

Remdesivir: A Closer Look at Its Effect in COVID-19 Pandemic

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Keywords

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiology of COVID-19 pandemic, resulted in significant harm to the affected countries in every aspect of life. The virus infected over 139 million patients and resulted in over 2.9 million deaths until April 16, 2021. New variants of this virus were identified that spread rapidly worldwide. **Summary:** Remdesivir, a prodrug of adenosine nucleotide analog, is an antiviral with a broad spectrum of activity that was tested on SARS and Middle East respiratory syndrome infections. In vitro studies conducted on SARS-CoV-2 revealed that remdesivir inhibited viral replication with high selectivity index in cell cultures. In vivo studies showed that remdesivir reduced viral load in bronchoalveolar lavage fluid and attenuated pulmonary infiltrates in infected animals. Further, remdesivir showed promising results in terms of clinical improvement, shortening the recovery time, mortality rate, and the duration of oxygen need, despite that some clinical trials did not reveal significant ef-

fect on remdesivir use. Several studies showed positive results of remdesivir against the new variants. **Key Messages:** Remdesivir showed a promising beneficial effect against new variants of SARS-CoV-2, but more clinical evidence is needed to confirm this effect.

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Introduction

On March 11, 2020, the WHO declared coronavirus disease 2019 (COVID-19) as a global pandemic based on the rapid and widespread transmission of the disease [1, 2]. One month earlier, the International Committee of Taxonomy of Viruses (ICTV) identified the etiologic agent and named it severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3].

The coronaviruses belong to the nidovirales order of the coronaviridae family, with a single-stranded RNA of 26–32 kb in length as the nucleic material [4]. These viruses express crown-like spikes on their outer surface, for

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which they were named coronaviruses [4]. The coronaviruses include severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), and the new SARS-CoV-2 that first emerged in Wuhan City, China, in December 2019 [2, 4]. These viruses are known to cause acute respiratory distress syndrome (ARDS) and acute lung injury that may result in pulmonary failure and death [4].

In 2003, SARS-CoV infected the Chinese population and caused SARS that infected over 8,000 people with a mortality rate of 9% [4]. In 2012, MERS-CoV emerged in Saudi Arabia, and since then, it was transmitted to over 2,400 patients and caused death to 850 patients worldwide with a mortality rate of >30% [5]. On the other hand, SARS-CoV-2 infected over 70,000 and killed over 1,800 people within only 50 days of the epidemic in Wuhan, showing higher transmission but lower mortality rates [4].

Until April 16, 2021, >139 million cases and 2.9 million deaths were confirmed globally, with the highest number of cases being reported in the USA, followed by India, Brazil, France, the Russian Federation, and the UK [6]. In the USA, over 31 million cases and 550 thousand deaths were reported until April 16, 2021 [6]. Since it was first announced, the COVID-19 pandemic resulted in tremendous harm to the affected countries in every aspect of life [7]. In addition to the health aspect, the virus also had a major influence on almost every single daily aspect such as work, learning, traveling, and economic well-being [7].

Studies conducted on SARS-CoV-2 showed that 80% of the viral genome is identical to that of the SARS-like bat viruses, suggesting that bats could be the primary source of viral replication [4]. It is not fully known whether the virus was transmitted directly from bats to humans or indirectly via other species [4]. However, human to human transmission is known to occur through exposure to respiratory droplets expelled during talking, coughing, or sneezing and, to a lesser extent, through surface spread [8]. The virus could also spread by aerosol; however, the impact of this mode of transmission remains unclear [8]. Until now, the minimum infectious viral load for SARS-CoV-2 has not been defined, but researchers suggest that a few hundred would be enough to infect susceptible hosts [9].

