ejpmr, 2022,9(10), 131-138

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

AN OVERVIEW ON REMDESIVIR FOR THE TREATMENT OF COVID-19

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Article Received on 10/08/2022 **Article Revised on 30/08/2022** **Article Accepted on 20/09/2022**

1. ABSTRACT

The coronavirus disease 2019(covid-19) pandemic,has caused considerable challenges to the National healthcare systems in this world. Coronaviruses use an RdRp enzyme to carry out replication and transcription of their RNA genome. Discovered in the 1960s, they had been at the beginning idea to be only responsible for moderate disease, with lines such as HCoV 229E and HCoV OC43 accountable for the common cold. That modified in 2003 with the SARS pandemic and in 2012 with the outbreak of MERS, each zoonotic infections that resulted in mortality prices increased than 10% and 35%, respectively. The common symptoms include fever, cough, dyspnea, chest pain and pneumonia. Remedesivir is a phosphoramide prodrug is only approved drug for the treatment of covid-19 patients. The aim of the study to examines the structure, First approval, journey of remdesivir, registered pattern of remdesivir, mechanism of action, dosing, adverse effect, pharmacokinetics and pharmacodynamics, drug interactions of remdesivir.

KEYWORDS: COVID-19, Corono virus, Ebola virus, Remdesivir structure, pharmacokinetics, Pharmacodynamics, Drug interaction, adverse effect.

2. INTRODUCTION

2.1 Corona virus

Coronavirus are large, enveloped, positive strand RNA viruses that can be divided into four general alpha-coronavirus, beta-coronavirus and gamma-coronavirus. Alpha and beta-COV are known to cause human diseases.[1] Coronavirus is a beta coronavirus, belonging to the same genus as extreme acute respiratory syndrome (SARS)-COV and middle east respiratory syndrome (MERSS)- COV. Since, the first instances have been said in December2019, infection with the severe acute respiratory coronavirus.[2,3]

2.2 Remdesivir first approval

THE WORLD HEALTH ORGANIZATION (WHO) has viewed remdesivir drug as one of the promising therapeutics in the fight against covid-19. Multiple scientific trials are ongoing on the use of remdesivir for the treatment of covid-19 in the united kingdom of America (USA) and all round the world.[4] Phase three trials of remdesivir in covid-19 had been started as early as February 2020. Based on statistics from the multinational segment three ACTT-1 and SIMPLE-Severe trials, remdesivir acquired an emergency use authorization in the USA.[5] The US FDA(Food and drug authorizing) to give permission to furnish emergency use of authorization of remdesivir for extreme covid-19 victims with 12 years of age (or)older with pneumonia who require supplemental oxygen.[6] Remedesivir is only FDA approved drug for the treatment of covid-19 patients.[7,8,9,10] Remdesivir acquired its first conditional approval for use in victims with intense covid-19 in Taiwan in late may moreover 2020, with this conditional approval requiring the pharmaceutical corporation to put in pressure a hazard management layout to make positive safety.[6]

3. Discovery of remdesivir

Nucleoside and nucleotide analogs as small-molecule primarily based definitely antivirals have been explored for many years and structure the backbone of treatment in the route of viral infections, inclusive of HIV, Hepatitis B virus, and herpes virus infection.[11] Remdesivir(GS-5734), a nucleotide analog prodrug that inhibits viral RNA polymerases has proven in vitro interest in opposition to SARS-COV-2.As a nucleoside analog ,remdesivir act as an RNA hooked up RNA polymerase(RdRp) inhibitor, centered on the viral genome replication process. The parent molecules of remdesivir,GS-441524, was derived from a small molecule library of spherical 1,000 several nucleoside and nucleoside phosphonate analogs that have been assembled over many years of antiviral search for in particular in unique based on their feasible functionality to intention rising RNA viruses such as SARS-COV and MERS-COV of the corona viridae or zika and dengue viruses of the Flaviviridae family.[12]

