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REMDESIVIR A CRITICAL REVIEW

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ABSTRACT

Remdesivir is a once-daily, nucleoside ribonucleic acid polymerase inhibitor of severe acute respiratory syndrome. Preclinical data in animal models of coronavirus diseases, including COVID-19, have demonstrated that early treatment with remdesivir leads to improved survival, decreased lung injury, and decreased levels of viral RNA. Preclinical data in animal models of coronavirus diseases, including COVID-19, have demonstrated that early treatment with remdesivir leads to improved survival, decreased lung injury, and decreased levels of viral RNA. Recent clinical data have demonstrated the clinical activity of remdesivir in terms of faster time to recovery in patients with severe COVID-19 and higher odds of improved clinical status in patients with moderate COVID-19. Several clinical trials are ongoing for the management of COVID-19 using remdesivir.

KEYWORDS

Remdesivir, Prodrug, Clinical trials, Covid-19

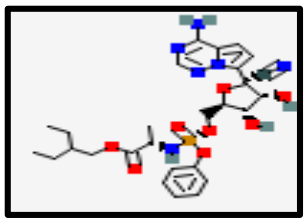
INTRODUCTION

Remdesivir (GS-5734) has been developed by Gilead Sciences, Inc. It is 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.GS-441524 and its S-acyl-2-thioethyl monophosphate prodrug had previously been reported in 2012 as potent leads from a series of 10- substituted 4-aza-7,9-dideazaadenosine C-nucleosides, with broad activity against a panel of RNA viruses: yellow fever virus (YFV), Dengue virus type 2 (DENV-2), influenza A, parainfluenza 3, and SARS[1-2]. It acts as a prodrug of adenosine analogue, inhibiting RNA-dependent RNA polymerase (RdRp) enzyme. Additionally, it also seems to block the viral genome replication process. Remdesivir is first metabolized within the host cells into an alanine metabolite (GS-704277), which is further processed into monophosphate derivative and then ultimately into the active nucleoside triphosphate (NTP) analogue. The NTP derivative now competes with alanine metabolite to get attached to nascent RNA strand.[3] This abnormal incorporation stops the elongation of RNA strand, terminating RNA synthesis prematurely. However, addition of remdesivir in the i-position of growing chain will not immediately stop the replication process. Instead, the strand replication stops at i+3 positions after incorporation of three more nucleotides.[4]

Remdesivir [chemical name: 2-ethylbutyl N-{(S)-[2-C(4- aminopyrrolo[2, 1-f][1,2,4]triazin-7-yl)-2-5-anhydro-daltrononitril-6-O-yl]phenoxyphosphoryl}-l-alaninate] is a low-molecular-weight (602.6 g/mol) prodrug with the molecular formula C27H35N6O8P[5] and a chemical structure as shown in Fig. 1. Remdesivir has broad-spectrum in vitro antiviral activity against members of the floviruses (including Ebola virus and Marburg virus), and other RNA viruses such as paramyxoviruses (respiratory syncytial virus, Nipah virus, and Hendra virus) and coronaviruses [CoV] (Middle East respiratory syndrome [MERS] CoV and SARS CoV).[6-8].

STRUCTURE[7]

Molecular Formula: - $C_{27}H_{35}N_6O_8P$



PHARMAKOKINETICS AND PHARMACODYNAMICS

Remdesivir is a potentially broad-spectrum antiviral agent against RNA viruses. It has been shown to reduce viral replication in vitro in human macrophages and lung microvascular endothelial cells infected with Pneumoviridae (e.g., respiratory syncytial virus) and Paramixoviridae (e.g., measles virus, mumps virus, and

parainfluenza virus 3)[7]. It has also been shown to exhibit antiviral activity against Filiviridae (e.g., Ebola virus and Marburg virus) in a variety of human cell types[9].