In the human body, the virus binds to angiotensin-converting enzyme 2 (ACE2) through the viral spike protein that has 2 regions; the S1 and S2 subunits [10]. The S1 domain mediates receptor binding, while the S2 do-

main mediates cell membrane fusion [10]. ACE2 enzyme is a membrane protein found on cells of the lung, kidney, heart, and intestines that function in regulating blood pressure and inflammation [11]. Once inside the cells, the viral RNA is released into the cell's cytoplasm where it is translated into polyproteins and structural proteins, and then the RNA genome starts to replicate [12]. Later, viral nucleocapsid is formed, and virus-containing vesicles fuse with the plasma membrane to release the virus to the surrounding tissues [12].

Infection with SARS-CoV-2 induces pulmonary local inflammatory response with release of several cytokines, including tumor necrosis factor- α , transforming growth factor- β , interleukin (IL)-1 β , and IL-6, in addition to several chemokines [13]. In severe cases, the inflammatory response may cause a cytokine storm that is manifested by dramatic increase in serum level of multiple cytokines including IL-2, IL-7, IL-10, tumor necrosis factor- α , monocytes chemotactic protein, and granulocyte colony-stimulating factor [14]. This cytokine storm is a key response that drives ARDS as well as extrapulmonary organ failure [14].

Similar to both SARS-CoV and MERS-CoV, patients with SARS-CoV-2 infection present with fever, dyspnea, nonproductive cough, fatigue, and myalgia with normal or low leukocyte count [12]. The disease severity ranges from mild to moderate disease that could be managed without hospitalization to severe disease with difficulty in breathing, chest pain, and loss of speech or movement that requires hospitalization and urgent management [11]. Chest X-rays show radiographic evidence of pneumonia characterized by bilateral ground-glass opacity lesions seen in the posterior and peripheral lungs [15]. However, pathological studies on biopsies from the lungs of deceased patients show damaged alveolar epithelial cells, hyperplasia of type 2 pneumocytes, hyaline membrane formation, and diffuse alveolar damage [15]. Biopsies of liver tissues from patients with moderate to severe disease reveal multifocal hepatic necrosis, steatosis, lymphocytic infiltration, and sinusoidal dilation [16]. Further, heart biopsies show focal fibrosis and mild myocardial hypertrophy [15].

As an RNA virus, SARS-CoV-2 continuously undergoes genomic mutations, most of which have minimal consequences; however, some mutations may alter the viral virulence and antigenicity [17]. To date, hundreds of mutations have been identified from viral isolates, of which, 23 mutations resulted in the introduction of the B.1.1.7 variant identified in the UK in December 2020 [18]. Eight of these mutations resulted in conformation-

al changes in viral shape and S protein, altering ACE receptor binding, antibody recognition, and infectivity [19]. The B.1.1.7 variant has higher viral load in the respiratory tract as well as higher transition rate that is, at least partially, related to the N501Y mutation that involves alteration in the receptor-binding motif [18]. It is also suggested that these mutations may alter viral susceptibility to antiviral drugs such as favipiravir and remdesivir, as well as monoclonal antibodies [18]. Moreover, several other variants were identified globally, including the South Africa variant (B.1.351), 2 related California variants (B.1.429 and B.1.427), and 2 Brazil variants (P.1 and P.2) [20]. The South Africa variant developed mutations in spike protein that reduce its susceptibility to treatment with monoclonal antibodies [20] in addition to the development of resistance toward AstraZeneca vaccine [21]. Similarly, the P.1 variant acquired 10 spike mutations in addition to mutations in the receptor-binding domain and the N-terminal domain, which could also impair the effectiveness of monoclonal antibodies [22]. The P.2 Brazil mutation has the same receptor-binding domain mutation (E484K amino acid replacement) similar to P.1 and B.1.351 which may enable vaccine escape [20]. The 2 California variants share 3 spike protein mutations (S13I, W152C, and L452R) that resulted in moderate resistance to the effect of neutralizing antibodies and vaccines which mandate more attention regarding the influence to cause future surges in COVID-19 cases [23]. It is expected that the mutations that could affect the response of remdesivir and favipiravir are in the viral polymerase, the target protein of these drugs. These drugs are unlikely to be impacted by spike mutations.

