to 541 who received Remdesivir)	The evaluation of experimental therapies' safety and effectiveness in treating hospitalized adults with COVID-19	February 2020	May 2020	Time to clinical recovery within 29 days of the patient (8-category ordinal scale)	In the Remdesivi group, the time to clinical improvement was 10 days, while it took 15 days in the placebo arm. (not statistically significant); mortality was reduced (11.6% to 8%)
NCT04292899	A Phase 3, Randomized Trial	Remdesivir	None	4891 participants	Remdesivir's antiviral effectiveness and safety among individuals with severe COVID-19	March 2020	June 2020	14-day clinical status (7-point ordinal scale)	There was no substantial distinction in effectiveness between Remdesivir therapy for 5- and 10 days
NCT04292730	Randomized, Open-label Trial	Remdesivir	None	1113 participants	To compare Remdesivir's antiviral effectiveness and safety	March 2020	June 2020	11-day clinical status (7-point ordinal scale)	At 10 days, there was no substantial distinction between Remdesivir therapy and

					to the standard of therapy in individuals with severe COVID-19				standard care; however, at 5 days, there was a significant variance
NCT04315948	Multi-centre, Adaptive, Randomized Trial	Remdesivir	Hydroxychloroquine, lopinavir/ritonavir, interferon/lopinavir, interferon alone	11266 participants	To measure the effectiveness of Remdesivir and other medications treatment of COVID-19 in hospital	March 2020	October 2023	In-hospital mortality In the 4 comparisons of each study drug vs. its controls	There were no discernible variations between the Remdesivir group and the control group in terms of total mortality, ventilation duration, or length of stay in the hospital
NCT04501952	Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial	Remdesivir	The same volume of placebo infusions	562 patients (279 patients In Remdesivir group, 283 in placebo group）	To assess Remdesivir's effectiveness and safety in treating COVID-19 in an outpatient setting	September 2020	May 2021	Hospitalization or all-cause mortality associated with COVID-19	Remdesivir reduced severe disease and mortality by 87% compared with placebo
NCT04330690	Multicentre, Adaptive, Randomized, Open-label, Controlled Clinical Trial	Baricitinib plus Remdesivir	Placebo	1033 patients	To investigate Baricitinib plus Remdesivir effectiveness in treating COVID-19	May 2020	July 2023	The time to recover	In patients with COVID-19, Baricitinib + Remdesivir was better than Remdesivir monotherapy in lowering recovery time and expediting improvements in health status
NCT04409262	Randomized, Double-Blind, Multicenter trial	Tocilizumab plus Remdesivir	Placebo plus Remdesivir	649 patients (434 were randomly assigned to cilizumab plus Remdesivir	To determine if cilizumab in combination with Remdesivir offers	June 2020	March 2021	Time to Hospital Discharge or "Ready for	When contrasted with placebo + Remdesivir in patients with severe COVID-19 pneumonia, tocilizumab + Remdesivir did

				and 215 to placebo plus Remdesivir)	patients with severe COVID-19 pneumonia a better benefit than Remdesivir monotherapy			Discharge" up to Day 28	not reduce the duration of hospital discharge or the "ready for discharge" status at day 28
NCT0449 2475	Multicenter, Adaptive, Randomized, Blinded, Controlled Tria	Interferon beta-1a plus Remdesivir	Placebo plus Remdesivir	969 patients [interferon beta-1a plus Remdesivir group (n=487); placebo plus Remdesivir group (n=482)]	To examine the effectiveness of Remdesivir combined with interferon beta-1a versus Remdesivir monotherapy among hospitalized patients with COVID-19	August 2020	December 2020	Time to Recovery for participants with Baseline ordinal Score 4, 5 and 6	In individuals with COVID-19 pneumonia, Remdesivir monotherapy did not outperform Interferon beta-1a +Remdesivir
NCT0450 1978	Multicenter, Adaptive, Randomized, Blinded Controlled Trial	LY-CoV555 plus Remdesivir	Placebo	314 patients (163 in the LY-CoV555 group and 151 in the placebo group)	To examine COVID-19 management using the monoclonal antibody LY-CoV555	August 2020	April 2022	Time from randomization to sustained recovery [Time Frame: Up to Day 90]	LY-CoV555 + Remdesivir was not effective for inpatients with Covid-19 without end-organ failure
NCT0464 0168	Multicenter, Adaptive, Randomized, Blinded, Controlled Trial	Baricitinib plus Remdesivir; Dexamethaso ne plus Remdesivir	Placebo	1010 patients	To study the efficacy of the combination in treating patients with oxygenated COVID-19 using Baricitinib + Remdesivir and	December 2020	May 2021	The difference in mechanical ventilation-free survival by day 29	By day 29, both baricitinib and dexamethasone with Remdesivir had identical rates of mechanical ventilation-free survival

