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Overview on Remdesivir

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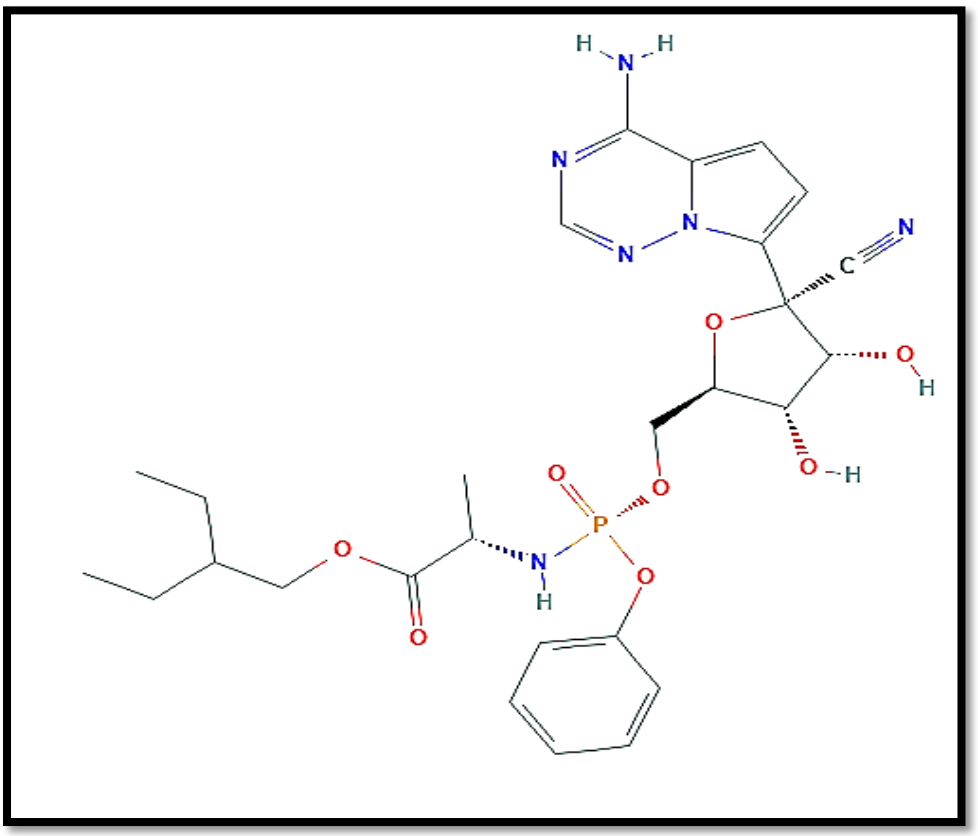
Abstract: ***Remdesiviris a broad range anti viral drug primarily discovered for the treatment for hepatitis C and respiratory syncytial virus (RSV), later used in the treatment of ebola and now is being used in the treatment of covid-spectrum antiviral agent that has previously demonstrated antiviral activity against filoviruses (ebola viruses, marburgvirus), coronaviruses (SARS-COV, MERS-CO-V, SARS-COV-2), paramyxoviruses (parainfluenza type iii virus, nipah virus, hendra virus, measles, and mumps virus), and pnemoviridae (respiratory syncytial virus). (1)***

Keywords: remdesivir, GS-441524, SARS-COV-2, COVID-19, nucleoside triphosphate, RNA dependant RNA polymerase, ebola.

1. Introduction

1.1 Structure and Chemistry

Remdesivir's IUPAC name is 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 with the molecular formula "c27h35n6o8p". Remdesivir has a molecular weight of 602.6 g/mol. Remdesivir is a nucleoside analogue under research that serves as a competitive inhibitor of viral RNA polymerase (RDRP). (2). Gilead sciences invented and developed Remdesivir in 2009 to treat hepatitis C and respiratory syncytial virus (RSV) and hold a patent till 16 September 2036.

