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Remdesivir: A Comprehensive Review As An , "Covid 19 "

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ABSTRACT : Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus.Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness. In the present era patients and physicians worldwide are facing tremendous health care hazards that are caused by the ongoing severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) pandemic. In this aspect Remdesivir is one of promising and significant medication. Remdesivir (GS-5734) is the first approved treatment for severe coronavirus disease 2019 (COVID-19). It is a novel nucleoside analog with a broad antiviral activity spectrum among RNA viruses, including ebolavirus (EBOV) and the respiratory pathogens Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV, and SARS-CoV. In vivo, remdesivir showed therapeutic and prophylactic effects in animal models of EBOV, MERS-CoV, SARS-CoV, and SARS-CoV-2 infection. Remdesivir is a prodrug that is showing intracellular delivery of GS-441524 monophosphate and subsequent biotransformation into GS-441524 triphosphate, a ribonucleotide analogue inhibitor of viral RNA polymerase. The progress on clinical trial of remdesivir is still going on and many studies about its repurposing effect is monitored therefore the further proof to prove remdesivir's efficacy against COVID-19 is of considerable international concern. Here, I provide an overview of remdesivir's mechanism of action, clinical usage, in vivo and in vitro studies. Finally, considering the public health and pharmacovigilance approach is also discussed.

KEYWORDS: Remdesivir, COVID-19, SARS-CoV-2, RNA dependent RNA polymerase, MERS

I. INTRODUCTION

[1,6]In December 2019 a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, central China as the cause of a respiratory illness designated coronavirus disease 2019, or Covid-19. Coronaviruses are a group of related RNA viruses that cause diseases in mammals and birds. In humans and birds, they cause respiratory tract infections that can range from mild to lethal. Mild illnesses in humans include some cases of the common cold. while more lethal varieties can cause SARS, MERS, and COVID-19.In cows and pigs they cause diarrhea, while in mice they cause hepatitis and encephalomyelitis.

[2,3] Coronaviruses constitute the subfamily Orthocoronavirinae. Several therapeutic agents have been evaluated for the treatment of Covid-19 but none have yet been shown to be efficacious. Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase with inhibitory activity against SARSCoV and the Middle East respiratory syndrome (MERS-CoV), was identified early as a promising therapeutic candidate for Covid-19 because of its ability to inhibit SARS-CoV-2 in vitro.

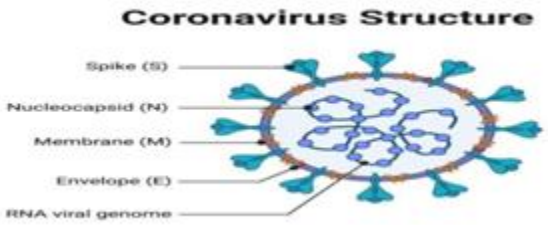
International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 352-363 www.ijprajournal.com ISSN: 2249-7781

[4,5,6] In addition, in nonhuman primate studies, remdesivir initiated 12 hours after inoculation with MERS-CoV reduced lung virus levels and lung damage.

ORIGIN OF VIRUS :

It circulate in a range of animals. Sometime these viruses jump from animals to humans it called as spillover.The range factors are mutations viruses and increasing the contact between humans and animals

Examples :-



Viruses	Animals
1) SARS – CoV	Civet cat
2) MERS – CoV	Camels
3) BCV	Cattle

TRANSMISSION :

The disease can spread from one person to other person from droplets. When infected person release those droplets through coughing, talking and sneezing. Coughs and sneezes can spread droplets of saliva and mucus. Tiny particles possibly produced by talking are suspended in the air for longer and travel further.

CERTAIN :

Environmental factors.
Infected person such as cold, cough
Impact of lungs

SYMPTOMS :

There are 3 kind of symptoms based on the situation:

1) Most common symptoms
2) Less common symptoms
3) Serious symptoms

- Most common symptoms :
  - Fever
  - Dry cough
  - Tiredness
- Less common symptoms :
  - Aches and pains
  - Sore throat
  - Diarrhea
  - Headache
  - Loss of taste or smell
  - A rash on skin
  - Conjunctivitis
- Serious symptoms :
  - Difficulty breathing
  - Chest pain or pressure
  - Loss of speech or movement

II. DEVELOPMENT OF REMDESIVIR

[7,8,9]Remdesivir (GS-5734) was developed by **Gilead Sciences** and emerged from a collaboration between Gilead, the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). At the beginning of discovery, a library of ~1000 small molecules focused around nucleoside analogues was compiled, based on prior knowledge of effective antiviral compounds targeting RNA viruses. Nucleosides are poorly cell-permeable (and therefore can have a low hit rate in cell-based screens such as antiviral screens), so modified nucleosides such as monophosphate, ester, and phosphoramidate prodrugs composed a significant portion of the library. Such prodrugs are typically more permeable and metabolized to liberate the nucleoside or phosphorylated nucleoside within cells.

