Remdesivir: A critical review

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Abstract

Remdesivir has appeared to be the most effective medication against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and is broadly administered to the coronavirus disease 2019 (COVID-19) patients around the world. Remdesivir is an RNA polymerase inhibitor with a broad spectrum of antiviral activities against RNA viruses in in-vitro and in-vivo models of SARS-CoV, the Middle East respiratory syndrome (MERS), and SARS-CoV-2. Remdesivir is the first Food and Drug Administration (FDA) approved anti-SARS-CoV-2 treatment for adult and pediatric patients and has been used intravenously for patients requiring hospitalization for COVID-19. However, questions have been raised about the value of remdesivir in treating COVID-19, and governing bodies worldwide have been hesitant to approve this medication. Nevertheless, in the context of the public health emergency and the urgent need for effective treatments for patients with COVID-19, remdesivir has been approved by several authorities worldwide. Here, we discuss characteristics and applications of remdesivir, and various challenging studies with different outcomes about its efficacy are also reviewed.

Remdesivir: A critical review

Running title: A critical review on remdesivir

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest disclosure

TTS reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no relevant financial interests to be declared.

Author Contributions

- **ZMA:** Data collection and writing the manuscript.
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- **TTS:** Contributed substantial revisions to the manuscript's content.
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- **KCC:** Helped with manuscript writing and contributed substantial revisions to the manuscript's content.
- **RH:** Data collection and helped with manuscript writing.
- **MB:** Data collection, helped with manuscript writing, and contributed substantial revisions to the manuscript's content.
- **SE:** Design of the research study and supervision.

Abstract

Remdesivir has appeared to be the most effective medication against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and is broadly administered to the coronavirus disease 2019 (COVID-19) patients around the world. Remdesivir is an RNA polymerase inhibitor with a broad spectrum of antiviral activities against RNA viruses in*in-vitro* and *in-vivo* models of SARS-CoV, the Middle East respiratory syndrome (MERS), and SARS-CoV-2. Remdesivir is the first Food and Drug Administration (FDA) approved anti-SARS-CoV-2 treatment for adult and pediatric patients and has been used intravenously for patients requiring hospitalization for COVID-19. However, questions have been raised about the value of remdesivir in treating COVID-19, and governing bodies worldwide have been hesitant to approve this medication. Nevertheless, in the context of the public health emergency and the urgent need for effective treatments for patients with COVID-19, remdesivir has been approved by several authorities worldwide. Here, we discuss characteristics and applications of remdesivir, and various challenging studies with different outcomes about its efficacy are also reviewed.

Keywords: SARS-CoV-2; COVID-19; Remdesivir; Antiviral

Introduction

COVID-19 is now prevalent over a whole country. The remdesivir, an antiviral drug, is becoming a 'molecule of expectancy' for this disease's behavior. USFDA gave emergency approval to this drug for the treatment of COVID-19 [1]. In this article, we tried to show the probable molecular mechanism of remdesivir to prevent the RNA synthesis of SARS-CoV-2. Up to now, remdesivir has appeared to be the most effective medication against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and is broadly administered to the coronavirus disease 2019 (COVID-19) patients around the world [2].

Remdesivir or GS-5734 is a broad-spectrum antiviral medication nucleoside analog against several single-stranded RNA viruses, including SARS-CoV-2 [3]. It was the first FDA-approved drug for clinical use in SARS-CoV-2 infection [4]. Recently, controversies have emerged in the remdesivir trials and its efficacy in reducing COVID-19-related morbidity and mortality. In this article, characteristics and applications of remdesivir are briefly reviewed, and various challenging studies with different outcomes about its efficacy are discussed.