Remdesivir in COVID-19

On October 22, 2020, the FDA approved Veklury (remdesivir) as the first antiviral treatment for COVID-19 [24]. The antiviral drug, remdesivir (GS-5734), was developed by Gilead Sciences as a result of intensive research that started in 2009 to target originally hepatitis C virus and respiratory syncytial virus [25]. However, the antiviral profiling that started in 2013 and 2014 suggested that remdesivir might have a broad-spectrum activity against several viruses. Gilead Sciences collaborated with academic institutions and federal agencies and tested the effectiveness of remdesivir in Ebola, SARS, and MERS infection [25]. Recently, remdesivir was tested as an investigational new drug on SARS-CoV-2.

Remdesivir (GS-5734) is a prodrug of the adenosine nucleotide analog that is metabolized to nucleoside monophosphate and further phosphorylated to the nucleoside triphosphate derivative [2, 26]. The nucleoside triphosphate derivative competes with native ATP to be utilized by viral RNA-dependent RNA-polymerase (RdRp), an important enzyme for the replication of the virus, resulting in premature termination of the viral RNA strand [27, 28]. Further, the incorporated nucleoside triphosphate form is not detected by the viral exonuclease-mediated proofreading [28, 29]. A molecular docking study showed that remdesivir would bind, at high affinity, to SARS-CoV-2 RdRp [30] confirming its molecular mechanism of action.

In vitro studies showed that remdesivir had a broad-spectrum antiviral activity by inhibiting replication of several RNA viruses including filoviruses, paramyxoviruses, pneumoviruses, arenaviruses, and coronaviruses, and it showed low cytotoxicity in cultured cells [31, 32]. Of interest, treating SARS-CoV-2-infected Vero E6 cells with remdesivir inhibited the viral replication at low concentration and showed high selectivity index (half-maximal effective concentration (EC_{50}) = 0.77 μ M, half-cytotoxic concentration (CC_{50}) >100 μ M, and selectivity index (SI) >129.87) [33]. The Vero E6 cell line is derived from monkey's kidney and is highly expressing ACE2 [34, 35]. Another study by Choy and colleagues [36] showed the ability of remdesivir to inhibit the replication of SARS-CoV-2 in Vero E6 cells with the estimated EC_{50} = 23.15 μ M. Further, Pruijssers and colleagues [37] found that remdesivir inhibited the replication of SARS-CoV-2 in primary human airway epithelial cells (EC_{50} = 0.01 μ M) more potently than in Vero E6 cells (EC_{50} = 1.65 μ M), and this could be due to low capacity of Vero E6 cells to metabolize remdesivir to the active triphosphate form.

The nonhuman primate animal model assists in determining the effectiveness of remdesivir. Williamson and colleagues [38] examined the effect of remdesivir administration to rhesus macaques that were inoculated with SARS-CoV-2 by different routes: intranasal, oral, ocular, and intratracheal. After the inoculation, specifically 12 h later, the animals received 10 mg/kg remdesivir loading dose and then 5 mg/kg daily for 6 days. Remdesivir-treated macaques did not reveal any clinical features of respiratory disease where the viral load was reduced in the retrieved bronchoalveolar lavage fluid, and the pulmonary infiltrates were attenuated compared to placebo-treated macaques [38].

There are limited data on remdesivir in rodents as rodents have high level of esterase that degrades remdesivir

immediately [39]. Therefore, to examine the effect of remdesivir in rodents, they must lack the carboxyl esterase 1c (Ces1c) [37]. Further, mice studies should consider expressing human ACE2 as SARS-CoV-2 binds to all ACE2 receptors except the mice ones [40]. To test the effectiveness of remdesivir in the mice model, Pruijssers and colleagues [37] engineered a chimeric SARS-CoV that encodes RdRp of SARS-CoV-2, the target of remdesivir. Mice that were infected by this chimeric virus and treated with remdesivir showed significant reduction in virus replication and improved lung function compared to vehicle-treated animals [37]. However, the lung hemorrhage and weight reduction was not different between remdesivir- and vehicle-treated infected animals [37].