[10,11] No data from the original full screen have been disclosed, firstly called as a 1′-CN modified adenosine C-nucleoside hit (GS-441524), along with a prodrug form of the monophosphate of GS-441524 (GS-5734, later renamed as remdesivir), was found to be highly potent. Warren et al. showed that remdesivir also had antiviral activity against several other viruses, including the coronavirus MERS, with an IC50 of 340 nM in vitro.

[12,15,16]With the demonstration that GS-5734 (remdesivir) possessed broad activity against RNA viruses, multiple groups assessed antiviral activity both in vitro and in vivo, validating its activity against coronaviruses. Antiviral activity was confirmed against SARS, MERS zoonotic coronaviruses as well as the circulating human coronaviruses HCoV-OC43 and

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HCoV-229E, causative agents of the common cold.

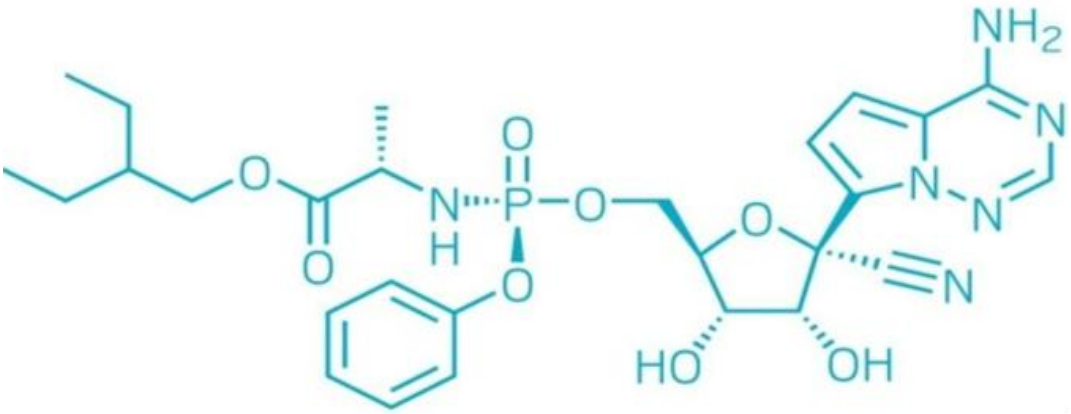
[14,17]Furthermore, de Wit et al. demonstrated that remdesivir had both prophylactic and therapeutic activity against MERS in a nonhuman primate in vivo model. The pharmacokinetics of remdesivir have been summarized in compassionate use documentation published by the European Medicines Agency (EMA, 2020). Remdesivir is administered via an intravenous injection (IV) with a loading dose on day 1 (200 mg in adults, adjusted for body weight in pediatric patients) followed by a daily maintenance dose (100 mg in adults) for up to 10 days. In nonhuman primates, daily administration of 10 mg/kg of remdesivir yielded a short plasma half-life of the prodrug (t1/2= 0.39 h), but sustained intracellular levels of the triphosphate form.

[12,13]Gilead Sciences first initiated clinical evaluation of remdesivir for EBOV. Gilead pursued FDA evaluation under the FDA's Animal Rule, permitting the reliance on efficacy findings from animal studies for drugs in which it is not feasible or ethical to conduct human trials. As such, remdesivir was included in a randomized, controlled trial of Ebola virus therapeutics in patients within the Democratic Republic of the Congo (NCT02818582); however, midstudy primary analyses found remdesivir inferior to the antibody based therapeutics MAb114 and REGN-EB3, with respect to mortality, and the remdesivir intervention arm was terminated.

19] Mulangu et al. reported one serious adverse event related to remdesivir, which was hypotension, along with elevated creatinine and aspartate aminotransferase plasma levels.

III. STRUCTURE

[14] Remdesivir is a prodrug of an adenosine triphosphate (ATP) analog, with potential antiviral activityagainst a variety of RNA viruses. The chemical name for remdesivir is : 2 - Ethylbutyl(2S) -2-{(S) –{[2R, 3S, 4R, 5R) -5-(4-aminopyrrolo[2, 1-F][1,2,4]triazin-7-yl) -5-cyano-3,4 - dihydroxytetrahydrofuran -2-yl]methoxy} (phenoxy) phosphoryl] amino}propanoate.



Remdesivir

IV. [15] SYNONYMES

- GS-5734
- REMDESIVIR [INN]
- Remdesivirum
- Remdesivir [USAN]
- Veklury
- 2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin- 7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate
- GS 5734 [WHO-DD]
- REMDESIVIR [WHO-DD] etc.

