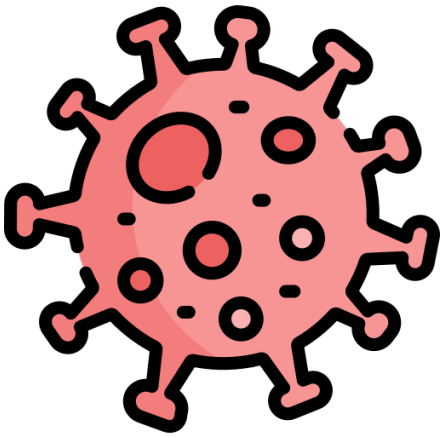

HOW DOES REMDESIVIR INHIBIT SARS-COV2

A COVID-19 Research Paper

By: Allan Yin

Table of Contents

I. BACKGROUND

Coronavirus disease 2019 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and is responsible for the COVID-19 pandemic.

SARS-CoV2 is a novel severe acute respiratory syndrome coronavirus and was first detected and isolated from three individuals in Wuhan, China. The SARS-CoV2 is closely linked to the 2003 SARS-CoV and is currently thought to have zoonotic origin.

SARS-CoV2 belongs to the family of coronaviruses and is the seventh known coronavirus to infect humans. SARS-CoV2 is a beta-coronavirus. There, are in total, four genera (Alpha, Beta, Gamma, and Delta) of coronaviruses. They are all enveloped, positive-sense, single-stranded RNA viruses of zoonotic origin. The beta-coronaviruses of the greatest clinical importance concerning humans are OC43 and HKU1 (which can cause the common cold) of lineage A, SARS-CoV and SARS-CoV-2 of lineage B and MERS-CoV of lineage C. MERS-CoV is the first beta-coronavirus belonging to lineage C that is known to infect humans.

Coronaviruses are a group of related RNA viruses that can cause disease in mammals and birds. Through genetic analysis, bats have been identified as a natural reservoir for coronaviruses. Both SARS-CoV and SARS-CoV-2 are closely related and originated in bats, who most likely serve as reservoir host for these two viruses[1]. Whereas palm civets and racoon dogs have been identified as intermediate hosts for SARS-CoV between bats and humans, the intermediate hosts for SARS-CoV2 are unknown. In the case of humans, it causes people to develop respiratory tract infections with the lethality of the disease varying between individuals.

The human immune response in mild cases can be characterized by a robust type I interferon antiviral response. One difference between mild cases and severe cases is the initial response time of the immune system. In severe cases, there is likely an initial delay in antiviral response, leading to an increased amount of inflamed cytokines and an influx of neutrophils and monocytes into the lung.