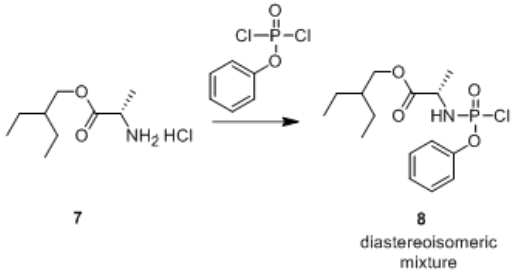


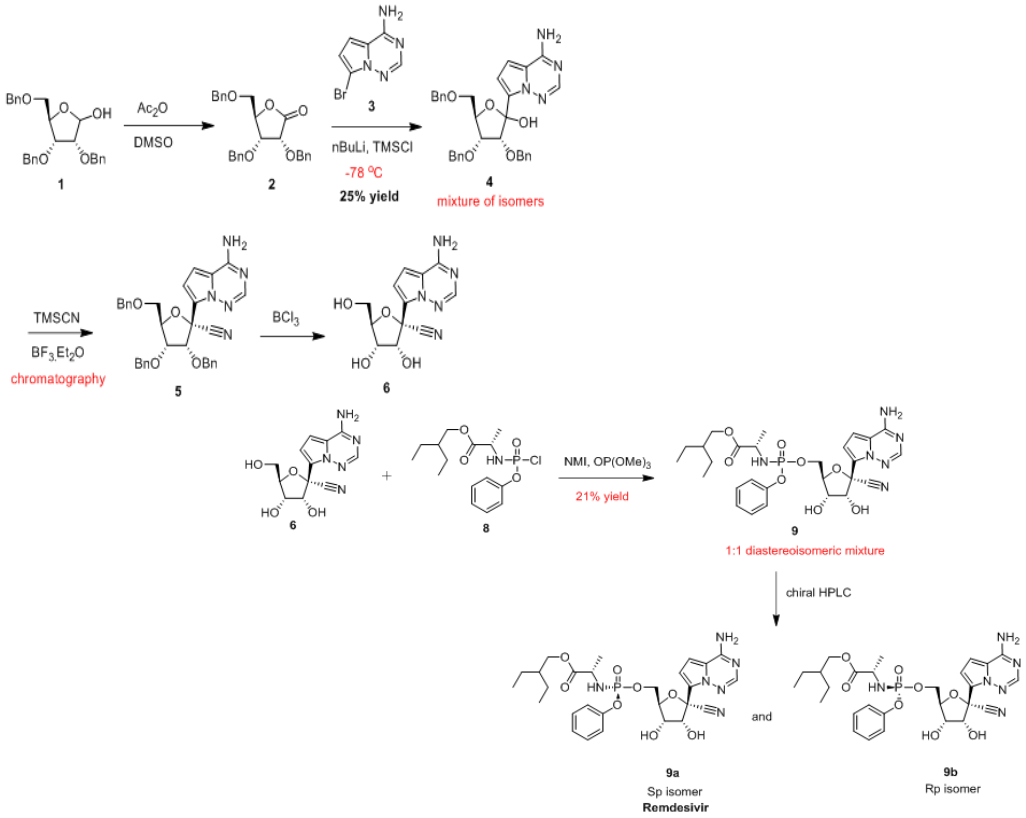
2. Synthesis

First generation synthesis

The single sp phosphoramidate prodrug is oxidised to its equivalent lactone **2** after being protected by a commercially available tribenzyl. The C-C bond forming glycosylation reaction of the ribolactone **2** with a bromo pyrrolotriazine nucleus **3** is the next crucial step. The N-Silyl protection in step 3 makes this easier, followed by a lithium-halogen exchange using excess buli at -78°C. After chromatographic purification, the lithiated pyrrolotriazine is combined with ribolactone **2** to yield a mixture of 1' isomers of nucleoside **4**, followed by 1'- cyanation to yield the β –anomer b-**5**. The 1-cyano modified adenine nucleoside **6** was obtained by