Clinical Evidence of the Role of Remdesivir in COVID-19

The provided remdesivir by Gilead Sciences on a compassionate use to 61 patients with severe COVID-19 disease, who had oxygen saturation $\leq 94\%$, showed clinical improvement in about 68% of patients [41]. Hence, evaluating the effectiveness of remdesivir in the treatment of COVID-19 was of an outstanding importance. In all clinical studies, the therapeutic regimen of remdesivir consisted of 200 mg intravenous remdesivir on day 1 and 100 mg daily thereafter. The first randomized, double-blinded, placebo-controlled clinical trial evaluated the effectiveness of remdesivir in patients with severe COVID-19 who had pneumonia and oxygen saturation $\leq 94\%$. Patients received either remdesivir ($n = 158$) or placebo ($n = 79$) for 10 days. This study did not complete the target enrollment because of the local measures to control the outbreak at Wuhan, China, and was not statistically powered. Remdesivir did not affect the time to clinical improvement, mortality rate, viral load, length of oxygen therapy, and period of hospital admission [42]. However, the duration of mechanical ventilation was shorter in patients who received remdesivir compared to placebo, though the difference was not significant [42]. It has been shown that higher proportion of patients in the remdesivir arm discontinued the study because of serious side effects such as respiratory failure and ARDS. However, patients who received remdesivir showed clinical improvement faster than who received placebo but still not statistically significant [42]. Therefore, more clinical studies are needed to withdraw firm conclusions.

Another randomized, double-blinded, placebo-controlled trial tested remdesivir in patients with COVID-19

who were admitted to the hospital and had lower respiratory tract infection [43]. Patients received either remdesivir ($n = 541$ patients) or placebo ($n = 521$) for 10 days. Remdesivir shortened the recovery time, in moderate and severe cases, in which the median time to recovery was 10 days in the remdesivir arm compared to 15 days in placebo [43]. Additionally, oxygen therapy was needed for fewer days compared to placebo, and the mortality estimates were lower in the remdesivir arm compared to placebo, both at day 15 (6.7% vs. 11.9%) and day 29 (11.4% vs. 15.2%) [43]. The development of serious side effects was higher in patients who received placebo compared to remdesivir [43]. These findings showed promising results of the effectiveness of remdesivir.

Gilead Sciences funded a randomized, open-label phase 3 study to compare 5 days ($n = 200$ patients) and 10 days ($n = 197$ patients) of IV remdesivir in patients with severe disease and with pulmonary infiltrate and oxygen saturation $\leq 94\%$ [44]. The clinical improvement was not different between the 2 groups. Nausea, respiratory failure, increased level of aminotransferase enzyme, and constipation were among the most encountered side effects [44]. However, there was no placebo group to withdraw definitive conclusion on the effectiveness of remdesivir. Spinner and colleagues [45] conducted a multicenter, open-label clinical trial that was sponsored by Gilead Sciences where patients had moderate pneumonia, oxygen saturation $> 94\%$, and presence of pulmonary infiltrates. The patients received remdesivir either for a 5-day course ($n = 199$) or 10-day course ($n = 197$) or standard care ($n = 200$). Patients who received 5-day remdesivir showed significant clinical improvement than those who received standard therapy on days 11 and 14 while the 10-day course showed significant clinical improvement on days 14 and 28. However, higher percentage of patients who received 10-day course of remdesivir suffered from side effects such as nausea, hypokalemia, and headache.

