Remdesivir to battle COVID-19: An initial verdict

Sumit Garai, Geetanjali Saini

Introduction

COVID-19 is an ongoing pandemic caused by the highly contagious Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The novel disease is rapidly spreading round the globe, taking a heavy toll on human lives and economies, such that even nations with robust healthcare are crumbling in its wake. Several therapies and vaccines to combat the virus are in development, however, these processes are often long drawn. In such a pressing time, repurposing existing drugs is a prudent approach since toxicity studies for such drugs are available, and clinical trials to determine efficacy and optimal therapeutic dosage against the coronavirus can be achieved in a relatively shorter period. The nucleotide analogue Remdesivir, is one such drug that has shown promise against the coronavirus.

Nucleotide analogues mimic natural nucleotides and upon incorporation in a growing DNA/RNA strand, halt viral polymerases, leading to chain termination. Thus, these molecules can act as antiviral drugs. Coronaviruses however, harbor a CoV nonstructural protein 14 (nsp14), with proofreading function (encodes a 3'-to-5' exoribonuclease activity (ExoN)), and is thus able to evade many nucleotide analogues[1]. This hampers the development of an effectual nucleotide analogue based antiviral drug, and several nucleotide analogues in the past have failed to inhibit coronavirus replication[2]. More recently though, the nucleotide analogue GS-5724 commonly known as Remdesivir, has yielded positive results against SARS-CoV-2.

Tracing the development and usage of Remdesivir

The broad-spectrum antiviral was originally developed by Gilead Sciences in 2009, to tackle hepatitis C failing which, [16]it was tested against Ebola and Marburg viruses [17.], [18]. Although yielding promising results in early Ebola trials, it was dropped in favor of the far more effective monoclonal antibody treatments [19]. Subsequently, in *in vitro* experiments remdesivir was shown to have antiviral activity against multiple filoviruses, pneumo viruses, paramyxoviruses, and coronaviruses[20].

Remdesivir is designed as a ‘prodrug’, which is metabolised in the body to its active form, i.e the nucleotide analogue (Fig.1). This molecule evades proofreading by ExoN and interferes with the action of the viral RNA-dependent RNA polymerase, [4]causing chain termination. It was also seen that the chain termination occurs after five additional bases have been added to the growing RNA chain[13].

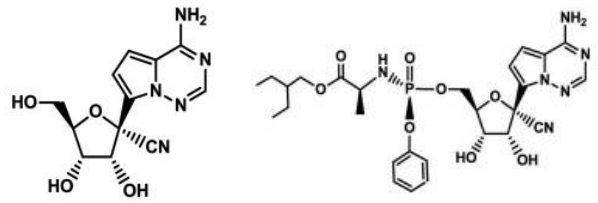

Figure 1 - Chemical structures of the nucleotide analogue (Remdesivir) and it's prodrug[3]

Remdesivir has been found effective in *in vitro* experiments against several human and animal SARS-CoV, MERS-CoV, bat CoV strains and SARS-CoV-2[9,10]. Furthermore, a study found it to be prophylactic in a mouse model[4]. In the mouse hepatitis virus (MHV), mutations emerged that led to partial resistance to remdesivir, however, overall these mutations also rendered the virus less infectious in nature[3].

The drug is usually intravenously administered[36] and Gilead has recently greenlighted an inhalable version of the drug for clinical trials [37].

Nucleotide analogues are generally safe and well tolerated as they are used by the viral, but not human, polymerases for DNA replication. Liver damage is seen as a common side-effect of such agents. Liver injury can be caused by the nucleoside analogue becoming incorporated into or blocking mitochondrial DNA synthesis. Mitochondrial injury can affect multiple tissues thereby causing myopathy, neuropathy, pancreatitis, bone marrow suppression and/or hepatic injury[15]. Other known adverse effects include respiratory failure and gastrointestinal distress[7]. Some reported side effects do not seem to have a direct correlation with the drug and may be indicative of a heightened immune response.

Remdesivir in COVID-19 Clinical Trials

Gilead Sciences began testing remdesivir against SARS-CoV-2 around January 2020, since its effectiveness against SARS-CoV and MERS-CoV viruses was previously documented[4]. In March 2020, two trials demonstrated that the drug prevented progression of COVID-19 in rhesus macaques [5,6].