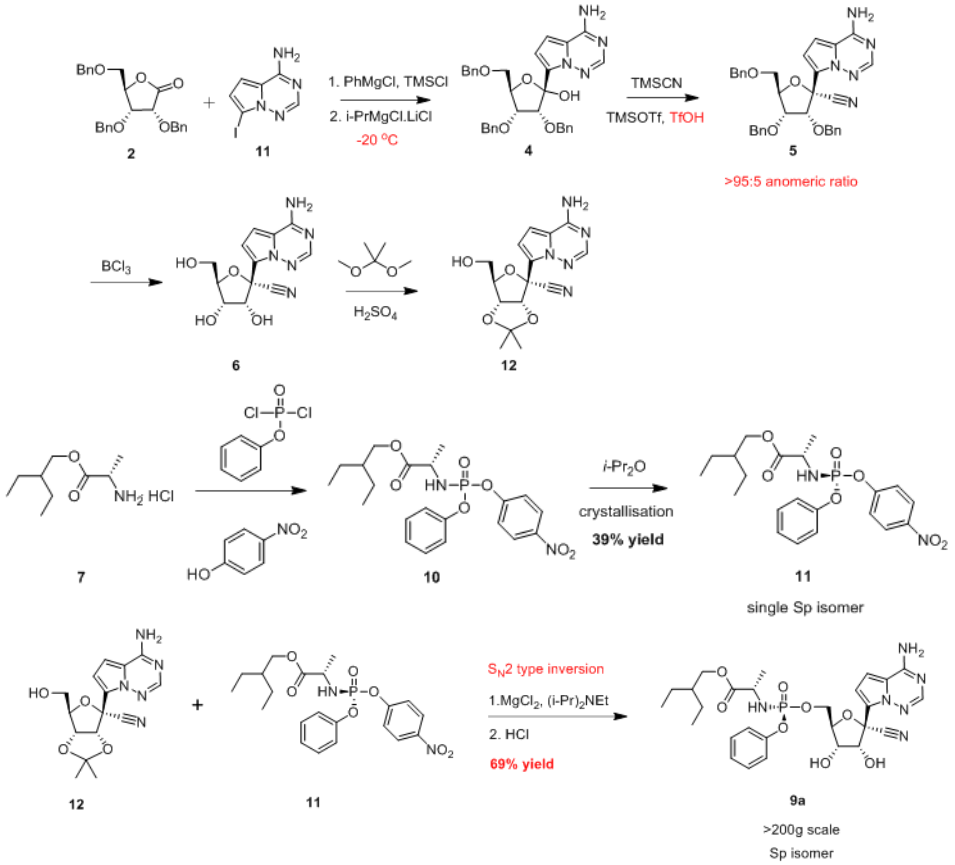
deprotecting it with tribenzyl. The l-alanine analogue **7** was used to make the diastereomeric combination of the phosphoramidoyl chloridate prodrug moiety **8**. Finally, the phosphoramidate prodrug mixture 9 was created by combining nucleoside **6** and chloridate 8 in a 1:1 diastereomeric ratio. Using Chiral HPLC, the two diastereomers were separated, yielding the sp isomer **9A** and RP isomer **9B,** respectively.





Second generation synthesis

Remdesivir's second-generation synthesis is considerably superior in terms of scalability, yields, and stereoselectivity, as it avoids the bottleneck of uneven yields and Chiral separation. The first-generation synthetic approach was judged unscalable due to the usage of cryogenic temperatures, reliance on the rate of addition of N-buli, unpredictable yields, and the need for chiral chromatography. Efforts are being made to use softer reagents and temperatures, as well as to improve selectivity. The most significant improvements in the approach was replacing the ineffective N-buli technique for glycosylation with a coupling accelerated by the turbo grignard reagent I-PRMGCLLICL. The introduction of PHMGCL and TMSCL improved amino protection control, while the IODO base 11 made metal-halogen exchange easier than the bromo counterpart. This nucleoside synthesis process produced consistent yields at lower temperatures, making it scale-up friendly. The product **5**, obtained by 1'-cyanating c-nucleoside **4**, has an anomeric ratio of >95:5, favouring the desired b-anomer. The presence of tfoh was identified to be responsible for the high yield and selectivity, mitigating the necessity for chiral separation. Following this, a significant shift in the protection-deprotection technique was implemented, with 2', 3'-acetonide protection of the hydroxyl moieties being carried out after the initial debenzylation to give **12**. When compared to the unprotected glycoside **6**, combining nucleoside **12** with the prodrug homologue **11** resulted in much higher yields. After resolution through solvent crystallisation, using a p-nitrophenolate prodrug precursor **10** instead of chloridate **8** yielded a single SP isomer **11**, which proved to be the essential step towards the stereoselective production of the final product. Through sn2 type inversion of the phosphorus stereocenter, the final reaction of the p-nitrophenolate 2-ethylbutyl-l-alaninate prodrug coupling partner **11** with the acetonide protected nucleoside 12 gave a diastereoselective product (exclusive sp isomer) in the presence of mgcl2. The sp isomer was determined in both cases using single x-ray crystallography. Remdesivir (**9A)** was obtained in 69 percent yield after final deprotection of the acetonide.