Molecular formula - C27H35N6O8P
Molecular weight - 602.6 g/mol.

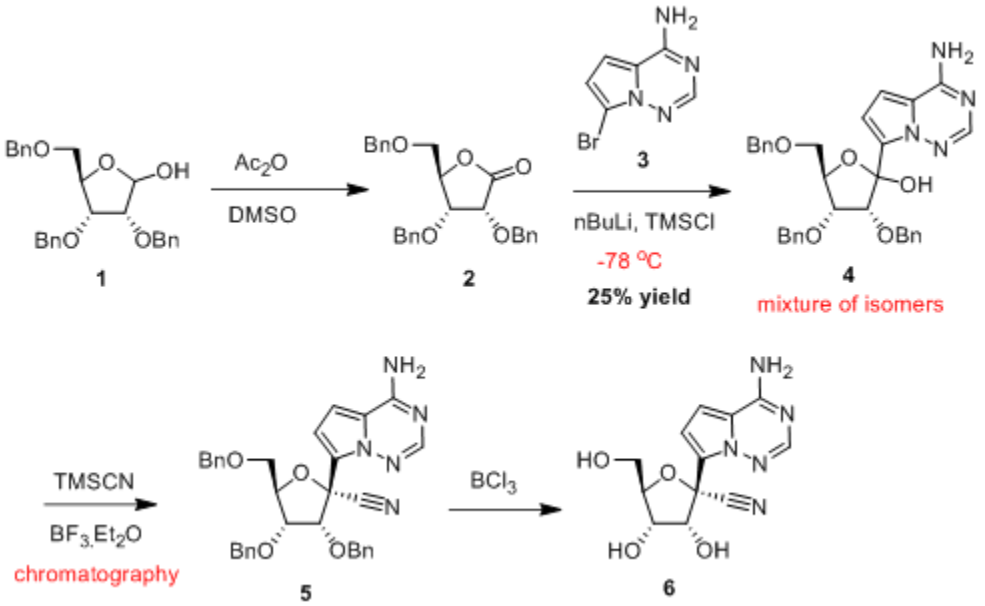
Physicochemical property: - Remdesivir is a white to video off white or yellow non hydroscopic solid.
Solubility- Partially soluble in water

V. SYNTHESIS OF REMDESIVIR

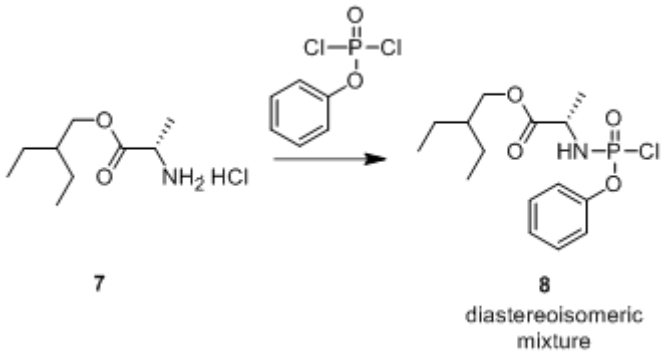
a) First Generation Synthesis of Remdesivir

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 352-363 www.ijprajournal.com ISSN: 2249-7781

[16]The scientists at Gilead started with the synthesis of their best lead and the single Sp phosphoramidate prodrug with a commercially available tribenzyl protected lactol **1** followed by oxidation to its corresponding lactone **2**. The next key step was the C-C bond forming glycosylation reaction of the ribolactone **2** with a bromo pyrrolotriazine nucleus **3**. This was facilitated by the N-silyl protection in **3**, followed by a lithium-halogen exchange using excess BuLi at -78°C. The lithiated pyrrolotriazine was coupled with ribolactone **2** to provide a mixture of 1' isomers of nucleoside **4** followed by 1'- cyanation to give the β-anomer **5** after chromatographic purification. Tribenzyl deprotection gave the 1-cyano modified adenine nucleoside **6**.



The diastereomeric mixture of the phosphoramidoyl chloridate prodrug moiety **8** was prepared from the L-alanine analogue **7**.



Finally, coupling of nucleoside **6** and chloridate **8** provided the phosphoramidate prodrug mixture **9** in ~ 1:1 diastereomeric ratio. The two diastereomers were resolved using chiral HPLC to afford the Sp isomer **9a** and Rp isomer **9b**, respectively.