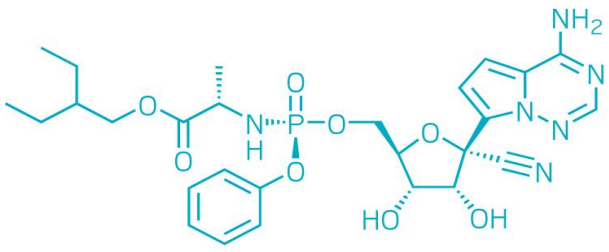
4. Journey of remedesivir

The 21st century has already considered a giant massive range of outbreaks: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and the Ebola virus (EBOV) in 2014. Presently, we are in the midst of an exceptional pandemic due to SARS-CoV-2, coronavirus disease 2019 (COVID-19.[13] Remedesivir (GS-5734) used to be developed by way of capability of Gilead sciences and emerged from a collaboration between Gilead, the U.S centers for disease control and prevention (CDC)the U.S Army medical research institute of infectious sickness (USAMRIID).[14] Remdesivir (GS-5734) is an investigational broad-spectrum antiviral drug that has validated activity against ribonucleic acid (RNA) viruses of endless families, consisting of Coronaviridae (such as SARS-CoV, MERS-CoV, and traces of bat coronaviruses), Paramyxoviridae (such as Nipah virus, respiratory syncytial virus, and Hendra virus), and Filoviridae (such as EBOV).[15,16]

5. Remdesivir structure

CHEMICAL NAME: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
Empirical formula: C27H35N6O8P
Formula weight: 602.6
Physicochemical properties:
Description: Remdesivir is a white to off-white or yellow solid.
Solubility: Remdesivir is very slightly soluble (0.35 mg/mL) at pH 2, practically insoluble (0.04 mg/mL) at pH 4, and practically insoluble (0.03 mg/mL) at pH 7. The partition coefficient (log P) is 3.2 and the pKa is 3.3.

6. Structure formula



Remdesivir

7. Mechanisum of action

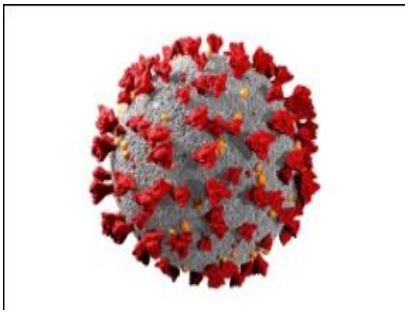
Remdesivir (GS-5734) potentially inhibited the replication of MERS coronavirus (MERS-COV) in vitro, and demonstrated efficacy against severe acute respiratory syndrome (SARS-COV) in a mouse model.

Pharmacologically, remdesivir has been designed to effectively deliver the monophosphate nucleoside analogue GS-441524 into cells.

Within cells, the GS-441524 monophosphate is rapidly converted to the pharmacologically active nucleoside triphosphate for GS-443902

Nucleoside triphosphate GS-443902 acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP substrate to selectively inhibits viral RNA-dependent RNA polymerase (RdRp)

The primary mechanism of inhibition is the incorpation of the GS-443902 nucleoside triphosphate into nascent RNA chains by viral RdRp resulting in delayed RNA chain termination during the process of viral replication.



SARS-COV-2

Host entry

Transaltion of viral RNA Genome

Cleavage of polyproteins PPIa and PPIab by viral proteases

NUCLEOTIDE ANALOGUE PRODRUG:

REMDESIVIR

Transcription and replication of viral RNA

Translation and production of structural and accessory proteins

Virion assembly and release

8. Dosage Forms and Strengths

Remdesivir for injection, 200 mg supplied as a sterile, preservative-free white to off- white to yellow lyophilized powder in unit -dose vial for reconstitution.

The drug was administered for 10 days .patients received 200mg of the drug intravenously on one day, and remdesivir 100mg daily was used for the remaining 9 days of the treatment cycle.[17]

9. DISCUSSION

Remdesivir Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of remdesivir have been summarized in documentation published by the U.S food and drug administration (FDA).[18]

Studies evaluating IM administration showed a gradual and variable onset from muscle, evidence of IM metabolism, and delayed onset of the pharmacologically active triphosphate GS-443902 in PMCS.I t was previously found that IV administration delivered GS-443902 to target cells faster and more consistently.

9.1 Adme

Absorption, distribution, and metabolism studies support the selection of Wistar–Han rat and cynomolgus monkey for the toxicological evaluation of remdesivir. Both rat and monkey produced the intermediate metabolite GS-704277 and the nucleoside metabolite GS-441524.GS-441524 is the predominant metabolite observed in all non clinical studies.