Pharmacology of Remdesivir

Remdesivir limits viral RNA synthesis by inhibiting RNA polymerase that is dependent on viral RNA (RDRP). Remdesivir triphosphate, the active form, competes with native adenosine triphosphate for chain inclusion, causing chain termination to be delayed. Remdesivir is not a substantial inhibitor of these enzymes because mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase, prefer atp to remdesivir triphosphate, which adds to its general tolerance and safety profile. (5) (4). Remdesivir has a long intracellular half-life (>35 hours for the active parent triphosphate) and linear pharmacokinetics. Remdesivir triphosphate was observed to accumulate in mononuclear cells in the peripheral circulation, implying that a loading dose could hasten the establishment of a steady state (4)

Antiviral activity:

Remdesivirpossesses antiviral activity against zoonotic and human infections from a variety of virus families in vitro. When tested against members of the filoviridae, paramyxoviridae, pneumoviridae, and corona viridae families, Remdesivir's activity was constant. (6) Remdesivir inhibits three of the endemic strains associated to respiratory illnesses (HCOV-OC43, 229E, and NL63), as well as MERS-COV, SARS-COV, and the novel SARS-COV-2. (7) Remdesivir is also effective against bat coronaviruses that are similar to SARS and MERS (HKU3, WIV1, SHC014, AND HKU5). 7 Remdesivir was also effective in non-human primate (nhp) models of MERS, Nipah virus infection, and EVD, despite the fact that most preclinical research was done in vitro. Remdesivir is less effective against flaviviridae viruses, having only moderate efficacy against hepatitis C, dengue fever, and yellow fever. Remdesivirhas little to no activity against tick-borne flaviviruses (alkhurma hemorrhagic fever, kyasanur forest sickness, OMSK hemorrhagic fever, tick-borne encephalitis), as well as west nile, lassa, vesicular stomatitis, rift valley fever, and crimean–congo hemorrhagic fever viruses. (7) (6).

Remdesivir in the treatment of Ebola

Preclinical data:

Remdesivir was discovered during a broad search for chemicals that could combat developing viruses. The initial screening procedure was focused on finding candidates that may suppress RNA viruses, specifically coronaviridae and flaviviridae. Following the EVD pandemic in West Africa from 2013 to 2016, some previously screened compounds were tested anew against EBOV. Remdesivir was found to be highly efficient against EBOV in a variety of cell lines, with an anti-ebov half maximum effective concentration (ec50) of 0.086 μm in human macrophages. Remdesivirwas chosen for further clinical development because of its efficacy and a molecular structure that may be scaled up quickly.19 in a non-human primate (nhp) model of EVD, the first in vivo efficacy investigation was done. Previously healthy rhesus monkeys were given an intramuscular EBOV injection in the NHP EVD model, which resulted in death after a clinical course that mimicked human EVD. NHP was infected with EBOV and given several Remdesivir dose regimens. Between study groups, the time from inoculation to Remdesivir commencement differed (as soon as 30 minutes after viral challenge and up to 3 days after viral challenge). Lower doses (3 mg/kg daily) were found to have a meaningful antiviral effect, with survival rates ranging from 33 to 66%. Higher doses, on the other hand, were most

promising, with 6/6 NHP surviving after commencing on day 3 with Remdesivir10 mg/kg daily. This was the first report of a chemical that provided post-exposure protection from EVD, indicating that Remdesivir should be studied further in human EVD.

Clinical efficacy

Prior to the completion of formal clinical studies, a small number of case reports described the use of Remdesivir treating EVD through emergency compassionate use guidelines. The first instance included a 39-year-old lady who had fully recovered from an incident of EVD 9 months prior and was treated with Remdesivir for EBOV meningoencephalitis. In the second case, a newborn with EVD was diagnosed on her first day of life after being born to an EBOV-positive mother. 28 despite the fact that both patients in these reports survived, it's difficult to say whether Remdesivir played a part in their recovery because various therapy were used. During the EVD outbreak in the DRC, a randomised multi-intervention trial was done. If they tested positive for EBOV, 18 patients of any age, including pregnant women, were eligible to participate. Patients received normal supportive care as well as a 1:1:1:1 allocation to one of four treatment arms. Zmapp (a triple monoclonal antibody), MAB114 (a single human monoclonal antibody obtained from an ebola survivor), REGN-EB3 (a combination of three human immunoglobulin g1 [IGG1] monoclonal antibodies), and intravenous Remdesivir were among the study's therapies. On day one, Remdesivir was given at a dose of 200 mg, followed by 100 mg daily for 9–13 days. Pediatric patients were given dosage based on their weight. At day 28, the major consequence was death. When an interim analysis led to the trial's early termination, nearly 700 patients had been randomised. The ZMAPP and Remdesivir groups had higher mortality than the mab114 and regn-eb3 groups, according to the data and safety monitoring board. Furthermore, the REGN-EB3 group had met a certain efficacy criterion. In the end, 673 patients were enrolled in the study. The average age of the recruited patients was 29 years, with women accounting for 56% of the total (6 percent of whom were pregnant). Remdesivir (53.1%), ZMAPP (49.7%), MAB114 (35.1%), and REGN-EB3 (35.1%) had the highest death rates at day 28. (33.5 percent). With Remdesivir, 85 percent of patients with high-viral loads at baseline and 29 percent of patients with low-viral loads at baseline died, respectively. In conclusion, despite robust in vitro activity against EBOV and extraordinary success in animal models of EVD, Remdesivir's journey for human EVD ended in disappointment. (4)