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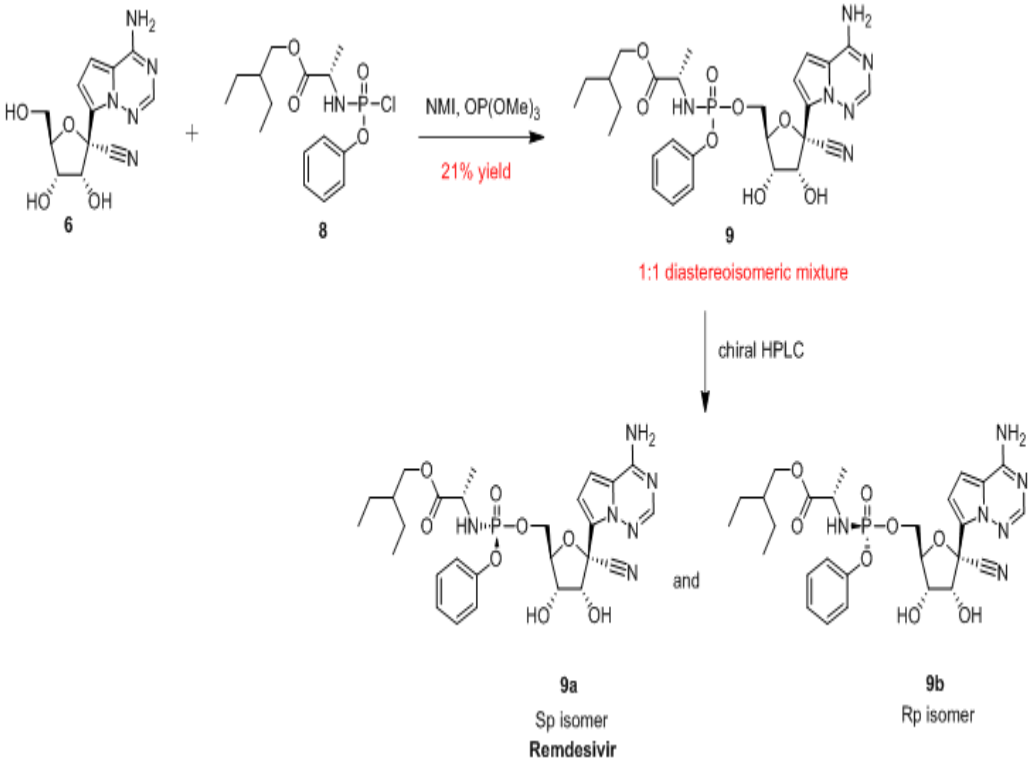

Second Generation Synthesis of Remdesivir

[16]The use of cryogenic temperatures, dependency on rate of addition of n-BuLi, unpredictable yields and need for chiral chromatography deemed the first-generation synthetic route unscalable. Efforts were directed towards using milder reagents and temperature and obtaining enhanced selectivity.

[17,18,19]The foremost changes in the method proceeded with replacement of the inconsistent n-BuLi method for the glycosylation reaction towards a coupling accelerated by the Turbo Grignard reagent i-PrMgCl·LiCl. The use of PhMgCl and TMSCl led to better control in the amino protection, and the iodo base **11** enabled a more facile metal-halogen exchange than its bromo equivalent. This method of the nucleoside synthesis allowed for consistent yields at milder temperatures, hence making it scale-up friendly.