Remdesivir is not suitable for oral administration as its poor hepatic stability would likely result in almost complete first-pass clearance.[17]

9.1.1 Absorption

Remdesivir formulations administered IV is 100%. Previously, following single IV dose of remdesivir -150 mg infused over 30 minutes in healthful subjects, remdesivir was primarily detectable in blood and plasma with peak concentrations begin reached at the end of the infusion.[19] Considering the FDA-approved EUA, remdesivir is administered using the intravenous route over 30-120 mis. For adult victims , a single loading dose of the(drug 200 mg on day 1) discovered by using the use of way of way of once- day through the usage of day maintenance doses (100 mg from day 2)has been recommemded. For victims requiring invasive mechanical ventilation and /or ECMO and situations now no longer requiring invasive mechanical ventilation and /or ECMO, remedy publications are 10 days and 5 days respectively. If the scientific improvement in the patients who not require invasive mechanical ventilation and/or ECMO is no longer given, the administration of remdesivir can also be sustained up to 5 days longer and a full course of treatment of upto 10 days (18).Remdesivir elimination (terminal elimination half-life [t1/2] approximately 1 h) is followed by the sequential appearance of GS-704277, GS-441524 in plasma, and pharmacologically active metabolite, GS-443902 in PBMCs.[19]

9.1.2 Distribution

Remdesivir has moderately protein bound in the human plasma (approximately 88-93.6%) . Protein binding in plasma is low for GS-704277 and GS-441524(1-2% bound).Remdesivir and GS- 704277 were distributed predominantly in plasma relative to the cellular components of blood with mean whole blood/plasma concentration ratios of 0.76 and 0.56.[19]

9.1.3 Metabolism and Elimination

The result for the human mass balance study showed that remdesivir is extensively metabolised and excreted in urine mainly as the nucleoside metabolite GS-441524.Following administration of a single 150 mg remdesivir to healthy male subjects, the mean overall radioactive recovery dose was >92%,consisting of approximately 74% and 18% recovered in urine and stool, respectively. The majority of the dose recovered in the urine was GS-4415249(48.6%), confirming that renal clearance(Clr)was a major pathway for elimination of this metabolite;10.3% of the dose was recovered in urine as RDV (unchanged).[19]

9.2 Pharmacodyanamics

Remdesivir is activated intracellularly to form GS-443902 can analog adenosine triphosphate, which selectively inhibits viral RNA polymerase and has broad spectrum activity against members of the covid-19.[20]

9.3 Pharmacokinetics between animal Model and Human

In animal studies, have found that rhesus monkeys are effectively protected against MERS-COV infection, when administered prior to infection. Reduction of lung damage with remdesivir administered 12 hours after virus infection.[21,22]

The basis for a PK bridge from animal information to human dosages and efficacy is primarily based on the consequences of studies conducted in healthy and MERS-infected rhesus monkeys and PK statistics from Phase 1 research in healthy volunteers. For therapy of COVID-19, the dose was selected to achieve exposures (plasma and PBMC) associated with efficacy at 10 mg/kg and 5 mg/kg, respectively, in the MERS-infected rhesus monkeys. This result in a dosing regimen (based on allometric scaling) that requires a loading dose of 200 mg followed by 100mg once daily for 9 days. The pharmacokinetics of a daily dose 5 mg/kg (7 days) in rhesus monkeys (Study AD-399-2030) and a repeat doses of a 100mg (5 to 10 days) in healthy adult volunteers (Study GS-US-399-5505), both administered as 30-min IV infusion, similar systemic plasma exposures of RDV were carried in both species. In addition, the intracellular exposures of the active nucleoside triphosphate metabolite GS-443902 observed in rhesus monkey PBMCs given a daily dose 5 mg/kg

daily dose (7 days) were comparable to concentration found in human PBMCs after administration of repeated doses of 100 mg RDV have been reached.[17]

10. Registered remedesivir

Contemporaneous to the improvement of the Chinese trials, the first instances of COVID-19 have been rising in the USA. On January 20, 2020, an affected individual in Snohomish country, washinton, presented for urgent treatment with a subjective fever and 4- day coughing spells that would later be identified as the first outstanding case of covid-19 in the US.[23] On the seventh day of hospitalization and after the scientific condition had deteriorated, the affected character was once given IV remdesivir under compassionate use (Gilead Sciences), with no adverse events from infusion.[23] The patient's scientific circumstance accelerated the subsequent although concurrent therapy with acetaminophen, ibuprofen, guaifenesin, vancomycin, cefepime, and supplemental oxygen confound the direct interpretation of remdesivir's impact.