Remdesivir is widely distributed in the body, predominantly in bladder, kidneys, liver, prostate, mandibular salivary gland, pancreas, seminal vesicle, epididymis, and testes. Remdesivir is not suitable for oral administration due to complete first-pass metabolism through the liver. Consequently, intramuscular (i.m.) and intravenous (i.v.) administration of remdesivir was evaluated in male rhesus monkeys[9]. The i.m. administration was suboptimal due to slow and variable release of remdesivir from the muscle, and the pharmacokinetics of subcutaneous administration has not been evaluated in humans. In contrast, the remdesivir administered via i.v. was rapidly eliminated and converted to the nucleoside analogue (GS-441524), indicating a more consistent and rapid delivery of remdesivir and higher maximal levels of the nucleoside analogue than were seen with the i.m. administration. remdesivir has a short plasma half-life (t1/2) of 1 h, as it is quickly metabolized by carboxylesterase 1 (CES1) to the intermediate alanine metabolite (GS-704277), followed by the predominant GS-441524 metabolite (t1/2 of 24.5 h)[10,11]. Remdesivir has moderate protein binding (approximately 88–93.6% bound) in human plasma. Protein binding in plasma is low for GS-704277 and GS-441524 (1–2% bound). Remdesivir and GS-704277 were predominantly distributed to plasma relative to the cellular components of blood. RDV is primarily metabolized (80% of total metabolism) in the liver by carboxylesterase 1, with cathepsin A, and cytochrome P450 (CYP) 3A, contributing to 10% each[12].

In 2016, the first clinical experience of using remdesivir against Ebola virus in human was reported. Ebola meningoencephalitis was diagnosed in a female nurse by detection of Ebola virus RNA in the plasma and cerebrospinal fluid. The patient was successfully treated by administration of corticosteroids and remdesivir for 2 weeks (once-daily administration of 150 mg over 2 h for 2 days, and then daily using of 225 mg for 12 days). In spite of a temporary increase in the levels of the enzyme amylase in serum, any serious adverse event was not observed[13]. In 2017, it was shown that remdisiver could prevent the replication of SARS and MERS coronaviruses and be effective against bat and circulating contemporary human coronaviruses in vitr remdesivir for prophylaxis and early treatment in a mouse model with SARS-CoV infection led to a decrease of the viral load in the lungs and improvement of the respiratory function[6].

REMDESIVIR IN COVID TREATMENT

The novel coronavirus 2019 (2019-nCoV), formally named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel human infectious coronavirus. The disease caused by SARS-CoV-2 is named COVID-19. Development and manufacturing of specific therapeutics and vaccines to treat COVID-19 are time-consuming processes. At this time, using available conventional therapeutics along with other treatment options may be useful to fight COVID-19. Remdesivir was recently approved by the Food and Drug Administration for the treatment of hospitalized patients with coronavirus disease 2019 (COVID-19). SARS-

CoV-2 is an enveloped, single, and positive stranded RNA virus. The virus particles are round or oval in shape, with a diameter about 60–140 nm. Based on sequence analysis, it shows that the novel coronavirus belongs to Beta coronavirus Lineage β, Sarbecovirus, where SARS-CoV and MERS-CoV are included. However, it forms a new clade different from SARS-CoV and MERS-CoV, and becomes the seventh member of the coronavirus family to infect humans[14].Wuhan Virus Research Institute, China, virus-infected Vero E6 cells treated with remdesivir showed that it blocked virus replication even at very low micromolecular concentration with high cell selectivity. The result assumed its effective role in monkeys with SARS-Co-2 infection[15]. Remdesivir is a phosphoramidate prodrug of an adenosine C-nucleoside. By entrance into respiratory epithelial cells in human, the prodrug is metabolized to a nucleoside triphosphate as the active form. The nucleoside analog inhibits the viral RNA-dependent RNA polymerase (RdRp) by competing with the usual counterpart adenosine triphosphate (ATP). The nucleoside analog is incorporated into the generating RNA strand and causes a delayed stop in the viral replication process.