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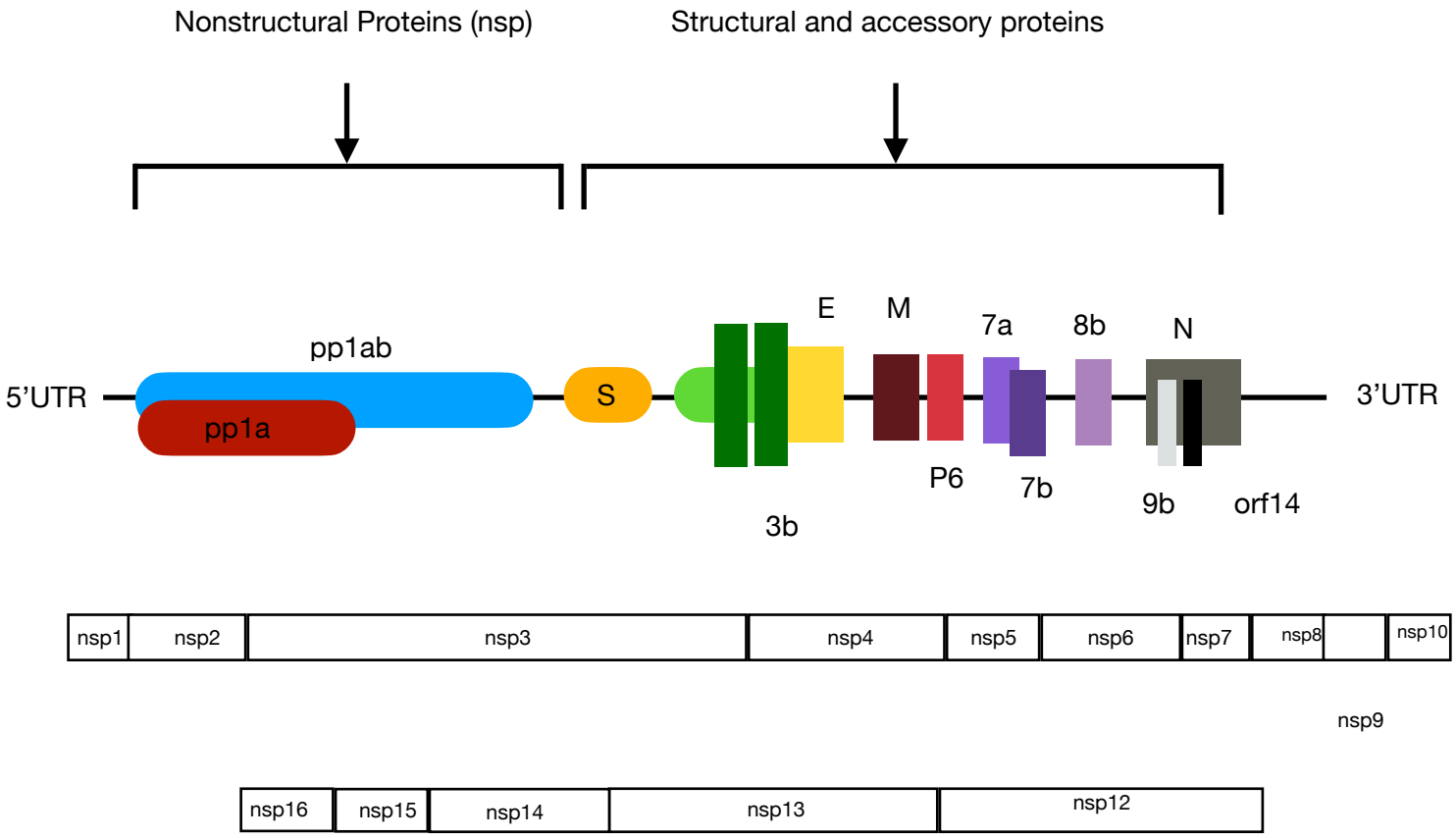
[1] Woo, P. C. Y., Lau, S. K. P., Chu, C.-ming, Chan, K.-hung, Tsoi, H.-wah, Huang, Y., … Yuen, K.-yung. (2005, January). *Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia*. Journal of virology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC538593/.

Figure 1: Encoded genome of 2019-nCoV



The SARS-CoV2 is a 30 kb RNA virus including 27 proteins[2]:

1. non-structure (NSP1 to NSP16) , NSP12 codes RNA Polymerase responsible for RNA replication for SARS-CoV2
2. Structure proteins (S protein, M protein, E protein, N protein).
3. Accessory proteins

The SARS-CoV2 virus is composed of a helical capsid formed by nucleocapsid (N) proteins by bound to the RNA genome and an envelope made of membrane (M) and envelope (E) proteins coated with trimeric spike (S) proteins.