Subsequently, 12 patients were infected with SARS-CoV-2 between January 20, 2020, and February 5, 2020(24). Of these 12 patients, seven have been hospitalized and three received remdesivir (Compassionate use access; Gilead Science). As the disease worsened. Treatment was as soon as endured for 4–10 days with 200 mg IV on the first day and a hundred mg every following day. Following the initial dose, all sufferers experience "transient gastrointestinal symptoms associated with nausea, vomiting, gastro paresis or rectal bleeding," although early therapy was withheld until improvement in respiratory symptoms, with all 12 patients reporting symptom selection via February 22, 2020.[24] The small sample size and lack of controlled randomization prevent evaluation of medical efficacy or safety.

The National Institute of Allergies and Infectious Diseases (NIAID), NIH initiated the Adaptive COVID-19 Treatment Trial (ACTT), a double-blind, randomized, placebo-controlled section three trial evaluate the protection and efficacy of remdesivir in contrast with a remdesivir placebo-control (NCT04280705).[25] NIAID developed this study entirely based in part on state-of –the-art Chinese medical studies and in consultation with WHO.[26] This study is engaged in patient and monitors the baseline outcome of the affected individuals's severity, on an eight-point ordinal scale, with more than one secondary impact of interest. A total seventy five medical internet web sites are expected to participate in the study, which will be disseminated across the United States, and an estimated important completion date of April 2023.

Subsequently, Gilead Sciences initiated two scientific trials that started in mid-March, comparing remdesivir to known treatment in patients with susceptible or extreme coronavirus disease (COVID-19) in an open-label, randomized trial, NCT04292899.[27] This trial will evaluate the safety and assess overall efficacy of remdesivir with prevailing care to observe how the 5 or 10 day dosing of remdesivir affects the necessary sequence of fever and oxygen saturation. NCT04292730 maintains three studies on fingers to look at remdesivir administered over 5 or 10 days, to general care alone, with the predominant effect being the proportion of patients discharged at the day 14.[28]

To determine greatest remedy for COVID-19 and ensure there is sufficient power to see definitive results, the WHO announced the SOLIDARITY scientific trial, a four-arm trial evaluating remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with interferon-β1a, and chloroquine or hydroxychloroquine (ISRCTN83971151). With the intention of shortening the trial design time, the WHO is trying to hastily facilitate the differentiation of medicines at the international level. The data, meanwhile, will be analyzed with the analyzed with the help of an impartial team of experts, the Global Data and Safety Monitoring Committee, which will allow for modification of the study outline if clear early remedies show promise. As of March 27, 2020, over 70 countries committed to participating.[29]

In a study sponsored by Oslo University Hospital, the WHO NOR (Norwegian)-COVID 19 study is a multicenter, adaptive, randomized, open label analysis to investigate the safety and efficacy of hydroxychloroquine, remdesivir, and current popularity of care (NCT04321616, 2020-001052-18).[30] The primary end point is all cause in-hospital mortality, with secondary measures of duration on mechanical ventilation, duration of intensive care unit, 28-day mortality, viral clearance, readmission, prevalence of co-infections, and organ dysfunction. Inclusion requirements consist of validated SARS-CoV-2 contamination by PCR, 18 years of age, and admission to the fitness facility ward or ICU. Importantly, due to the recognized toxicity issues associated with hydroxychloroquine,the exclusion requirements include a prolonged QT interval(>450 ms).

A GroupeHospitalierPitie-Salpetriere-subsidized observational study with collaborating partner CMC AmbroiseParé was initiated once to investigate adverse events in COVID-19 therapy (NCT04314817).[31] The global disease classification ICD-10, an lopinavir/ritonavir, chloroquine, azithromycin, remdesivir, and interferon-β1a, with likely future scope extensions ahead of the main completion date in January 2021.