In a randomized, double-blind, placebo-controlled, multicentre trial (NCT04257656) conducted in China (Feb - Mar 2020), remdesivir was deemed ineffective with adverse side-effects, which led to a premature trial termination[7]. Conversely, preliminary data from a similar, ongoing trial by NIAID-NIH (The Adaptive CoviD-19 Treatment Trial) showed that the drug was effective in reducing patient recovery time from 15 days to 11 days[8]. - the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo[8].

Recent preliminary results from a Phase 3 trial in patients with severe COVID-19 demonstrated that patients receiving a 10-day remdesivir treatment course achieved similar improvement in clinical status compared with those on a 5-day course[11]. A shorter (by half), just as effective treatment course in severe patients would have multiple obvious implications such as lesser side-effects from the drug, reduced burden of treatment expenses and freeing up of critical care facilities in hospitals that are stretched thin.

Recent data from the Phase-3 SIMPLE-severe trials showed that compared to standard care, remdesivir led to a 62% decrease in the mortality rate, and 74% of patients who received remdesivir recovered by day 14 compared to 59% receiving standard care. Moreover, subgroup analysis showed that traditionally marginalised subgroups and racial minorities experienced a similar benefit in clinical outcomes compared to overall patient population[43].

The World Health Organization is conducting an adaptive, randomized, open-label, multi-center clinical trial on the safety and efficacy of remdesivir and three other

investigational treatments in hospitalized adults with COVID-19. 3500 patients in 35 countries are already a part of the trial, while more than 100 countries have expressed interest in joining the trial., for which Gilead is providing cost-free study drugs and inputs on study design and conduct[22]. Along similar lines, Inserm in France is conducting a European study (DisCoVeRy Trials) evaluating remdesivir and other potential treatments, using a master protocol developed by WHO.

Table 1 summarizes various human trials in progress, around the world.

Organisation	Trial name/no.	Duration	Results
NIAID-NIH (ACTT)	NCT04280705, NCT04401579	21 Feb , 2020 - Ongoing	Preliminary results favorable
Gilead Sciences	NCT04292899, NCT04292730	27 Feb 2020 - Ongoing	Preliminary results favourable
U.S. Army Medical Research and Development Command	NCT04302766	10 Mar 2020 - Ongoing	Ongoing
World Health Organization - Solidarity	WHO Solidarity trial	18 Mar 2020 - Ongoing[22]	Ongoing
Inserm - DisCoVeRy	NCT04315948	20 Mar 2020 - Ongoing[21]	Ongoing
REMDACTA	NCT04409262	1 Jun 2020 - Ongoing	Ongoing

Table 1. A summary of the various ongoing clinical trials to determine the efficacy of remdesivir.

Current status of access and approval for COVID-19

Remdesivir access is classified as follows, for ease of access -

Access under trial - In these programs, the countries/regions are only allowed to use the drug as a part of a clinical trial. The inclusion criteria is trial specific.

Expanding access programs - This refers to the compassionate use of remdesivir outside

of clinical trials, when no satisfactory alternative therapy options are available . A detailed inclusion criteria for the Expanded Access Treatment Protocol by Gilead is accessible on ClinicalTrials.gov (NCT04323761). This includes patients with severe disease defined by the following parameters - SpO2≤ 94% on room air; having Alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN) and/or ALT < 3 x ULN and bilirubin < 2 x ULN.

Expanded access programs are now operational in the United States, Australia, Austria, Belgium, Canada, Cyprus, Czechia, Denmark, Estonia, France, Germany, Hungary, Iceland, Ireland, Israel, Italy, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Switzerland and the UK[32] (Figure 1).

Emergency usage authorization - This refers to the temporary authorization of drug usage in situations of emergency. In such cases, the scope of authorization as defined by the USFDA is followed[14]. The distribution of the drug is more tightly controlled by the Government. For COVID-19 disease, patients with severe disease (defined as SpO2≤ 94% on room air), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) are considered eligible.

USA, UK, India, Japan and South Korea have authorised emergency remdesivir usage[14, 33, 34, 35, 38] (Figure 1).

Other countries are likely to follow the guidelines as set by the USFDA. CDSCO (Central Drugs Standard Control Organisation), the Indian equivalent of FDA, has decided to follow a 5 day remdesivir treatment regimen.