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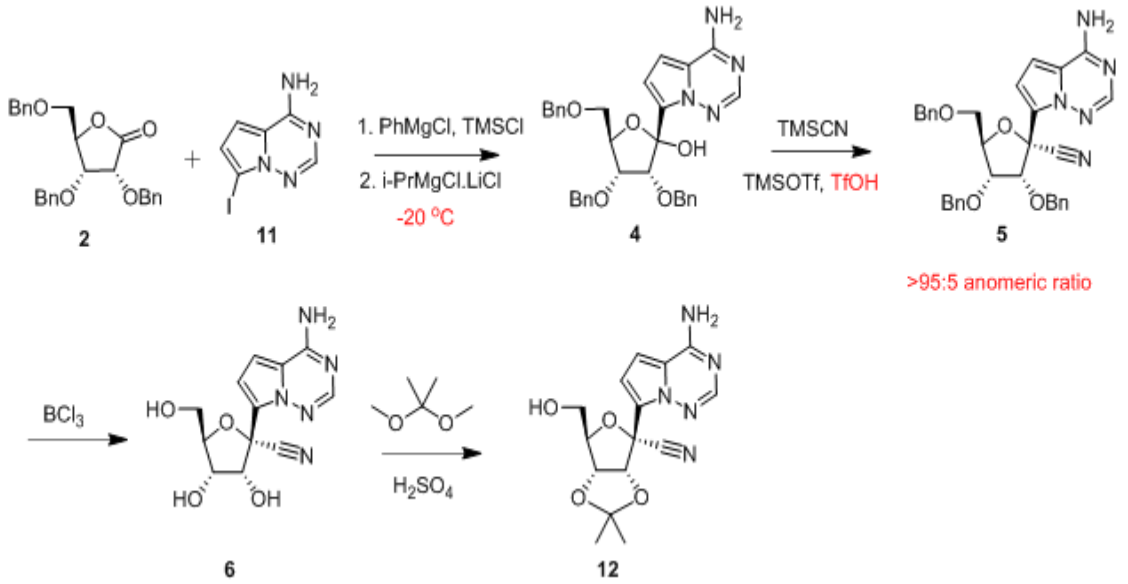
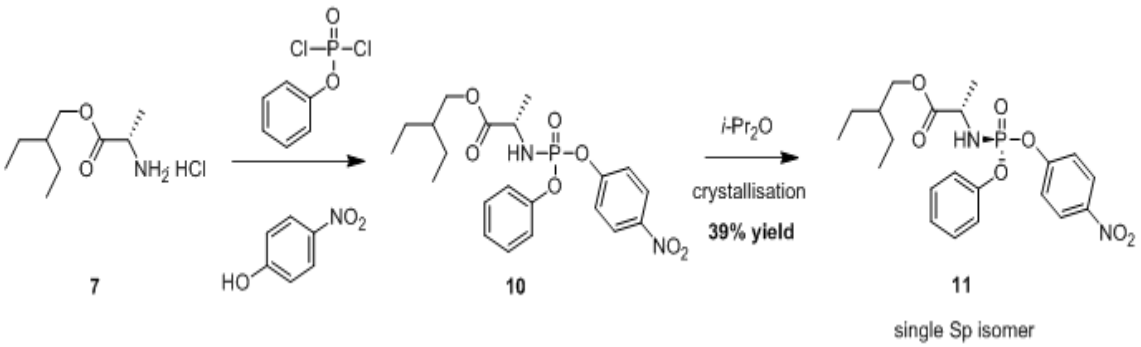
International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 352-363 www.ijprajournal.com ISSN: 2249-7781



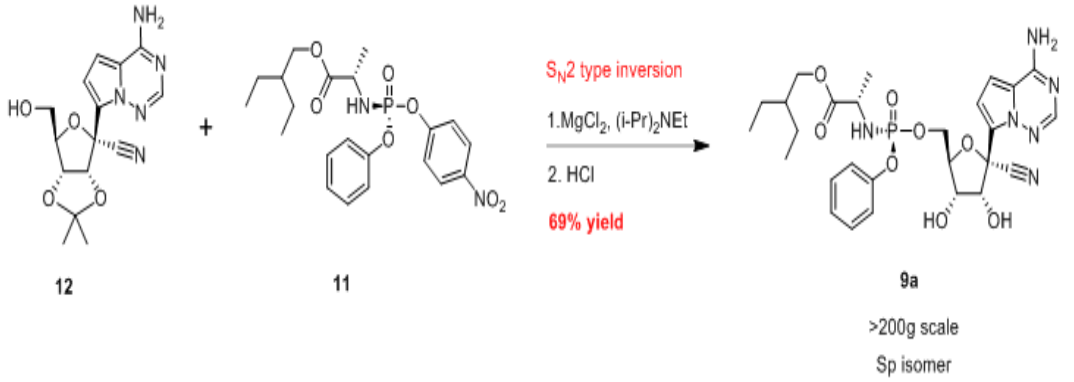
[20,21]The 1'-cyanation of C-nucleoside **4** gave the product **5** in >95:5 anomeric ratio favoring the desired β-anomer. The inclusion of TfOH was found to be responsible for the high yield and high selectivity, thereby bypassing the need for chiral separation. Henceforth, a crucial change in the protection-deprotection strategy was undertaken whereby after the initial debenzylation, 2',3'-acetonide protection of the hydroxyl moieties was carried out to give **12**.

[22]It was found that the coupling of nucleoside **12** with the prodrug counterpart **11** provided far better yields as compared to the unprotected glycoside **6**.Opting for a p-nitrophenolate prodrug precursor **10** instead of chloridate **8** afforded a single Sp isomer **11** after resolution through solvent crystallization, which proved to be the key step towards the stereoselective synthesis of the final product.