Mechanism of action and indications

Remdesivir is an adenosine analog with broad-spectrum antiviral activity against RNA viruses, such as filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses. It inhibits viral replication by causing a delayed chain termination of RNA synthesis [5-7], inhibiting SARS-CoV-2 in human airway epithelial cells (Figure 1) [8]. The active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (Exon), causing a decrease in viral RNA production [9, 10]. The active configuration of remdesivir takes action as a nucleoside analog and prevents the RNA-dependent RNA polymerase (RdRp) of coronaviruses, including SARS-CoV-2. The RdRp incorporates Remdesivir into the growing RNA product and permits the addition of three more nucleotides before RNA synthesis stalls [11]. In COVID-19, RdRp contains subunits nsp7, nsp8, and nsp12 under physiological conditions, but the functional RdRp complex can be reassembled in vitro, similar to MERS-CoV (Middle East Respiratory Syndrome coronavirus), containing only nsp8 and nsp12 subunits [12]. When using nucleotide analogs inclusive of remdesivir, the opportunity of everlasting accumulation of the mutation must be considered. Cleavage of analogs via way of means of the 3‘5'-exonuclease (ExoN) hobby of the replication complicated mediated in SARS-CoV-2 via way of means of the nsp14 subunit may be problematic [12].

Remdesivir enters the cells earlier than being cleaved to monophosphate shape through carboxylesterase 1 or cathepsin A. It is then phosphorylated through a kinase of unknown beginning to shape the lively triphosphate to shape remdesivir triphosphate (RDVTP or GS443902) [3]. Before the COVID-19 pandemic, the primary utilization of remdesivir had been for Ebola and Nipah viruses [5, 13]. Nevertheless, with the onset of the current pandemic, remdesivir has been introduced as a valuable medication with promising effects and good safety profiles [9].

Dosing, timing, and route of administration

Remdesivir should be administered intravenously with a loading dose of 200 mg diluted in normal saline (0.9%) or 5% dextrose given over 60 minutes on day 1, followed by 100 mg once daily for adults and children weighing [?] 40 kg [14]. For pediatrics weighing 3.5-40 kg, a loading dose of 5 mg/kg of body weight on the first day, followed by a maintenance dose of 2.5 mg/kg, is recommended [15]. The recommended duration for remdesivir therapy is 5-10 days [16]. If administered in an appropriate stage, it can significantly decrease the mortality of the patients with COVID-19 [17]. The best time to start remdesivir treatment is 10 days from the disease onset, preferably in the first 3 days, before developing host hyperinflammatory response [18-21]. However, due to the possible protracted viral shedding of SARS-CoV-2 in some patients, even late administration of remdesivir is suggested [22, 23].

Trials have shown that remdesivir can be the most beneficial in hospitalized patients with severe but non-critical forms of SARS-CoV-2 infection, who have not been admitted yet to the intensive care unit (ICU) or undergone mechanical ventilation [24]. Therefore, patients who already have signs of respiratory failure are not ideal for receiving this drug [22]. Furthermore, some studies have shown that early remdesivir treatment could also be considered in hospitalized patients with moderate COVID-19 with no need for supplemental

oxygen therapy [19]. At the beginning of the pandemic, remdesivir was recommended for a duration of up to 10 days in selected patients. Nevertheless, soon it was demonstrated that there is no significant difference between a 5-day and a 10-day course of this medication, even in severe COVID-19 patients. One explanation of such a finding is that a shorter treatment duration may cause fewer adverse drug reactions [25, 26]. Nonetheless, despite its rapid onset of action and the ability to suppress viral replication, some authorities have suggested that remdesivir may not be able to eradicate SARS-CoV-2 in immunosuppressed patients, especially those on T cell-or B cell-depleting therapies or other immunosuppressing agents. Hence, demonstrating the necessitation of a longer duration of therapy in these individuals [27, 28].