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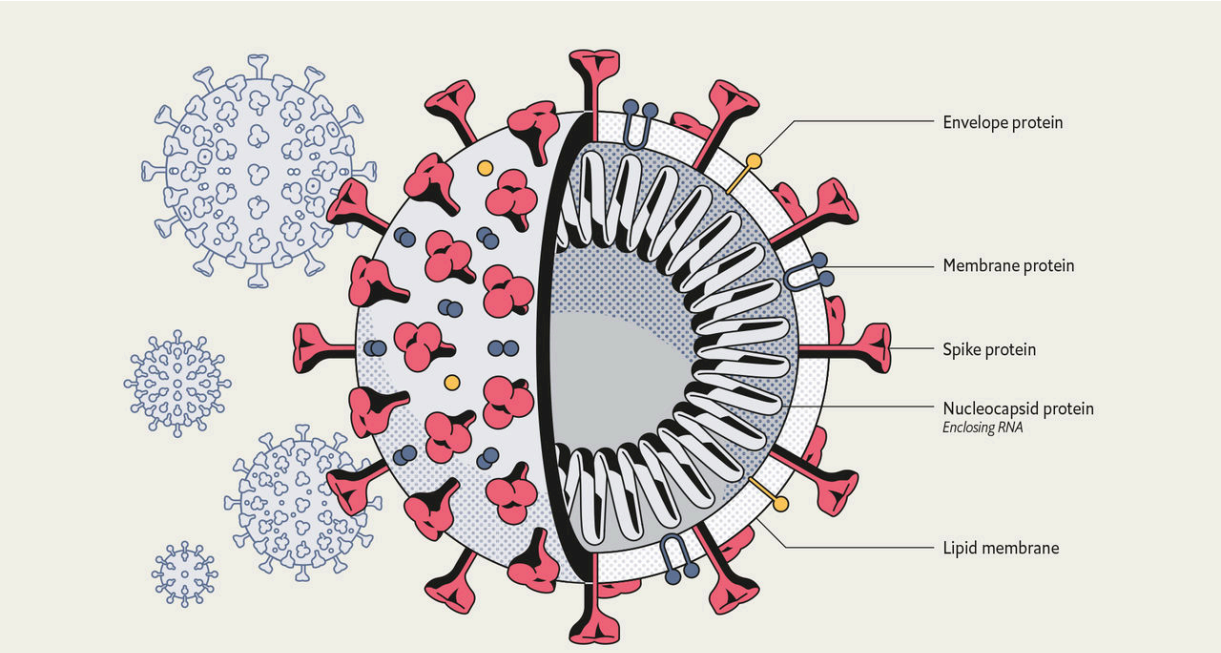
[2] Khailany, R. A., Safdar, M., & Ozaslan, M. (2020, April 16). *Genomic characterization of a novel SARS-CoV-2*. Gene reports. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7161481/.

Figure 1: Viral structure of SARS-CoV2



The image above is one of the viral structure of SARS-CoV2. The spike (S) glycoproteins are responsible for receptor binding and membrane fusion. They are targeted by hist neutralizing antibodies. The envelope protein (E) is crucial for virus infectivity. The membrane protein, also known as the metric glycoprotein, is the most abundant structural protein and interacts with the envelope (E) protein to form the viral envelope.

First identified in December 2019 in Wuhan, China, it has now spread to 213 countries and territories around the world. Emerging coronavirus (CoVs) cause severe disease in humans and yet, there have been no approved therapeutics available until Remdesivir.

II. SARS-CoV2 entry

Current evidence suggests that COVID-19 spreads between people through direct, indirect, or close contact with infected people via mouth and nose fluids. People who are in close contact (within 1 metre) with an infected person can catch

COVID-19 when droplets of secreted fluids from the mouth or nose of an infected person gets into an uninfected individuals mouth, nose or eyes.