The final reaction of the p-nitrophenolate 2-ethylbutyl-L-alaninate prodrug coupling partner **11** with the acetonide protected nucleoside **12** proceeded in the presence of $MgCl_2$ to give a diastereoselective product (exclusive Sp isomer) through S_N2 type inversion of the phosphorus stereocenter. In both cases, the Sp isomer was established through single X-ray crystallography. Final deprotection of the acetonide yielded Remdesivir (**9a**) in 69% yield.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 352-363 www.ijprajournal.com ISSN: 2249-7781

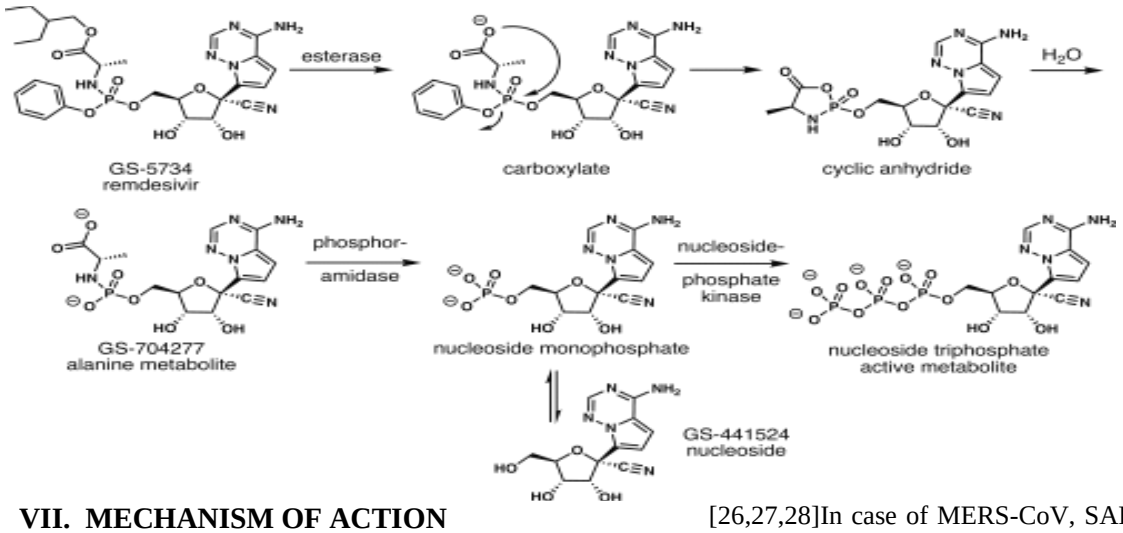


The second-generation synthesis of Remdesivir thus was a far better improvement in terms of scalability, yields and stereoselectivity bypassing the bottleneck of inconsistent yields and chiral separation.

VI. PHARMACOLOGY

1)Activation

[23,24]Remdesivir is a ProTide (Prodrug of nucleoTide). It is able to diffuse into cells where it is converted to GS-441524 mono-phosphate via the actions of esterases (CES1 and CTSA) and a phosphoamidase (HINT1); this in turn is further phosphorylated to its active metabolite triphosphate by nucleoside-phosphate kinases. This pathway of bioactivation is meant to occur intracellularly, but a substantial amount of remdesivir is prematurely hydrolyzed in plasma, with GS-441524 being the major metabolite in plasma, and the only metabolite remaining two hours after dosing.