Remdesivirin the Treatment of COVID-19

Preclinical data

Prior to the advent of SARS-COV-2, Remdesivir was known to inhibit corona virus replication. Wang and colleagues were the first to show that Remdesivir, together with other antivirals, could successfully stop SARS-COV-2 replication. 29 in non-human Vero E6 cells, the researchers tested the activity of seven medicines against SARS-COV-2: Ribavirin, Penciclovir, Nitazoxanide, Nafamostat, Chloroquine, Favipiravir, and Remdesivir. Remdesivir (0.77 μm) had the lowest ec50, followed by Chloroquine (1.13 μm). Remdesivir was expected to bind to SARS-COV-2 RDRP with great affinity in a simulated molecular docking experiment. 30 in recent years, Remdesivir for the treatment of SARS-COV-2 has piqued public and medical attention for a variety of reasons. First, SARS-COV-2 in vitro activity has been confirmed. Second, there is a well-established dose and safety profile for remdesivir. Finally, effective COVID-19 therapies are critically needed.

Clinical efficacy

As the COVID-19 pandemic progressed, patients with severe sickness who did not qualify for a clinical study were given emergency access to Remdesivir under a compassionate use programme. Individual requests for compassionate usage have subsequently been discontinued in favour of a newly expanded access scheme (with the exception of pregnant women and children under the age of 18). The first clinical efficacy data for Remdesivirin COVID-19 came from case reports in which patients were given Remdesivir through a compassionate use programme. Remdesivir200 mg intravenously was given to all of the patients on day 1, followed by 100 mg for up to 9 days. Remdesivir was used to treat the first patient diagnosed with COVID-19 in the United States. A 35-year-old male with no prior medical history and recent travel to Wuhan, China, arrived to the facility. He was taken to a hospital and placed on airborne isolation and monitoring. Due to increased oxygen requirements and continuing pyrexia, Remdesivir was started on hospital day 7. The patient's condition improved the next day, and by the time the article was published, he was mostly symptom-free. Remdesivir was used in a 40-year-old male who was hospitalised with severe covid-19 and required mechanical ventilation, according to a more recent report. Remdesivir was started on the 13th day of the sickness. The patient was extubated 72 hours later, and at the time of publication, a full recovery was expected. The researchers believe that Remdesivir may have a therapeutic effect even if it is begun late in the course of the disease. A non-peer reviewed publication describing the outcomes of the first 12 covid-19 patients in the united states is available. Three patients were given remdesivir, and all 12 patients recovered clinically. Covid-19 results in patients requiring extracorporeal membrane oxygenation (ECMO) and those with a history of solid organ transplantation have been described in retrospective cohort studies. Remdesivir was administered to 3/5 survivors and 1/10 non-survivors in the ecmo cohort. Only 2/90 patients in the transplant cohort received remdesivir, and their individual outcomes were not recorded. Compassionate use approvals were only given to hospitalised patients who had an oxygen saturation of 94 percent or needed oxygen support on room air. Patients have to have a CRCL more than 30 ml/min and hepatic transaminases less than five times the upper limit of normal. There were no set endpoints or enrolment objectives. In the end, 53 patients were enrolled in the study (8 patients were excluded due to missing or erroneous data). At baseline, the median age was 64 years old, and 64% of patients were on invasive ventilation (including 7 percent receiving ECMO). The median period from the beginning of symptoms to the start of Remdesivir treatment was 12 days. 36 of 53 patients (68%) improved after receiving Remdesivir. (4)