Data from preliminary studies conducted in US demonstrate significant clinical improvement in COVID-19 patients when treated with remdesivir. Goldman et al (2020) did a randomized, open-label, phase 3 trial including hospitalized patients with COVID-19. Patients were randomly divided to receive 5-day and 10-day courses of the intravenous remdesivir. In patients with severe Covid-19 not needing mechanical ventilation, there was not any significant difference between the 5-day and 10-day durations of the intravenous remdesivir. Due to lack of a placebo control, the degree of benefit cannot be ascertained. Two double-blinded, placebo-controlled trials recruiting in China were designed to evaluate the efficacy and safety of intravenous remdesivir targets 308 hospitalized adults with mild-to-moderate COVID-19 and another trial (ClinicalTrials.gov identifier: NCT04257656) targets 452 hospitalized adults with severe COVID-19. In both trials, in a 10-day regimen, the initial dose of remdesivir is 200 mg on day 1, followed by 100 mg once-daily for remaining days.39,40 In both trials, the primary outcome measure is the time to clinical recovery[16].National Institute for Allergy and Infectious Disease (NIAID) has conducted an Adaptive COVID-19 Treatment Trial. The objective of this study was to find out the optimal duration of remdesivir therapy in SARS-CoV-2 infection. It was a double blind, placebo-controlled, multicentric study with 1,063 randomized patients. Results showed that remdesivir use was associated with survival benefit and faster recovery rates with a median time to recovery of 11 days compared to 15 days with placebo.[17] The common adverse event noted during compassionate use of remdesivir in patients with COVID-19 by Grein et al. include rash, diarrhea, hypotension, abnormal liver function and renal impairment. Serious adverse events (acute kidney injury, septic shock, multi-organ failure) was noted in 23%, while 60% had at least one adverse event and 8% discontinued due to various side effect of remdesivir[18]

In a rhesus monkey model infected with MERS-CoV, treating with remdesivir 24 h before infection can completely prevent symptoms caused by MERSCoV, strongly inhibit viral replications in the respiratory tract,

and prevent the formation of pulmonary lesions. Administering remdesivir 12 h after infection provides clear clinical benefits, reducing clinical symptoms, lung virus replication, and lung lesions[19]

In this comparative effectiveness research study of adults hospitalized with COVID-19, receipt of remdesivir was associated with faster clinical improvement in a cohort of predominantly non-White patients. Remdesivir plus corticosteroid administration did not reduce the time to death compared with remdesivir administered alone. Out of 2483 consecutive admissions, 342 individuals received remdesivir, 184 of whom also received corticosteroids and 158 of whom received remdesivir alone. For these 342 patients, the median age was 60 years (interquartile range, 46-69 years), 189 (55.3%) were men, and 276 (80.7%) self-identified as non-White race/ethnicity. Remdesivir recipients had a shorter time to clinical improvement than matched controls without remdesivir treatment (median, 5.0 days [interquartile range, 4.0-8.0 days] vs 7.0 days [interquartile range, 4.0-10.0 days]; adjusted hazard ratio, 1.47 [95% CI, 1.22-1.79]). Remdesivir recipients had a 28-day mortality rate of 7.7% (22 deaths) compared with 14.0% (40 deaths) among matched controls, but this difference was not statistically significant in the time-to-death analysis (adjusted hazard ratio, 0.70; 95% CI, 0.38-1.28). The (continue addition of corticosteroids to remdesivir was not associated with a reduced hazard of death at 28 days (adjusted hazard ratio, 1.94; 95% CI, 0.67-5.57)[20]. While in an another study the experimental drug-Remdesivir did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19, nonetheless, clinically meaningful differences and numerical reductions in some clinical parameters cannot be excluded. The place of ongoing studies is encouraged to promote better understanding of the intervention effect in larger sample sizes of severely ill COVID-19 patients[21]. A Gilead-sponsored study with 596 participants compared the effectiveness and safety of two durations of active treatment (RDV 100 mg for 5 or 10 days) against standard care. The clinical trial had an open-label, randomised, controlled, multicentre design. All participants were adults or adolescents ≥ 12 years and Covid-19 confirmed cases, admitted with moderate severity (oxygen saturation > 94% and radiological evidence of pulmonary infiltrates). The main outcome was defined as clinical status on day 11 on a 7-point ordinal scale. Exploratory outcomes were also established, including all-cause mortality, duration of hospitalization, time to recovery or time to clinical improvement[22]. Viral infections undoubtedly constitute one of the biggest pandemic threats in the modern era. By nature, viruses are obligate intracellular pathogens that utilize host cell for their survival. Hence, an important consideration for antiviral drug candidates includes non-impairment of host cell function despite killing or arresting viral multiplication. Other consideration includes structure (i.e., differences between RNA and DNA viruses), degree of host cell interaction, and acquired drug resistance.