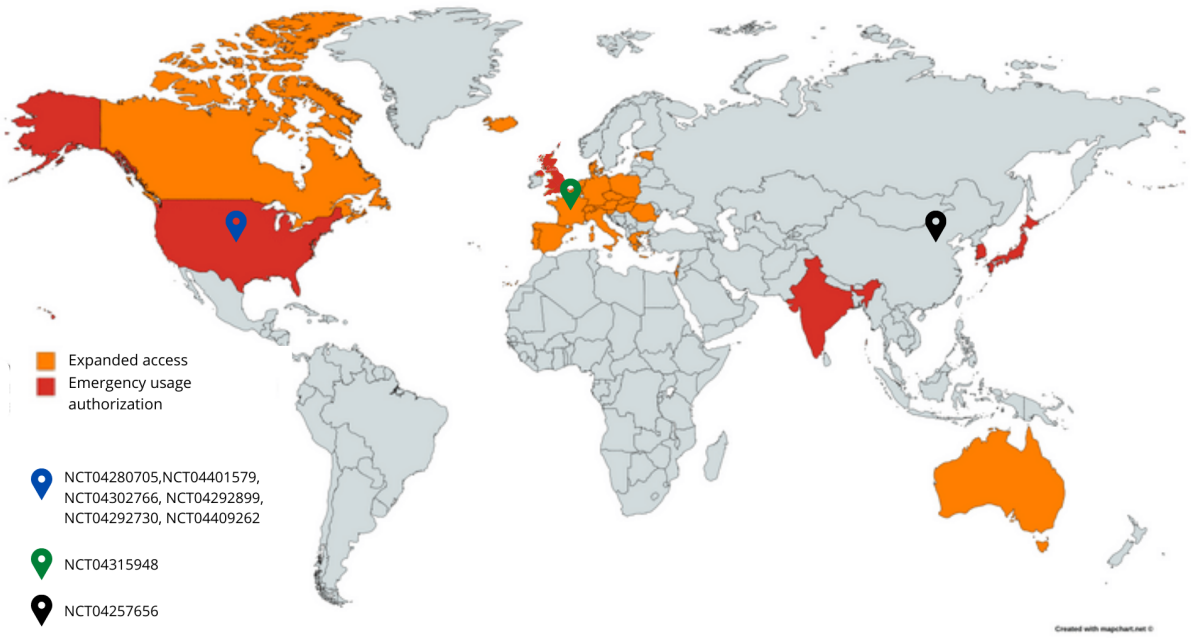

Figure 1: A world map showing the countries with different stages of Remdesivir access and the location of major human trials.

Future Perspectives

Initial results from the remdesivir trials show promise at least in patients on supplemental oxygen, with moderate disease. Ongoing clinical trials will be able to further clarify the efficacy and side-effects of the drug. Additionally, adequate drug availability and pricing are practical considerations to bear, that can be limiting factors. The production of remdesivir is costly and time-intensive, reportedly requiring 70 raw materials, reagents, and catalysts, and 9-10 months to generate the final product (ref). Even with subsidised pricing, it will remain out of reach of the uninsured and underprivileged. The lengthy process doesn't bode well for the burgeoning COVID-19 cases as demand far exceeds drug supply. Other pharmaceutical companies (eg.. Mylan, Cipla, Hetero Labs, Jubilant Life Sciences, Ferozsons Laboratories) are joining forces with Gilead to cater to the growing demand.

Similar to remdesivir, other potential nucleoside/nucleotide analogues that can either evade recognition by ExoN or be inserted in the elongating strand at a rate exceeding ExoN excision kinetics, should be tested against SARS-CoV. Some such potential antiviral molecules include Ribavirin[23,24], Beta-d-N4-hydroxycytidine (NHC)[25,26], Lopinavir/Ritonavir[27], Remdesivir in combination with lopinavir, ritonavir, and interferon beta[12], Galidesivir or BCX4430[30] and 6-azauridine[31].

Conclusion

Available data from clinical trials and studies strongly suggests that the benefits of remdesivir outweighs its risks. As the number of COVID-19 patients swell worldwide with no signs of near abatement, healthcare systems flounder and mortality mounts, remdesivir and other repurposed drugs can provide a much needed reprieve.