Absorption and excretion

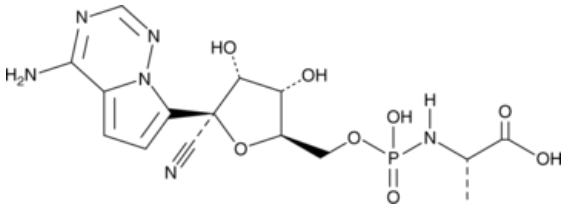
Remdesiviris rapidly absorbed; after a single 30-minute intravenous infusion, peak plasma concentrations are obtained in 0.67-0.68 hours (Tmax). After repeated dosage, the cmax (coefficient of variation in percent) is 2229 (19.2) ng/ml, and the auctau is 1585 (16.6) ng*h/l. [l18438]. Tmax 1.51-2.00 hours, cmax145 (19.3) ng/ml, auctau 2229 (18.4) ng*h/ml, and ctrough 69.2 (18.2) ng/ml have been measured for Remdesivir metabolite [gs-441524]. Tmax 0.75 hours, cmax 246 (33.9) ng/ml, AUC 462 (31.4) ng*h/l, and an unknown c trough have been measured for another metabolite, GS-704277. [l18438] within 4 hours, a 10mg/kg intravenous dose administered to cynomolgus monkeys reaches the testes, epididymis, eyes, and brain.

Elimination

Remdesiviris excreted in the urine in 74% of cases and in the faeces in 18% of cases. [l13239] the metabolite [gs-441524] accounts for 49% of the dose recovered, with the unmetabolized parent molecule accounting for 10%. [l13239] the [gs-441524] metabolite is present in faeces in a minor proportion (0.5 percent). [l18438].

Metabolism

Remdesiviris a prodrug that must be transformed to its triphosphate metabolite in order to be therapeutically effective. Remdesiviris thought to be hydrolyzed by esterase to a carboxylate form, then cyclized to eject the phenoxide component, and finally hydrolysis of the cyclicanhydride to generate the detectable alanine metabolite (GS-704277). The monophosphate form of Remdesiviris either hydrolyzed again to generate the bare nucleoside metabolite [GS-441524] or phosphorylated by cellular kinases to give the active triphosphate form.



(**GS-704277**)

Toxicity

Hepatotoxicity

Remdesivirtreatment for 7 to 14 days in human volunteers was related with mild serum amino transferase increases (less than 5 times ULN) but no other signs of hepatic damage. In controlled trials of Remdesivirin covid-19 patients hospitalised, serum alt increases were equivalent or lower in the Remdesivirgroup than in the placebo group. Nonetheless, between 10% and 50% of patients treated with Remdesivirexhibited transient, mild-to-moderate blood alt and ast elevations within 1 to 5 days of initiating medication without changes in serum bilirubin or alkaline phosphatase levels in most uncontrolled studies and case series.

Elevations of more than 5 times the upper limit of normal (ULN) were recorded in up to 9% of patients in several clinical trials, although the abnormalities disappeared with discontinuation and were not linked to clinically apparent damage. Rare cases of marked alt elevations with jaundice have been reported with the increased use of Remdesivirfor covid-19, but these were mostly in patients who were critically ill with multi-organ failure or sepsis, or who had received other potentially hepatotoxic agents such as intravenous amiodarone (case 2). Serum aminotransferase increases are prevalent after symptomatic SARS-COV-2 infection, further complicating the situation (case 1), present in up to 60% of patients, and more common in patients with severe disease and those who have established covid-19 severity risk factors such as male sex, older age, higher BMI, and diabetes. As a result, serum aminotransferase increases are prevalent after Remdesivirtherapy, though they are usually asymptomatic, temporary, and unrelated to jaundice. Hepatotoxicity may become more apparent if this antiviral is used more widely in individuals without severe or critical illness and for longer periods of time.