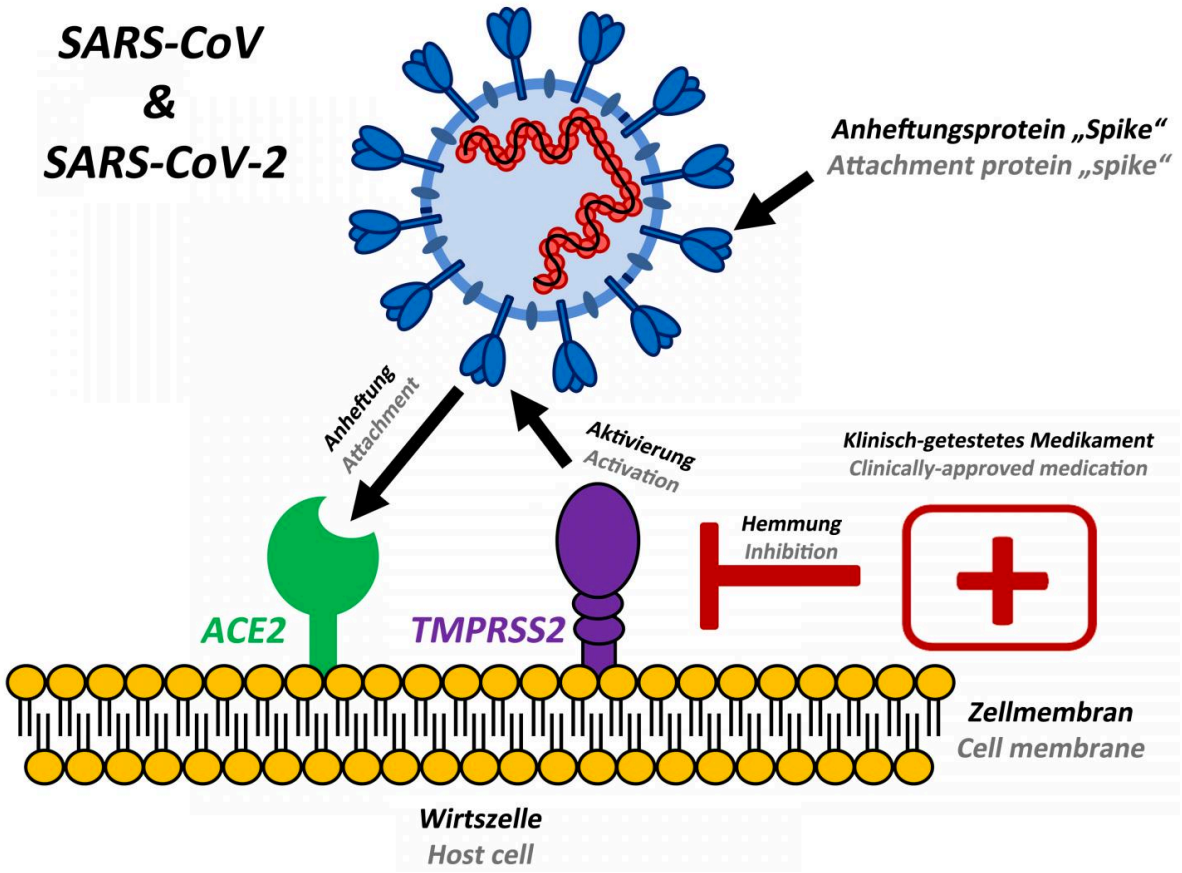


Figure 2: SARS-CoV2 entry into host cell
Figure description:

Coronavirus entry into host cells is mediated by transmembrane spike (S) glycoprotein. As mentioned above, spike (S) glycoproteins are responsible for receptor binding and membrane fusion. S glycoproteins are comprised of two functional subunits: S_1 subunit, helps cell bind the host cell, and S_2 subunit, fusion of the viral and cellular membrane.

III. ANTIVIRAL TARGET OF SARS-CoV2

Currently, there is no specific drug that has been proven effective as treatment for patients with severe COVID-19[3] except Remdesivir. Many antivirals gone through clinical trial, only Remdesivir has...

List more antivirals that have been tested

IV. HISTORY OF REMDESIVIR

In 1947, researchers from a commercial drug company discovered chloramphenicol, a molecule that had the ability to fight bacteria from multiple families[4]. It was among the first broad-spectrum antibiotics approved by the FDA. However, it was utilized only as an emergency drug due to the side effects.

Figure 3: Capsule of Remdesivir

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[3] Grein, J., Al., E.,Center, A. A. F. C. S. M., M. G. Baker and Others, D. R. Boulware and Others, & A. B. Cavalcanti and Others. (2020, June 18). *Compassionate Use of Remdesivir for Patients with Severe Covid-19: NEJM*. https://www.nejm.org/doi/full/10.1056/NEJMoa2007016.

[4] Eastman, R. T., Roth, J. S., Brimacombe, K. R., Simeonov, A., Shen, M., Patnaik, S., & Hall, M. D. (2020, May 27). Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. ACS central science. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202249/.

After the discovery of chloramphenicol, researchers found a new target for chloramphenicol: viruses. In 1963, the FDA approved the first antiviral, which paved the way for modern-day drugs. Some of which are hyper-focused on a certain virus (e.g this is the case for many HIV-1 treatment methods), some work on multiple types of viruses within the same family, but, rarely are there medicines which stretch across viral families.

This state makes searching for a treatment for SARS-CoV2 difficult. There is no broad-spectrum antiviral approved for SARS-CoV2.[5] Remdesivir was first noticed in 2015 during the Ebola outbreak. At that time, the U.S Army Medical Research Institute of Infectious Diseases declared a partnership with biopharmaceutical company, Gilead Sciences. They had discovered the first molecule that could protect a host cell from the deadly effects of Ebola. In cells in the lab, it hampered not only Ebola viruses but also several others, including the coronavirus that caused MERS.