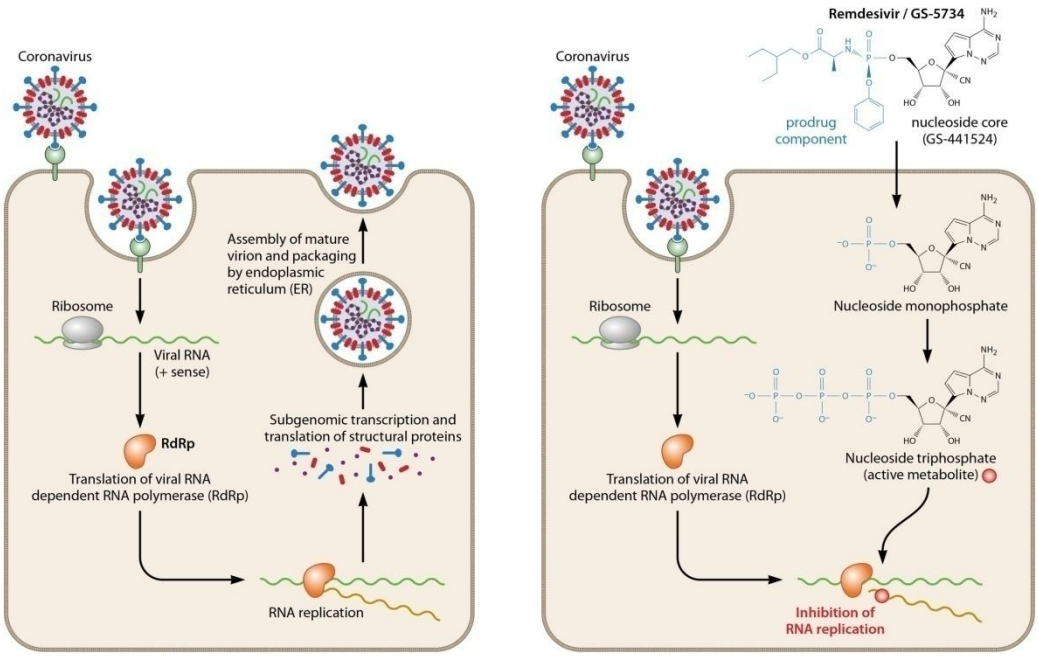
VII. MECHANISM OF ACTION

[25] The active metabolite of remdesivir adenosine nucleoside triphosphate analog (GS-443902) interferes with the action of viral RNA-dependent RNA polymerase in presence viral exoribonuclease (ExoN), causing a decrease in viral RNA production.

[26,27,28]In case of MERS-CoV, SARS-CoV-1, and SARS-CoV-2 the RNA-Dependent RNA Polymerase, arrest of RNA synthesis occurs after incorporation of three additional nucleotides.

[29,30] Hence, remdesivir is classified as a direct-acting antiviral agent that works as a delayed chain terminator.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 352-363 www.ijprajournal.com ISSN: 2249-7781



[31,32](Fig-Intracellular activation of remdesivir (GS-5734) and inhibition of coronavirus replication. Passage through the cell membrane by remdesivir is facilitated by the prodrug component attached to the nucleoside core. Upon entering the target cell, the pronucleotide undergoes further phosphorylation steps to become the active triphosphate metabolite that effectively inhibits viral RNA replication. Delayed chain termination is caused by the following processes: (i) misintegration of nucleoside triphosphate (NTP) into replicating RNA by RdRp, (ii) prevention of further chain elongation after NTP plus 3 additional nucleosides, and (iii) premature termination of RNA synthesis.)

VIII. PHARMACOKINETICS

[33]During animal studies it was found that the plasma half-life of the prodrug is 20 minutes, two metabolite formed.

a) Nucleoside,
b) GS-441524.

After two hours of injection, the main metabolite GS-441524 is present at micromolar concentrations, so intact Remdesivir is no longer detectable. Because of this rapid extracellular conversion to the nucleoside GS-441524 took place so question arrived in front of researchers that the active nucleotide triphosphate is truly derived from Remdesivir pro-drug removal or whether it occurs by GS-441524 phosphorylation, and whether direct administration of GS-441524 would constitute a cheaper and easier to administer COVID-19 drug compared to Remdesivir.The activated nucleotide triphosphate form has sustained intracellular levels in peripheralblood mononuclear cell as well as in other cell.

IX. CLINICAL STUDIES OF COVID19

[34]As we all know that IV route is the best one. During covid studies Remdesivir is a provided through intravenous (IV) infusion for 2 hours available as a lyophilized powder(freeze dried powder) and concentrated solution most preferable for the patients with invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), the recommended treatment duration is 10 days. If invasive mechanical ventilation or ECMO is not require then recommended total treatment duration is 5 days.

X. DOSAGE

1. The recommended dose for adult patients weighing 40kg or higher is 200mg on day 1 followed by 100mg from day 2.
2. The recommended dose for pediatric patients weighing 3.5kg to less than 40kg is 5mg/kg on day 1 followed by 2.5mg/kg once daily from day 2.

XI. CONTRAINDICATION

[34]Remdesivir is contraindicated in patients with hypersensitivity reaction to any ingredient of it.

International Journal of Pharmaceutical Research and Applications
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XII. SIDE EFFECT

[35,36]Respiratory failure
Blood biomarkers of organ impairment,

a) Low albumin
b) Low potassium
c) Low count of red blood cells
d) Low count of thrombocytes
e) Elevated bilirubin (jaundice).
f) Other reported adverse effects include gastrointestinal distress.
g) Elevated transaminase levels in the blood (liver enzymes).
h) infusion site reactions.
i) Electrocardiogram abnormalities.
j) Infusion- related reactions, including low blood pressure, nausea, vomiting, sweating or shivering.
k) In case of abnormal liver blood tests increase in levels of liver enzymes was observed in some patients.
l) Increases in levels of liver enzymes have been seen in people who have received remdesivir, which may be a sign of inflammation or damage to cells in the liver.