3. Mechanism of Action

COVID-19 is caused by the coronavirus 2, a positive-sense RNA virus that causes severe acute respiratory syndrome (SARS-COV-2). Replication of the viral genome is a crucial phase in the infectious cycle of RNA viruses, such as those belonging to the filoviridae, paramyxoviridae, pneumoviridae, and coronaviridae families, and is carried out by viral rna-dependent rna polymerase (RDRP) enzymes or complexes. Under physiological conditions, the RDRP of both SARS-COV and SARS-COV-2 contains the NSP7, NSP8, AND NSP12 subunits, although functional RDRP complexes including only the NSP8 and NSP12 subunits may be reassembled in vitro, comparable to the middle east respiratory syndrome coronavirus (MERS-COV). Remdesiviris a phosphoramidite prodrug of a 1'-cyano-substituted adenosine nucleotide analogue that competes with atp for inclusion by the matching RDRP complex into newly generated viral RNA. Remdesivirenters cells before being broken down into its monophosphate form by carboxylesterase 1 or cathepsin a. It is then phosphorylated by unknown kinases to produce Remdesivirtriphosphate (RDV-TP or GS-443902), which is the active triphosphate form. The SARS-COV-2 RDRP complex efficiently incorporates RDV-TP, with a 3.65-fold selectivity for RDV-TP over endogenous ATP. Remdesivir, unlike several nucleoside analogues, has a free 3'-hydroxyl group, allowing for continuous chain elongation. However, modelling and in vitro experiments suggest that the 1'-cyanogroup of Remdesivirsterically clashes with SER-861 of the RDRP at i + 4 (corresponding to the position for the incorporation of the fourth nucleotide following RDV-TP incorporation), preventing further enzyme translocation and terminating replication at position i + 3. This mechanism was nearly identical in SARS-COV, SARS-COV-2, and MERS-COV, and genome comparisons show that SER-861 is conserved across alpha-, beta-, and delta coronaviruses, implying that Remdesivircould have broad antiviral action. The potential accumulation of resistance mutations is a factor to consider when using nucleotide analogues like remdesivir. Excision of analogues by replication complexes' 3'-5' exonuclease (EXON) activity, which is mediated in SARS-COV by the nsp14 subunit, is a potential source of concern. The postulated mode of action is supported by the fact that MHVs lacking exon activity are about 4-fold more sensitive to remdesivir. [a191400] the relatively minor benefit of exon

activity to Remdesivirresistance is thought to be due to its delayed chain termination mechanism, which involves the incorporation of extra endogenous nucleotides after RDV-TP. In addition, recurrent passage of MHV in increasing concentrations of the Remdesivirparent molecule [GS-441524] resulted in the establishment of resistance mutations F476l and V553l, which keep SARS-COV active. In the absence of selective pressure, however, these mutant viruses are less fit than wild-type in both competitive experiments and in vivo. No clinical data on SARS-COV-2 resistance to Remdesivirhas been published to date.

Adverse effects

Based on a review of available literature from randomized clinical trials, the following are the potential organ-based adverse effects reported with the use of remdesivir. (10). Mucormycosis, a fungal disease seen in patients recovered from covid-19 is predicted to be a side effect overdose of remdevisir which is a steroid and supresses the immune system, but no evident data is not available to support this hypothesis.

- **Cardiovascular**: hypotension, arrhythmias, and cardiac arrest.
- **Pulmonary:** dyspnoea, acute respiratory failure, acute respiratory distress, pneumothorax, pulmonary embolism.
- **Haematological:** anaemia, lymphopenia.
- **Endocrine**: hyperglycaemia.
- **Infectious**: pneumonia, septic shock.
- **Gastrointestinal:** elevated lipase, nausea, vomiting, diarrhea, constipation, poor appetite, gastroparesis, and lower GI bleeding.
- **Hepatic:** hepatic manifestation characterized by grade 1-4 increase in serum transaminases (ALT and/or AST) are the most common adverse effects seen in patients treated with remdesivir. Other abnormalities include hyperbilirubinemia.
- **Renal and metabolic:** acute kidney injury or worsening of underlying chronic kidney disease, hypernatremia, hypokalaemia.
- **Neurological**: headache, light-headedness.
- **Skin:** rash, contact dermatitis, pruritus.
- **Psychiatric**: delirium.
- **Other adverse effects:** pyrexia, insomnia, multi-organ dysfunction, DVT, and hypersensitivity/anaphylactic reactions related to the infusion.

4. Conclusion

To conclude, we need to learn more about the mechanism of action of a small molecule pro-drug like Remdesivir before considering it as the drug of choice for COVID-19 treatment. We also need more favourable clinical trial data. There are more steps in the current synthetic approaches for remdesivir. To make it commercially, we need to devise a simpler synthetic technique. The mechanism of action, synthetic techniques, and clinical trial data based on Remdesivir as potential COVID-19 medicines were all discussed in this review.

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