The WHO conducted a randomized controlled trial on hospitalized COVID-19 patients, where participants were randomly assigned to receive local standard care alone or with one of the trial drugs (remdesivir, hydroxychloroquine, lopinavir, or interferon beta-1a) [46]. Remdesivir was given as 200 mg IV on day 0 and 100 mg IV on days 1–9. The intention-to-treat analysis examined the in-hospital mortality rate in the trial drug arms compared to the standard care alone arm. Three hundred and one patients died in the remdesivir arm ($n = 2,743$) compared to 303 in its control arm ($n = 2,708$, $p = 0.5$) [46]. The need for ventilation and the time to discharge (as secondary out-

comes) were not significantly different between the remdesivir arm compared to the control [46].

Currently, there are 45 registered clinical trials that are in the recruiting phase to further evaluate remdesivir in patients with COVID-19 [47]. On November 20, 2020, the WHO released a conditional recommendation due to insufficient evidence toward the use of remdesivir in hospitalized patients [48].

The Efficacy of Remdesivir against the New Variants

After the emergence of new variants of SARS-CoV-2, it is important to assess the efficacy of remdesivir against these variants as it is the only FDA-approved antiviral agent for the treatment of hospitalized COVID-19 patients [49]. A study analyzed the sequence of proteins that form viral spike and RdRp of SARS-CoV-2 as these are target sites for several vaccines and drugs including remdesivir [50]. Among the emergent variants, a mutation was reported in one of the remdesivir-binding residues in nsp12 [50]. This high conservation of remdesivir-binding residues indicates the absence of evidence for remdesivir-resistant mutations [50].

In addition, the SARS-CoV-2 full genome sequence of globally circulating clinical isolates including B.1.1.7 and B.1.351 variants and mink isolates was studied [49]. It has been shown that both variants had low variation in all gene coding proteins of the RNA replication complex with the most frequent amino acid substitution nsp12 P323L [49]. Another frequent substitution was on nsp13 and was noted in both variants: K460R in the B.1.17 variant and T588I in the B.1.351 variant [49]. These substitutions in nsp12 did not affect the susceptibility to remdesivir as they did not have any direct interaction with pre-incorporated remdesivir triphosphate [49]. Moreover, nsp12 residues, which are responsible for pre-existing resistance to remdesivir, were highly conserved in clinical isolates, and no change was reported in both variants [49].

Several *in vitro* studies were conducted to assess the efficacy of remdesivir in new variants. Remdesivir inhibited the viral replication of both early SARS-CoV-2 and B.1.1.7 variant in intestinal epithelial Caco-2 cells and Calu-3 human lung epithelial cells [51]. The inhibitory effect of RdRp inhibitors, including remdesivir, on early SARS-CoV-2, B.1.1.7 variant, and B.1.351 variant was examined by assessing *in vitro* viral replication capacity after remdesivir administration in each lineage utilizing Vero and Calu-3 cells [52]. Despite several changes of

amino acid sequences in viral spike protein in these 2 variants compared to early SARS-CoV-2, nsp12 was highly conserved, and no difference in amino acid sequence was observed in the 3 lineages [52]. Hence, no difference in drug efficacy was noticed between early SARS-CoV-2 and these new variants [52]. The impact of SARS-CoV-2 mutations on resistance to remdesivir was also examined *in vitro* where >200,000 sequences of these virus variants like B.1.1.7, B.1.351, and P.1 were tested and revealed that there was selectivity in remdesivir resistance but without proof about the worldwide spread of resistant strains of remdesivir [53]. The results of all previous studies highlight the promising effect of remdesivir as a treatment option against the new variants and dictate the need for more studies to confirm these findings.