XIII. INVITRO STUDIES

[37]For In vitro studies of Remdesivir Replication three cell types Vero E6, Vero, Calu3 were used 2B4 cells were seeded in 24 well plates and allowed to stick for twenty four hours. Cells were adsorbed with 100 µl SARS-CoV-2 in gel saline for half-hour (min) at 37°C with manual rocking every 10 min. Virus inoculum was removed, cells were washed in PBS, and 0.5 mL medium was added to every well. Supernatant was collected at 0, 24, 48, and 72 h post-infection, and infectious viral titer in supernatants was decided by plaque assay.In vitro studies, carried out mainly on cell culture or isolated tissue samples, are used extensively in toxicological investigation. Human and animal cell cultures are derived either from a primary explant or a cell line. Commonly used metrics in these studies are the half maximal effective concentration (EC50), which is the drug concentration at which half of the maximum response is attained after exposure, or the half maximal inhibitory concentration (IC50), which is the drug concentration at which half of the height inhibiting effect of the drug against a specific viral function is achieved. Lower EC50 and IC50 values indicate higher potency.[37]

XIV. INVIVO STUDIES

[37,40]Formulations for in vivo studies RDV was solubilized at 2.5 mg/mL in vehicle containing 12% sulfobutylether-b-cyclodextrin sodium salt in water (with HCl/NaOH) at pH 5.0. In vivo efficacy studies All animal experiments were performed in accordance with the University of North Carolina at Chapel Hill Institutional Animal Care and Use Committee policies and guidelines. To achieve a pharmacokinetic profile similar to that observed in humans, we performed therapeutic efficacy studies in Ces1c/ mice (stock 014096, The Jackson Laboratory), which lack a serum esterase not present in humans that dramatically reduces RDV half-life (Sheahan et al., 2017). 17 week-old female Ces1c/ mice were anaesthetized with a mixture of ketamine/xylazine and intranasally infected with 103 PFU SARS1/SARS2-RdRp in 50 mL. One dpi, vehicle (n = 7) and RDV (n = 7) dosing was initiated (25 mg/kg subcutaneously) and continued every 12 h until the end of the study at five dpi. To monitor morbidity, mice were weighed daily. Pulmonary function testing was performed daily by whole body plethysmography (WBP) (Data Sciences International) (Sheahan et al., 2017). At five dpi, animals were sacrificed by isoflurane overdose, lungs were scored e4 Cell Reports 32, 107940, July 21, 2020 Article ll OPEN ACCESS for lung hemorrhage, and the inferior right lobe was frozen at 80C for viral titration via plaque assay on Vero E6 cells[38]. Lung hemorrhage is a gross pathological phenotype readily observed by the naked eye and driven by the degree of virus replication, where lung coloration changes from pink to dark red (Sheahan et al., 2017, 2020a). For the plaque assay, 5 3 105 Vero E6 cells/well were seeded in 6-well plates. The following day, medium was removed, and monolayers were adsorbed at 37C for one h with serial dilutions of sample ranging from 101 to 106 . Cells were overlayed with 1X DMEM, 5% Fetal Clone 2 serum, 1 3 antibiotic-antimycotic, 0.8% agarose. Viral plaques were enumerated three days later.

XV. PHARMACOVIGILENCE

[38]Approach Studies showing multiple adverse effect linked to remdesivir usage. Though remdesivir is somewhat harmful and healthier. It also has certain negative impacts that are not insignificant and cannot be disregarded.
Most frequently co- reported terms in the 138 reports of acute renal failure associated with remdesivir are as followed.

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Effect	Number of reports	Percentage
Respiratory failure	11	8.0% (11/138)
Aspartate aminotransferase increased	8	5.8% (8/138)
Acidosis	7	5.1% (7/138)
Alanine aminotransferase increased	7	5.1% (7/138)
Acute respiratory distress syndrome	6	4.3% (6/138)
Hypotension	6	4.3% (6/138)
Hypoxia/ Multiple organ dysfunction syndrome	6	4.3% (6/138)

XVI. CONCLUSION

[39,40,41]At this time there are no therapies that have been scientifically proven to improve mortality in COVID- 19. Current management is essentially focused on supportive care and prevention of complications. Efficacious and safe antiviral agents are therefore urgently needed to alleviate the burden on health- care systems. As detailed in this review, remdesivir is a nucleoside analogue pro- drug with unique structural features that allow high concentrations of the active triphosphate metabolite to be delivered intracellularly. It inhibits SARSCoV-2 RdRp and its antiviral activity against SARS-CoV-2 have been shown both in vitro and in vivo studies. It evades proofreading to successfully inhibit viral RNA synthesis and has demonstrated potent antiviral activity against β- Remdesivir has been used in several countries as an emergency drug for patients with COVID-19 coronaviruses and some patient showed improved clinical outcomes. However, large-scale clinical trials should be conducted to confirm the efficacy of remdesivir in treating patients with COVID-19. The adverse consequences of using remdesivir toward COVID-19 could not be ignored. Usage of remdesivir can only be done following medical advice.

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