NCT04501978	A Multicenter, Adaptive, Randomized, Blinded Controlled Trial	Ensovibep plus Remdesivir	Placebo	485 patients	Dexamethasone + Remdesivir To determine if ensovibep, in addition to Remdesivir and other conventional therapy, enhances clinical results among hospitalized COVID-19 patients	August 2021	November 2021	Early futility based on pulmonary ordinal scores at day 5 and time to sustained recovery through day 90	Ensovibep did not enhance clinical results for COVID-19 undergoing conventional therapy, particularly Remdesivir, as compared to placebo; no safety issues were found

Note: - indicates no data

7. Discussion

At the beginning of 2022, the Omicron BA.2 variant replaced the Delta strain, which became the dominant infecting variant in multiple countries. Although the Omicron BA.2 variant causes milder infections, it is more contagious and dangerous. It seems that SARS-CoV-2 virus did not progress in an increasingly weak direction. Today, the BA.4/BA.5 mutant, which swept the world, has broken this fantasy. At present, Omicron BA.4/5 has a more significant effect on human health compared to the original BA.2. After the outbreak and control of SARS-CoV in 2003, a comprehensive study on this type of coronavirus was not continued, which resulted in a scarcity of data and reference that can be applied to manage this COVID-19 pandemic. At the same time, the SARS-CoV-2 virus is susceptible to gene mutation under the natural replication process and the external environmental pressure imposed by drugs, which brings more difficulties and challenges to drug research and development. Fortunately, establishing cell and animal models enables the progress of drug screening and downstream experiments, but the development of drugs still faces great challenges. Pharmaceutical development at this stage is still focusing on the novel uses of existing medications since a verified effective antiviral drug has to be based on the promising results derived from in vitro and in vivo experiments in animals while guaranteeing effectiveness and safety in clinical practice.

Many drugs appear to have potential applications in SARS-CoV-2 treatment, but clinical trials are still ongoing, and rigorous clinical data have not yet been supported. Remdesivir is a drug that deserves attention, and it can be used in combination with other medications to treat critically ill patients. Antiviral therapy is best to be performed as soon as possible, within 72 hours, before the virus significantly destroys the host cells, as seen in influenza virus infection. Due to the lack of severe cases in children, the prevalence of asymptomatic or mild cases, and the paucity of effectiveness-associated clinical investigations, there is still an urgent need for more large-sample, multicenter trials.

In the long run, it is necessary to develop drugs that can directly target virus-encoded components (structural proteins, non-structural proteins, viral genomes) or interfere with the interaction between viruses and host receptors (DAAs). Also, drugs that can exert antiviral effects in the early stage of disease progression or the presence of high viral loads are preferred. Host-targeting antivirals (HTA) that exert antiviral effects by inhibiting host components necessary for viral replication or activating the host antiviral immune response can be used as the main means of emergency treatment when the pathogen is unknown. Further antiviral drugs targeting the host are not prone to drug resistance and have a wide antiviral spectrum. Additionally, HTA can be used as a monotherapy for viral diseases or in combination with DAA.

Therefore, Remdesivir, a drug for acute viral diseases, continuously requires attention to improve efficacy and potency, as it could be considered a reserved drug.

As we know, it is not a feasible strategy to design a specific drug for the structure elucidation of new SARS-CoV2. Given that the mechanism of action is poorly understood, it is unreasonable to anticipate that a single drug will have a significant curative effect. Instead, the drug's action mechanism must be comprehended to properly use it and maximize its impact when combined with other drugs in various disease stages. Furthermore, it is critical to promptly develop study criteria and models in compliance with international standards to deal with the significant problem that the novel SARS-CoV-2 virus could coexist with humans in the long run.

8. Conclusion

Remdesivir has received the most clinical attention for COVID-19 management in many clinical studies. The application potential of Remdesivir in reducing hospitalization rates and recovery times among patients with mild and early infections has been demonstrated in several clinical trials. At present, problems such as dosage, timing of use, and unknown interaction still need to be solved by clinical validation. It is encouraging that Remdesivir-related clinical trials are still underway and that pertinent data will soon be made accessible. This information can help to guide Remdesivir's clinical use better. Remdesivir is safe and effective in several clinical trials, despite specific adverse effects when treating COVID-19.

Additionally, we recommend real-time monitoring of hepatic and renal function in administered patients to prevent Remdesivir from causing adverse effects. More RCTs are needed to verify whether Remdesivir is safe and effective in non-hospitalized and hospitalized infected patients, children, and pregnant women and to develop new therapeutic agents or better treat infected patients. In conclusion, the article reviews the action mechanism and clinical trial status of Remdesivir. It comprehensively summarizes the drugs for COVID-19 management to provide some guiding suggestions for the treatment and research on COVID-19.

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