Remdesivir, known as GS-5734, was originally created to kill other viruses, not SARS-CoV2. Rather, it was developed to treat hepatitis C and tested against Ebola virus. Remdesivir is a nucleoside analogue prodrug and has inhibitory effects on pathogenic animal and human coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, and inhibits Middle East respiratory syndrome coronavirus, SARS-CoV-1, and SARS-CoV-2 replication in animal models.[6]

Remdesivir currently stands as the only therapeutic, although issued only for emergency use, authorized by the FDA and many countries around the world. While there is still very limited information known about the safety and effectiveness of using Remdesivir, its has been crucial in the fight against COVID-19. However, it is in short supply and is not accessible for everyone at the moment.

The molecular formula for remdesivir is: $C_{27}H_{35}N_6O_8P$. Below is a ball and stick model of the molecular structure of remdesivir.

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[5] Eastman, R. T., Roth, J. S., Brimacombe, K. R., Simeonov, A., Shen, M., Patnaik, S., & Hall, M. D. (2020, May 27). Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. ACS central science. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202249/.

[6] Beigel, J. H., Al., E., for the ACTT-1 Study Group Members*, Author AffiliationsFrom the National Institute of Allergy and Infectious Diseases, Hirsch, R. D. and M. S., M. G. Baker and Others, … A. B. Cavalcanti and Others. (2020, May 27). *Remdesivir for the Treatment of Covid-19 - Preliminary Report: NEJM*. New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa2007764.

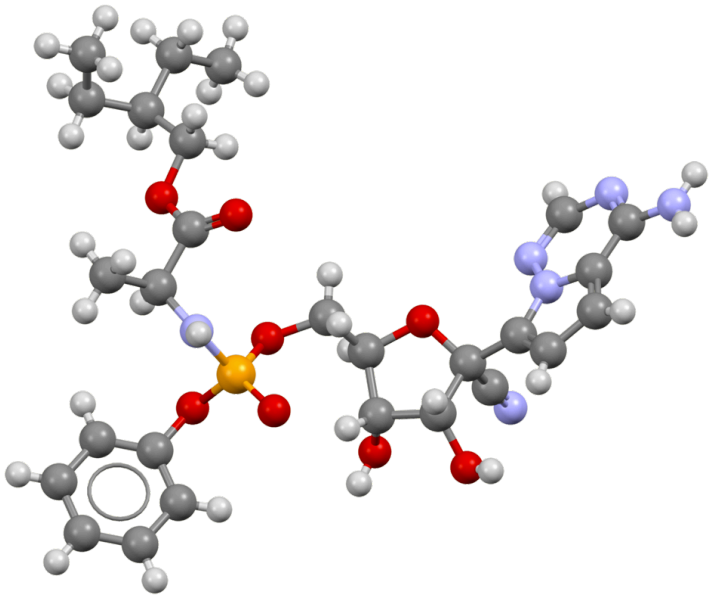


Figure 4: Ball and stick model of molecular structure of remdesivir
Figure Description: *Remdesivir found in a crystal structure. In the diagram the grey balls are carbon, white balls are hydrogen, blue balls are nitrogen, red balls are oxygen, and orange balls are phosphorus.*

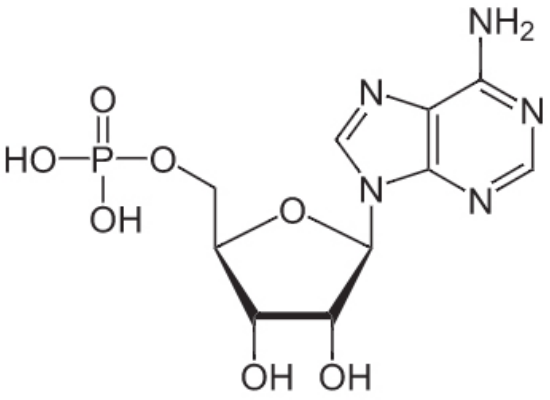
V. HOW DOES IT WORK?

As mentioned previously, remdesivir is an antiviral drug. The time of using remdesivir is to minimize symptoms and infectivity as well as shorten the life span of the virus in the human. Remdesivir attacks the replication process of viruses at different stages. As SARS-CoV2 is a RNA virus, remdesivir subdues it by interfering with replication.