The Discovery trial is an adaptive, open-label, randomized interventional trial that consists of 5 therapy modalities (NCT04315948): remdesivir, hydroxychloroquine, lopinavir and ritonavir, or lopinavir, ritonavir, and interferon-β1a.[32] The

remdesivir dosing regimen is consistent with current trials, with maintenance dosing lasting up to 10 days. Lopinavir and ritonavir pills are to be administered each and every 12 h for 14 days (400 mg of lopinavir /100 mg of ritonavir). In mixture with the lopinavir/ritonavir schedule, interferon-β1a will be administered subcutaneously at a dose of 44 μg, for three doses in 6 days (day 1, day 3, and day 6). Hydroxychloroquine will be given 400 mg, twice on the first day, followed by using four hundred mg once every day for 9 days. Initially, the study will consist of 5 French hospitals (Paris – Hôpital Bichat-AP-HP, Lille, Nantes, Strasbourg, Lyon) with viable extension to other participants sites.[33] The prinicipal impact shows the seven-point ordinal scale, assessed on the 15 day, with secondary consequences tracking a range of physiological and medical metrics.

11. Drug interactions

A pharmacological interaction is described as the change of the pharmacodynamics and/or pharmacokinetics of the drug as a result of its concomitant administration with other medicaments, dietary elements (nourishment, diet, medicinal plants), social habits (smoking, alcohol consumption), or underlying pathologies.[34] Two most integral interactions have been described, 277 common drug interactions, and one alcohol/food interaction.[35,36] The most essential interactions are with chloroquine and hydroxychloroquine13; it has been decided that co-administration with chloroquine or hydroxychloroquine can further reduce the therapeutic consequences of remdesivir, and co-administration should be avoided.[36,37] Remdesivir's pharmacological interactions with tablets frequently prescribed in dentistry are all average drug interactions, and (according to drug group) are: (1) antibiotics: azithromycin, clavulanate, doxycycline, erythromycin, levofloxacin; (2) antifungals: clotrimazole, fluconazole, itraconazole, ketoconazole; (3) non-steroidal anti-inflammatories (NAIDS): celecoxib diclofenac, etodolac, flurbiprofen, ibuprofen, ketoprofen, ketorolac, mefenamic acid, naproxen, piroxicam.[35,36]

11.1 Considering liver function

Mild to moderate elevation in ALT, AST, or both have been observed in patients with severe covid-19 patients disease in studies of healthy volunteers and patients infected with the Ebola virus.[38] However considering the frequency of hepatic dysfunction in patients with covid-19, attribution of hepatotoxicity to either remdesivir or an underlying disease is challenging. Liver damage in patients with coronavirus could be directly caused by the viral infection of liver cells.[38]

11.2 Considering kidney function

The pharmacokinetics of remdesivir have no longer been evaluated in victims with renal impairment. Creatinine clearance must be determined in adult and pediatric victims (28>days old),and in term neonates(>7days to <28 days)serum creatinine should be determined prior to dosing. Remdesivir is not motivated in adults and pediatric patients (>28 days old) with eGFR much less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine ≥1 mg/dL unless the potential advantage outweighs the manageable risk.[39]

12. Adverseeffect[40]

Adverse effects of remdesivir	
Organ dysfunction	Low albumin
	Low potassium
	Low rbc count
	Low platelets count
	Yellow discoloration
	Gastrointestinal upset
	Increased level of transaminases in the blood(liver enzymes)
More common	Back pain
	Chest pain
	Chills
	Cough
	Dark coloured in urine
	Difficulty in swallowing
	Fast heartbeat
	Fever
	Flushing
	Headache
	Itching
	Light colour stool
	Nausea and vomiting
	Trouble in breathing

	Yellow eye or skin
	Unusal tiredness or weakness
	Stomach pain
Less common	Seizure
	skin rash
	Respiratory failure

13. CONCLUSION

Remdesivir should only be given in a hospital or in a healthcare facility that can capable of providing acute care comparable to inpatient hospital care. Several large, randomized trials of remdesivir use in patients with COVID-19 have been published. Food Drug Administration(FDA), National Institutes Of Health(NIH), World health organization(WHO), Infectious Diseases Society Of America(IDSA) Guidelines are recommended the use of remdesivir against COVID-19 patient. This article summarizes the important information regarding the use of remdesivir (VEKLURY) to treat the COVID-19 for its approved use is available in the prescribing information which includes dosing instruction, potential side effects and drug interaction.

Pharmacokinetics of remdesivir are

Protein binding: Remdesvir 88% to 93.6%; GS- 441524: 2%; GS-704277: 1%

Half life elimination: Remdesivir: ~1 hour GS-441524: 27hour; GS-704277:1.3 hours.

Excretion: Urine: Remdesivir: 10%; GS-441524: 49%; GS- 704277: 2.9%

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