References

1. Case JB, Li Y, Elliott R, et al. "Murine Hepatitis Virus nsp14 Exoribonuclease Activity Is Required for Resistance to Innate Immunity". *J Virol*. 2017;92(1):e01531-17. Published 2017 Dec 14. doi:10.1128/JVI.01531-17
2. Chu CK, Gadthula S, Chen X, Choo H, Olgen S, Barnard DL, Sidwell RW. "Antiviral activity of nucleoside analogues against SARS-coronavirus (SARS-coV)." *Antivir Chem Chemother*. 2006; 17(5):285-9.
3. Agostini, Maria L et al. "Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease." *mBio* vol. 9,2 e00221-18. 6 Mar. 2018, doi:10.1128/mBio.00221-18
4. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. (June 2017). "Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic

coronaviruses". *Science Translational Medicine*. **9** (396): eaal3653. doi:10.1126/scitranslmed.aal3653
5. Munster V, Feldmann F, Williamson B, Van Doremalen N, Perez-Perez L, Schultz J, et al. (March 2020). "Respiratory disease and virus shedding in rhesus macaques inoculated with SARS-CoV-2". bioRxiv 10.1101/2020.03.21.001628
6. Williamson B, Feldmann F, Schwarz B, Meade-White K, Porter D, Schulz J, et al. (April 2020). "Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2". bioRxiv 10.1101/2020.04.15.043166
7. Cao B, Wang C, Wang Y, Zhou F, Zhang D, Zhao J, Du R, Hu Y, Cheng Z, Gao L, Jin Y (29 April 2020). "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial". *The Lancet*: S0140673620310229. doi:10.1016/S0140-6736(20)31022-9
8. J Beigel *et al*. Remdesivir for the Treatment of COVID-19 – Preliminary Report. *The New England Journal of Medicine* DOI: 10.1056/NEJMoa2007764 (2020)
9. Sheahan TP, Sims AC, Graham RL. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9
10. Brown AJ, Won JJ, Graham RL. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res. 2019;169
11. "Gilead Announces Results From Phase 3 Trial of Investigational Antiviral Remdesivir in Patients With Severe COVID-19". *Gilead Biosciences* (Press release). 29 April 2020.
12. Sheahan, T.P., Sims, A.C., Leist, S.R. *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* **11,** 222 (2020). https://doi.org/10.1038/s41467-019-13940-6
13. Tchesnokov EP, Feng JY, Porter DP, Götte M (April 2019). "Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir". *Viruses*. **11** (4): 326. doi:10.3390/v11040326. PMC 6520719
14. "Remdesivir EUA Letter of Authorization", Retrieved from - https://www.fda.gov/media/137564/download
15. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Nucleoside Analogues. [Updated 2020 May 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548938/
16. Stephens, Bret (18 April 2020). "The Story of Remdesivir". *The New York Times*. p. A23. Retrieved 11 May 2020.
17. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. (March 2016). "Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys". *Nature*. **531** (7594): 381–5. Bibcode:2016Natur.531..381W. doi:10.1038/nature17180. PMC 5551389. PMID 26934220.
18. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. (March 2016). "Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys". *Nature*. **531** (7594): 381–5. Bibcode:2016Natur.531..381W. doi:10.1038/nature17180. PMC 5551389. PMID 26934220.
19. Molteni M (12 August 2019). "Ebola is Now Curable. Here's How The New Treatments Work". *Wired*. Retrieved 13 August 2019.
20. Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL, et al. (March 2017). "GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses". *Scientific Reports*. **7**: 43395. Bibcode:2017NatSR...743395L. doi:10.1038/srep43395. PMC 5338263. PMID 28262699.