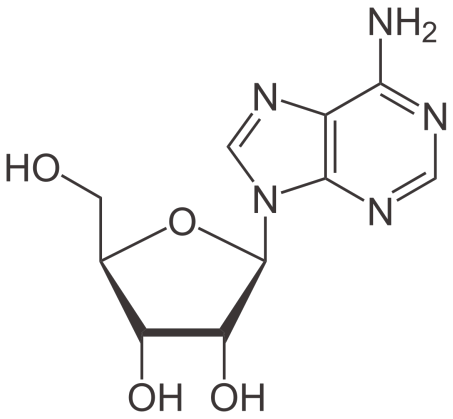
Upon injection, remdesivir becomes nucleoside analog. Essentially, it imitates adenosine and tricks the virus into using it in its replication process. However, the analog's molecular makeup differs from real adenosine just enough to grind the copying process to a halt.

Figure 5: Comparison of molecular structure between remdesivir and adenosine

Lewis structure of remdesivir

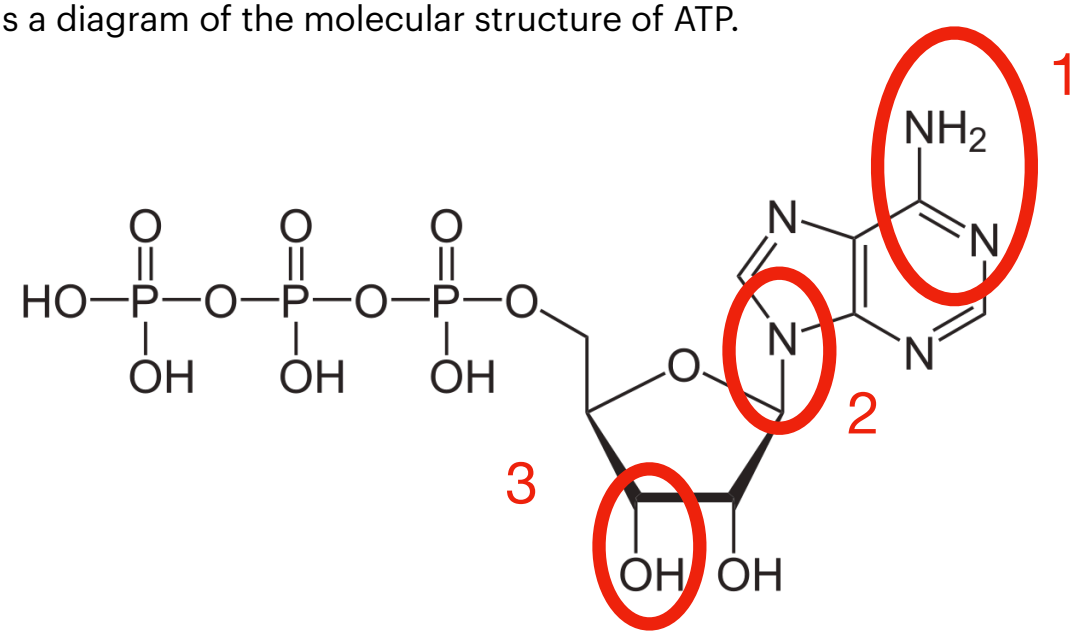


Lewis structure of adenosine



As seen from above, remdesivir resembles the RNA base adenosine. Adenosine consists of an adenine attached to a ribose via a β-N_9-glycosidic bond. Adenosine is one of four nucleoside building blocks to RNA, which is essential for all life. It is shown as a monophosphate in the image above. Remdesivir has some distinctive differences from ATP (Adenosine triphosphate).

Below is a diagram of the molecular structure of ATP.



Remdesivir and ATP have some noticeable differences, but also, very select features bear similarity. Here are some similarities that have been highlighted above:

1. Base pairing to uracil: The section of adenosine in double-stranded RNA is important for base-paining with uracil. The 2 hydrogens have 2 roles - being proton donors and acceptors. By sharing this feature with ATP, remdesivir is able to insert itself into a growing RNA strand of SARS-CoV2 polymerases.[7]

2. C-nucleoside bond: Remdesivir and ATP share this glucosidic bond. Under normal circumstances, this connects the 1' carbon in the ribose ring to the nitrogenous base. However, in Remdesivir, the nucleobase and sugar are connected by a bond by 2 carbon atoms.