DOSAGE AND DRUG ADMINISTRATION

Adult and pediatric patients with moderate or severe COVID-19 can receive a treatment duration of up to 5 days, which can be extended for up to 10 days if patients do not demonstrate clinical improvement.[23,24] Remdesivir is currently supplied as two different preservative-free formulations containing 5 mg/ml

remdesivir, including a water-based concentrated solution and a lyophilized powder formulation, both provided in 100-mg vials. The recommended dosing for adults and for pediatric patients weighing 40 kg is a single loading dose of 200 mg on day 1, followed by a daily maintenance dose of 100 mg. For pediatric patients weighing more than 3.5 kg and less than 40 kg, the lyophilized formulation is preferred. A single loading dose of 5 mg/kg of body weight should be administered on day 1 followed by a maintenance dose of 2.5 mg/kg. Doses should be administered intravenously and infused over 30 to 120 min[23]; Although rare to date, in some patients with severe immunocompromising conditions, especially those who receive combined T-cell-depleting and B-cell-depleting agents for hematological malignancies or autoimmune diseases, we have had to administer additional courses of remdesivir over time for recrudescent clinical disease.[25-27]

RISK FACTOR OF REMDESIVIR

Luke et al study on animals shows the SBECD accumulation with liver necrosis and renal tubule obstruction,1 which occurred in animals at doses 50- to 100-fold higher than expected for a 5- to 10-day remdesivir course. SBECD accumulation may be due to remdesivir has limited water solubility, the intravenous preparation contains the vehicle SBECD[28]. It can also lead to mitochondrial injury in renal tubular epithelial cells, kidney toxicity occurs after prolonged exposure and therefore, would be extraordinarily rare to occur within a 5- or 10-day therapy course.In addition, a study by Mulangy et al haven't reported significant renal adverse events when remdesivir was used in a clinical trial for Ebola[29-30]. The Ebola phase 3 trial reported one serious adverse effect, a fatal episode of peri-infusional hypotension, deemed potentially related to remdesivir administration[31].

Remdesivir is a RNA polymerase inhibitor and it inhibits infection of SARS-CoV-2 virus in a human cell line, in vitro. In an animal model of SARS-CoV and MERS-CoV infections, Remdesivir also showed decreased viral load and improved pulmonary function. Remdesivir's situational and political superiority, as well as its previous research results and application effects make it imperative to carry out the clinical trials focusing on the SARS-CoV-2. Among the candidate therapies, remdesivir has demonstrated efficacy in both in vitro and in vivo models against coronaviruses. Recently, through a compassionate use indication, remdesivir has supportive evidence for yielding some clinical improvement in COVID19 patients.[32]

CONCLUSION

Remdesivir is an important therapeutic option for patients with COVID-19 based on the described clinical pharmacology properties, safety profle, potency, and low DDI potential. SARS-CoV-2 is an RNA virus that is easy to mutate, the rapid starting of clinical trials is undoubtedly a right choice to prevent the resistance mutation due to blind medication. Remdesivir is an anti-viral agent that has shown significant inhibitory effect in vitro and in vivo studies against SARS-CoV-2 and appears to be ahead to other repurposed drug being tried for the treatment of COVID-19. Ongoing clinical pharmacology studies focus on the characterizing efect of

renal and hepatic disfunction on the PK of remdesivir, and will further support the use of RDV for the treatment of COVID-19. Remdesivir is an important therapeutic option for patients with COVID-19 based on the described clinical pharmacology properties, safety profle, potency, and low DDI potential. Ongoing clinical pharmacology studies focus on the characterizing efect of renal and hepatic disfunction on the PK of remdesivir, characterizing DDI with strong CYP3A inducers, and will further support the use of RDV for the treatment of COVID-19. Knowledge about the potential efficacy of remdesivir against coronaviruses has been restricted to in vitro studies and animal models. However, information related to COVID-19 is rapidly growing. Several clinical trials are ongoing for the management of COVID-19 using remdesivir. Potential clinical benefi t in SARS-CoV-2 infection upon remdesivir treatment has been established. Recently, FDA has granted full approval for the clinical use of remdesivir for COVID therapy.

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