Conclusion

COVID-19 is accelerating rapidly; until April 16, 2021, >139 million cases and 2.9 million deaths were confirmed globally. Additionally, hundreds of mutations were identified from viral isolates which resulted in the emergence of new variants that spread rapidly worldwide. Unfortunately, there is no fundamental therapy of COVID-19 till now. Remdesivir became the first FDA-approved antiviral agent for the treatment of hospitalized patients with COVID-19. Despite the revealed beneficial effect of remdesivir in SARS-CoV-2 in animal and *in vitro* studies, clinical trials showed conflicting results in which some clinical trials did not show significant effect of remdesivir in the treatment of COVID-19 patients while others showed promising results in terms of recovery time, oxygen need, mortality rate, and clinical improvement. Additionally, remdesivir had a positive effect against new variants including B.1.17 and B.1.351 according to several studies. Therefore, further studies are highly recommended to help in making clear recommendations about remdesivir use in these emergent variants.

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Conflict of Interest Statement

All authors reported no conflicts of interest.

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Author Contributions

H.R.T., N.K., F.S., and N.A.A.-S. participated in writing the initial draft of the manuscript and critically reviewed the manuscript. All authors approved the final draft of the manuscript.

References

- 1 Dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. *Biomed Pharmacother.* 2020;129:110493.
- 2 Eastman RT, Roth JS, Brimacombe KR, Simonov A, Shen M, Patnaik S, et al. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. *ACS Cent Sci.* 2020; 6(5):672–83.
- 3 Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, et al. A systematic review of asymptomatic infections with COVID-19. *J Microbiol Immunol Infect.* 2021;54(1):12–6.
- 4 Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res.* 2020;24:91–8.
- 5 Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun.* 2020; 11(1):222.
- 6 WHO. WHO coronavirus (COVID-19) dashboard. 2021 [updated 2021 Apr 16]. Available from: <https://covid19.who.int/>.
- 7 Morens DM, Daszak P, Markel H, Taubenberger JK. Pandemic COVID-19 joins history's pandemic legion. *mBio.* 2020;11(3): e00812–20.
- 8 Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA.* 2020;324(8):782–93.
- 9 Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: a critical review on the unresolved dichotomy. *Environ Res.* 2020;188:109819.
- 10 Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181(2):271–80. e8.
- 11 Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeili SM, Bahreini E. A comprehensive review of COVID-19 characteristics. *Biol Proced Online.* 2020;22: 19.
- 12 Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal.* 2020;10(2):102–8.
- 13 Shi Y, Wang G, Cai XP, Deng JW, Zheng L, Zhu HH, et al. An overview of COVID-19. *J Zhejiang Univ Sci B.* 2020;21(5):343–60.
- 14 Ye Q, Wang B, Mao J. The pathogenesis and treatment of the “Cytokine Storm” in COVID-19. *J Infect.* 2020;80(6):607–13.
- 15 Tian S, Xiong Y, Liu H, Niu L, Guo J, Liao M, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol.* 2020; 33(6):1007–14.
- 16 Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med.* 2020;382(19):1787–99.
- 17 Zeng L, Li D, Tong W, Shi T, Ning B. Biochemical features and mutations of key proteins in SARS-CoV-2 and their impacts on RNA therapeutics. *Biochem Pharmacol.* 2021;189:114424.
- 18 Nikhra V. Evolving patterns in COVID-19: the virus, its variants and infectivity-cum-virulence. *Biomed J Sci Tech Res.* 2021;33(2).
- 19 Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature.* 2021; 593(7857):130–5.
- 20 Long SW, Olsen RJ, Christensen PA, Subedi S, Olson R, Davis JJ, et al. Sequence analysis of 20,453 severe acute respiratory syndrome coronavirus 2 genomes from the houston metropolitan area identifies the emergence and widespread distribution of multiple isolates of all major variants of concern. *Am J Pathol.* 2021;191(6):983–92.
- 21 Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 covid-19 vaccine against the B.1.351 variant. *N Engl J Med.* 2021; 384(20):1885–98.
- 22 Wang P, Wang M, Yu J, Cerutti G, Nair MS, Huang Y, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. *bioRxiv.* 2021 Mar 2. Epub ahead of print.
- 23 Deng X, Garcia-Knight MA, Khalid MM, Servellita V, Wang C, Morris MK, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. *medRxiv.* 2021 Mar 9. Epub ahead of print.
- 24 FDA. FDA approves first treatment for COVID-19. 2020. Available from: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19>.
- 25 Gilead Sciences, Inc. Development of remdesivir. 2020. Available from: https://www.gilead.com/-/media/gilead-corporate/files/pdfs/covid-19/gilead_rdv-development-fact-sheet-2020.pdf.
- 26 Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature.* 2016; 531(7594):381–5.
- 27 Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem.* 2020;295(20):6785–97.
- 28 Al-Tannak NF, Novotny L, Alhunayan A. Remdesivir – bringing hope for COVID-19 treatment. *Sci Pharm.* 2020;88(2):29.
- 29 Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio.* 2018;9(2).
- 30 Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. *Life Sci.* 2020;253:117592.
- 31 Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature.* 2016; 531(7594):381–5.
- 32 Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Sci Rep.* 2017;7:43395.
- 33 Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269–71.
- 34 Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003;426(6965):450–4.
- 35 Kaye M. SARS-associated coronavirus replication in cell lines. *Emerg Infect Dis.* 2006; 12(1):128–33.
- 36 Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KPY, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res.* 2020;178:104786.
- 37 Pruijssers AJ, George AS, Schäfer A, Leist SR, Gralinski LE, Dinnon KH 3rd, et al. Remdesivir inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. *Cell Rep.* 2020;32(3):107940.