21. Retrieved from - https://clinicaltrials.gov/ct2/show/NCT04315948
22. Solidarity clinical trial for COVID-19 treatments Retrieved from - https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
23. Chen F., Chan K.H., Jiang Y., Kao R.Y.T., Lu H.T., Fan K.W., Cheng V.C.C., Tsui W.H.W., Hung I.F.N., Lee T.S.W. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004;31:69–75.
24. Chan J.F.W., Chan K.-H., Kao R.Y.T., To K.K.W., Zheng B.-J., Li C.P.Y., Li P.T.W., Dai J., Mok F.K.Y., Chen H. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect. 2013;67:606–616.
25. Barnard D.L., Hubbard V.D., Burton J., Smee D.F., Morrey J.D., Otto M.J., Sidwell R.W. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARSCoV) by calpain inhibitors and beta-d-N4-hydroxycytidine. Antivir Chem Chemother. 2004;15:15–22.
26. Pyrc K., Bosch B.J., Berkhout B., Jebbink M.F., Dijkman R., Rottier P., van der Hoek L. Inhibition of human coronavirus NL63 infection at early stages of the replication cycle. Antimicrob Agents Chemother. 2006;50:2000–2008.
27. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. (March 2020). "A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19". *New England Journal of Medicine*.
28. Westover JB, et al. Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters. *Antiviral Res*. 2018 Aug;156:38-45. Westover, J. B.; Mathis, A.; Taylor, R.; Wandersee, L.; Bailey, K. W.; Sefing, E. J.; Hickerson, B. T.; Jung, K. H.; Sheridan, W. P.; Gowen, B. B. (2018). "Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters". *Antiviral Research*. **156**: 38–45.
29. Praveen Duddu. Coronavirus outbreak: Vaccines/drugs in the pipeline for Covid-19. clinicaltrialsarena.com 19 February 2020. Retrieved from - https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/
30. A Study to Evaluate the Safety, Pharmacokinetics and Antiviral Effects of Galidesivir in Yellow Fever or COVID-19 - Retrieved from - https://clinicaltrials.gov/ct2/show/NCT03891420
31. Pyrc K, Bosch BJ, Berkhout B, Jebbink MF, Dijkman R, Rottier P, van der Hoek L. Inhibition of human coronavirus NL63 infection at early stages of the replication cycle. Antimicrob Agents Chemother. 2006 Jun;50(6):2000-8. doi: 10.1128/AAC.01598-05. PMID: 16723558; PMCID: PMC1479111.
32. Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection (COVID-19). Retrieved from - https://clinicaltrials.gov/ct2/show/NCT04323761
33. India Approves Emergency Use Of Gilead's Remdesivir To Treat Covid-19 Patients - https://www.bloombergquint.com/coronavirus-outbreak/india-s-drug-regulator-grants-gilead-sciences-marketing-authorisation-for-remdesivir-2
34. Gilead Announces Approval of Veklury® (remdesivir) in Japan for Patients With Severe COVID-19 - Retrieved from-https://www.gilead.com/news-and-press/press-room/press-releases/2020/5/gilead-announces-approval-of-veklury-remdesivir-in-japan-for-patients-with-severe-covid19
35. South Korea approves emergency use of Gilead's anti-viral drug to treat COVID-19-Retrieved from-https://www.reuters.com/article/us-health-coronavirus-southkorea-drug/south-korea-approves-import-of-anti-viral-drug-remdesivir-for-coronavirus-treatment-idUSKBN23A0DH

36. FACT SHEET FOR HEALTH CARE PROVIDERSEMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734™) - Retrieved from - https://www.fda.gov/media/137566/download

37. Daniel O'Day, An Open Letter from Daniel O'Day, Chairman & CEO, Gilead Sciences. Retrieved from - https://stories.gilead.com//articles/an-open-letter-from-daniel-oday-june-22

38. Roberts M (26 May 2020). "Anti-viral drug that speeds recovery offered by NHS". BBC News Online. Retrieved 26 May 2020.

39. Langreth R (14 May 2020). "All Eyes on Gilead". *Bloomberg Businessweek*. Retrieved 14 May 2020.

40. Working to Supply Remdesivir for COVID-19 - Gilead.com, Retrieved on 11 July

41. Gilead remdesivir deal signed with five manufacturers - Pharmaceutical-technology.com, Retrieved on 11 July

42. Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M. L., Lescure, F.-X., Nicastri, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Bernett, J., Chelliah, D., … Flanigan, T. (2020). Compassionate Use of Remdesivir for Patients with Severe Covid-19. New England Journal of Medicine, 382(24), 2327–2336. https://doi.org/10.1056/nejmoa2007016

43. Gilead Presents Additional Data on Investigational Antiviral Remdesivir for the Treatment of COVID-19 https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19

1.

1. Case JB, Li Y, Elliott R, et al. "Murine Hepatitis Virus nsp14 Exoribonuclease Activity Is Required for Resistance to Innate Immunity". J Virol. 2017;92(1):e01531-17. Published 2017 Dec 14. doi:10.1128/JVI.01531-17
https://doi.org/10.1128/JVI.01531-17

2. Chu CK, Gadthula S, Chen X, Choo H, Olgen S, Barnard DL, Sidwell RW. "Antiviral activity of nucleoside analogues against SARS-coronavirus (SARS-coV)." Antivir Chem Chemother. 2006; 17(5):285-9.
https://doi.org/10.1177/095632020601700506