3. 3' hydroxy group: Different classes of nucleoside/nucleotide analogs have different effects on polymerases. Remdesivir is in a class called non-obligate chain terminators, because it should, in theory, be possible to add more nucleotides to a strand of RNA after remdesivir has been added due to the presence of the hydroxyl group at carbon 3 in the sugar. Those additional nucleotides may help shield remdesivir from coronavirus proofreading enzymes that are known to remove unnatural nucleotide analogs.

Overall, by disrupting the replication process, the viruses spread is effectively stopped. By preventing the virus from replicating, the immune system can kill whatever of the virus that remains in the body.

[7] Oldach, L. (2020, March 17). Anatomy of a molecule: What makes remdesivir unique? Retrieved September 27, 2020, from https://www.asbmb.org/asbmb-today/science/031720/what-makes-remdesivir-a-promising-antiviral

VI. METHOD

In a study authorized by the Government of Canada, Researchers provided Remdesivir on a compassionate use to severe COVID-19 patients. Patents were selected if they had an oxygen saturation of 94% or less while they were breathing ambient air or were receiving oxygen support.[8] Patients followed a 10-day routine of remdesivir consumption:

- 10-day course of remdesivir
- 200 mg administered intravenously on day 1
- 100 mg daily for the remaining 9 days of treatment.

This was conducted from January 25, 2020, through March, 7, 2020.

VII. CLINICAL REPORT OF REMDESIVIR IN COVID-19 PATIENTS

Below is the information of the 61 patients involved in the study that received doses of remdesivir. Of the 61, there were 8 patients whose data could not be analyzed

- 1 had a dosing error
- The other 7 did not have any post-treatment data

The other 53 patients were able to be analyzed. Below are data gathered about the test patients:

- 30 patients (57%) were receiving mechanical ventilation
- 4 (8%) were receiving extracorporeal membrane oxygenation.
- During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class

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[8] Grein, J., Al., E.,Center, A. A. F. C. S. M., M. G. Baker and Others, D. R. Boulware and Others, & A. B. Cavalcanti and Others. (2020, June 18). *Compassionate Use of Remdesivir for Patients with Severe Covid-19: NEJM*. https://www.nejm.org/doi/full/10.1056/NEJMoa2007016.

- A total of 25 patients (47%) were discharged
- 7 patients (13%) died[9]
- Mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.[10]

VIII. FUTURE DIRECTIONS

Undoubtedly, the current COVID-19 situation has made the process of approving remdesivir unconventional. Under normal circumstances, drug studies and clinical trials would take at least years before becoming commercialized for use. In less than two months of the COVID-19 pandemic in the U.S and many other countries, Gilead has shown that 31 percent of patients who take remdesivir improve.

Doctors can now prescribe remdesivir to patients, but remdesivir can only be administered intravenously at the hospital. As a majority of patients will need medication at home, a next step is to develop more delivery mechanisms for remdesivir. Ideas such as pills, nasal sprays and injections are all being studied for outpatient use.

The future of remdesivir is being predicted to be similar to the path of AZT, the first drug shown to aid patients against HIV. While AZT was not a miracle drug that was incredibly strong, it was crucial in paving the way for other drugs being developed that would later be used in combination with AZT to treat for HIV, tuberculosis and other diseases.

Now that it has been approved, it will become the new placebo. Remdesivir will become the standard of care. A primary objective of remdesivir is to aid the development of other antivirals and potentially, a cure. Other developing treatments will undergo testing and trials against or in combination with remdesivir. [11]

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9 Government of Canada, H. C. (2020, July 28). *Remdesivir authorized with conditions for the treatment of patients in Canada with severe COVID-19 symptoms*. Recalls and safety alerts. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/73621a-eng.php.

10 Grein, J., Al., E.,Center, A. A. F. C. S. M., M. G. Baker and Others, D. R. Boulware and Others, & A. B. Cavalcanti and Others. (2020, June 18). *Compassionate Use of Remdesivir for Patients with Severe Covid-19: NEJM*. https://www.nejm.org/doi/full/10.1056/NEJMoa2007016.

11 Marchione, M. (2020, May 01). Remdesivir seems to work against coronavirus. What's next? Retrieved September 27, 2020, from https://abc7news.com/remdesivir-coronavirus-drug-fauci/6143066/