- 38 Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. [bioRxiv](#). 2020;585(7824):273–6.
- 39 Bahar FG, Ohura K, Ogihara T, Imai T. Species difference of esterase expression and hydrolase activity in plasma. *J Pharm Sci*. 2012; 101(10):3979–88.
- 40 Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270–3.
- 41 Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382(24):2327–36.
- 42 Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020; 395(10236):1569–78.
- 43 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 – final report. *N Engl J Med*. 2020;383(19):1813–26.
- 44 Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med*. 2020;383(19):1827–37.
- 45 Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048–57.
- 46 WHO Solidarity Trial Consortium; Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid-19 – interim WHO solidarity trial results. *N Engl J Med*. 2021;384(6):497–511.
- 47 Clinicaltrials.gov. 2021.
- 48 Organization WHO. 2020 [updated 2020 Nov 20]. Available from: <https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients>.
- 49 Martin R, Li J, Parvangada A, Perry J, Cihlar T, Mo H, et al. Genetic conservation of SARS-CoV-2 RNA replication complex in globally circulating isolates and recently emerged variants from humans and minks suggests minimal pre-existing resistance to remdesivir. *Antiviral Res*. 2021;188:105033.
- 50 Showers WM, Leach SM, Kechris K, Strong M. Analysis of SARS-CoV-2 mutations over time reveals increasing prevalence of variants in the spike protein and RNA-dependent RNA polymerase. [bioRxiv](#). 2021 Mar 5. Epub ahead of print.
- 51 Reuschl AK, Thorne L, Zuliani Alvarez L, Bouhaddou M, Obernier K, Soucheray M, et al. Host-directed therapies against early-lineage SARS-CoV-2 retain efficacy against B.1.1.7 variant. [bioRxiv](#). 2021 Jan 24. Epub ahead of print.
- 52 Lee J, Lee J, Kim HJ, Ko M, Jee Y, Kim S. TM-PRSS2 and RNA-dependent RNA polymerase are effective targets of therapeutic intervention for treatment of COVID-19 caused by SARS-CoV-2 variants (B.1.1.7 and B.1.351). [bioRxiv](#). 2021 Apr 8. Epub ahead of print.
- 53 Szemiel AM, Merits A, Orton RJ, MacLean O, Pinto RM, Wickenhagen A, et al. In vitro evolution of remdesivir resistance reveals genome plasticity of SARS-CoV-2. [bioRxiv](#). 2021 Feb 10. Epub ahead of print.