3. Agostini, Maria L et al. "Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease." mBio vol. 9,2 e00221-18. 6 Mar. 2018, doi:10.1128/mBio.00221-18
https://doi.org/10.1128/mBio.00221-18

4. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. (June 2017). "Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses". Science Translational Medicine. 9 (396): eaal3653. doi:10.1126/scitranslmed.aal3653
https://doi.org/10.1126/scitranslmed.aal3653

5. Munster V, Feldmann F, Williamson B, Van Doremalen N, Perez-Perez L, Schultz J, et al. (March 2020). "Respiratory disease and virus shedding in rhesus macaques inoculated with SARS-CoV-2". bioRxiv 10.1101/2020.03.21.001628
https://doi.org/10.1101/2020.03.21.001628

6. Williamson B, Feldmann F, Schwarz B, Meade-White K, Porter D, Schulz J, et al. (April 2020). "Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2". bioRxiv 10.1101/2020.04.15.043166
https://doi.org/10.1101/2020.04.15.043166

7. Cao B, Wang C, Wang Y, Zhou F, Zhang D, Zhao J, Du R, Hu Y, Cheng Z, Gao L, Jin Y (29 April 2020). "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial". The Lancet: S0140673620310229. doi:10.1016/S0140-6736(20)31022-9
https://doi.org/10.1016/S0140-6736(20)31022-9

8. J Beigel et al. Remdesivir for the Treatment of COVID-19 - Preliminary Report. The New England Journal of Medicine DOI: 10.1056/NEJMoa2007764 (2020) https://doi.org/10.1056/NEJMoa2007764

9. Sheahan TP, Sims AC, Graham RL. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9 https://doi.org/10.1126/scitranslmed.aal3653

10. Brown AJ, Won JJ, Graham RL. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res. 2019;169 https://doi.org/10.1016/j.antiviral.2019.104541

11. "Gilead Announces Results From Phase 3 Trial of Investigational Antiviral Remdesivir in Patients With Severe COVID-19". Gilead Biosciences (Press release). 29 April 2020.

12. Sheahan, T.P., Sims, A.C., Leist, S.R. et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 11, 222 (2020). https://doi.org/10.1038/s41467-019-13940-6 https://doi.org/10.1038/s41467-019-13940-6

13. Tchesnokov EP, Feng JY, Porter DP, Götte M (April 2019). "Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir". Viruses. 11 (4): 326. doi:10.3390/v11040326. PMC 6520719 https://doi.org/10.3390/v11040326

14. "Remdesivir EUA Letter of Authorization", Retrieved from - https://www.fda.gov/media/137564/download

15. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Nucleoside Analogues. [Updated 2020 May 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548938/

16. Stephens, Bret (18 April 2020). "The Story of Remdesivir". The New York Times. p. A23. Retrieved 11 May 2020.

17. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. (March 2016). "Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys". Nature. 531 (7594): 381-5. Bibcode:2016Natur.531..381W. doi:10.1038/nature17180. PMC 5551389. PMID 26934220.
https://doi.org/10.1038/nature17180

18. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. (March 2016). "Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys". Nature. 531 (7594): 381-5. Bibcode:2016Natur.531..381W. doi:10.1038/nature17180. PMC 5551389. PMID 26934220.
https://doi.org/10.1038/nature17180

19. Molteni M (12 August 2019). "Ebola is Now Curable. Here's How The New Treatments Work". Wired. Retrieved 13 August 2019.

20. Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL, et al. (March 2017). "GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses". Scientific Reports. 7: 43395. Bibcode:2017NatSR...743395L. doi:10.1038/srep43395. PMC 5338263. PMID 28262699.
https://doi.org/10.1038/srep43395

21. Retrieved from - https://clinicaltrials.gov/ct2/show/NCT04315948

22. Solidarity clinical trial for COVID-19 treatments Retrieved from - https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

23. Chen F., Chan K.H., Jiang Y., Kao R.Y.T., Lu H.T., Fan K.W., Cheng V.C.C., Tsui W.H.W., Hung I.F.N., Lee T.S.W. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004;31:69-75.
https://doi.org/10.1016/j.jcv.2004.03.003

24. Chan J.F.W., Chan K.-H., Kao R.Y.T., To K.K.W., Zheng B.-J., Li C.P.Y., Li P.T.W., Dai J., Mok F.K.Y., Chen H. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect. 2013;67:606-616.
https://doi.org/10.1016/j.jinf.2013.09.029

25. Barnard D.L., Hubbard V.D., Burton J., Smee D.F., Morrey J.D., Otto M.J., Sidwell R.W. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARSCoV) by calpain inhibitors and beta-d-N4-hydroxycytidine. Antivir Chem Chemother. 2004;15:15-22.
https://doi.org/10.1177/095632020401500102

26. Pyrc K., Bosch B.J., Berkhout B., Jebbink M.F., Dijkman R., Rottier P., van der Hoek L. Inhibition of human coronavirus NL63 infection at early stages of the replication cycle. Antimicrob Agents Chemother. 2006;50:2000-2008.
https://doi.org/10.1128/AAC.01598-05

27. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. (March 2020). "A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19". New England Journal of Medicine.

28. Westover JB, et al. Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters. Antiviral Res. 2018 Aug;156:38-45. Westover, J. B.; Mathis, A.; Taylor, R.; Wandersee, L.; Bailey, K. W.; Sefing, E. J.; Hickerson, B. T.; Jung, K. H.; Sheridan, W. P.; Gowen, B. B. (2018). "Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters". Antiviral Research. 156: 38-45.
https://doi.org/10.1016/j.antiviral.2018.05.013

29. Praveen Duddu. Coronavirus outbreak: Vaccines/drugs in the pipeline for Covid-19. clinicaltrialsarena.com 19 February 2020. Retrieved from - https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/

30. A Study to Evaluate the Safety, Pharmacokinetics and Antiviral Effects of Galidesivir in Yellow Fever or COVID-19 - Retrieved from - https://clinicaltrials.gov/ct2/show/NCT03891420

31. Pyrc K, Bosch BJ, Berkhout B, Jebbink MF, Dijkman R, Rottier P, van der Hoek L. Inhibition of human coronavirus NL63 infection at early stages of the replication cycle. Antimicrob Agents Chemother. 2006 Jun;50(6):2000-8. doi: 10.1128/AAC.01598-05. PMID: 16723558; PMCID: PMC1479111.
https://doi.org/10.1128/AAC.01598-05

32. Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection (COVID-19), Retrieved from - https://clinicaltrials.gov/ct2/show/NCT04323761

33. India Approves Emergency Use Of Gilead's Remdesivir To Treat Covid-19 Patients - https://www.bloombergquint.com/coronavirus-outbreak/india-s-drug-regulator-grants-gilead-sciences-marketing-authorisation-for-remdesivir-2

34. Gilead Announces Approval of Veklury® (remdesivir) in Japan for Patients With Severe COVID-19 - Retrieved from-https://www.gilead.com/news-and-press/press-room/press-releases/2020/5/gilead-announces-approval-of-veklury-remdesivir-in-japan-for-patients-with-severe-covid19

35. South Korea approves emergency use of Gilead's anti-viral drug to treat COVID-19-Retrieved from- https://www.reuters.com/article/us-health-coronavirus-southkorea-drug/south-korea-approves-import-of-anti-viral-drug-remdesivir-for-coronavirus-treatment-idUSKBN23A0DH

36. FACT SHEET FOR HEALTH CARE PROVIDERSEMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734™) - Retrieved from - https://www.fda.gov/media/137566/download

37. Daniel O'Day, An Open Letter from Daniel O'Day, Chairman & CEO, Gilead Sciences. Retrieved from - https://stories.gilead.com//articles/an-open-letter-from-daniel-oday-june-22

38. Roberts M (26 May 2020). "Anti-viral drug that speeds recovery offered by NHS". BBC News Online. Retrieved 26 May 2020.

39. Langreth R (14 May 2020). "All Eyes on Gilead". Bloomberg Businessweek. Retrieved 14 May 2020.

40. Working to Supply Remdesivir for COVID-19 - Gilead.com, Retrieved on 11 July

41. Gilead remdesivir deal signed with five manufacturers - Pharmaceutical-technology.com, Retrieved on 11 July

42. Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M. L., Lescure, F.-X., Nicastri, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Bernett, J., Chelliah, D., … Flanigan, T. (2020). Compassionate Use of Remdesivir for Patients with Severe Covid-19. New England Journal of Medicine, 382(24), 2327-2336. https://doi.org/10.1056/nejmoa2007016 https://doi.org/10.1056/NEJMoa2007016

43. Gilead Presents Additional Data on Investigational Antiviral Remdesivir for the Treatment of COVID-19 https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19