Adverse drug reactions

Hepatotoxicity

The maximum scientific research the use of remdesivir confirmed no extensive affiliation among remedy and hepatotoxicity, however in a few smaller research, remdesivir can motive improved ALT / AST levels. Therefore, liver feature exams for remdesivir have to be cautiously monitored and stated in the in-depth care unit if there are records of liver disease [29]. In a few cases, increased aminotransferases following remdesivir initiation in three COVID-19 patients [30]. According to a study on compassionate-use remdesivir against COVID-19, 23% of the patients reported increased hepatic enzymes, and thus, two of them were discontinued remdesivir prematurely [31]. Together, monitoring liver function tests (LFTs) in these patients is warranted.

Gastrointestinal symptoms

There were three COVID-19 patients treated with remdesivir, of which two of them manifested with nausea, and one suffered from gastroparesis after the treatment initiation [30]. Based on a study in China, a higher proportion of remdesivir recipients than placebo recipients had dosing prematurely stopped because of anorexia, nausea, and vomiting [32].

Respiratory toxicity

In an in vitro experiment, remdesivir became proven to inhibit TGFβ1-brought on activation of lung fibroblasts and dose-dependently decreased TGFβ1-brought on mesenchymal metastasis in the alveolar epithelium. Our consequences imply that remdesivir can proactively alleviate the severity of pulmonary fibrosis and offer hints for stopping pulmonary fibrosis in sufferers with COVID-19 [33]. Based on the findings from a study in China, more patients in the remdesivir group than the placebo group suffered from respiratory failure or acute respiratory distress syndrome (10% versus 8%), and therefore, discontinued the study drug (5% versus 1%) [32].

Cardiovascular toxicity

The cardiotoxicity of remdesivir is because of its binding to human mitochondrial RNA polymerase. Remdesivir, on the alternative hand, prolongs the period of the electrical discipline ability via lowering Na^+ top amplitude and dose-structured spontaneous pulsation rate, which might also additionally result in QT prolongation and torsades du point [34]. One case of hypotension was reported to be potentially related to remdesivir in a study on experimental therapies against Ebola [35]. Although relatively rare, hypersensitivity reactions, including infusion-related reactions and anaphylaxis, have been observed after remdesivir administration [36]

Nephrotoxicity

The renal toxicity of remdesivir is due to distinct mechanisms. First, remdesivir triphosphate itself has a low cap potential for mitochondrial toxicity because it motives mitochondrial damage in renal tubular epithelial cells and weakly inhibits mammalian DNA and RNA polymerase [37]. Acute kidney failure (AKI) has been reported after the initiation of remdesivir [32]. Thus, monitoring renal function biomarkers is mandated in these patients.

Pregnancy risks

While it is not recommended to use in pregnant women, remdesivir could be administered in special cases after carefully weighing the pros and cons of the treatment. Based on previous reports of its use against Ebola, remdesivir appears safe in human pregnancies. However, the safety of remdesivir in this special group of patients needs to be further evaluated by clinical trials on pregnant women of COVID-19 [35].

Interactions

In the type of steroids, drugs like dexamethasone and betamethasone induce cytochrome P450 enzymes (CYP3A4) and thus will rapidly eliminate remdesivir [38].

Doctors need to be careful about this interaction. Rifampicin, rifabutin, and rifapentine strongly induce the CYP3A4 enzyme. These medications are used in the treatment of tuberculosis and leprosy. Remdesivir has no known interactions with any bronchodilators and beta-blockers, and antivirals, including oseltamivir [39].

Up to now, no significant drug-drug interactions between remdesivir and other medications have been reported. Nonetheless, it is recommended not to start remdesivir concomitantly with vasopressors, primarily as those already on vasopressors are more likely to suffer from end-organ failure, making remdesivir therapy not beneficial for them. Another relative contraindication for this drug is the concomitant use of chloroquine (CQ)/hydroxychloroquine (HCQ) due to these drugs' antagonistic effect on antiviral activity remdesivir. There are also trials showing that CYP450 inducers, such as rifampicin, carbamazepine, and phenytoin, may decrease remdesivir serum levels [40, 41]. On the other hand, due to the increased risk of hepatic impairment with remdesivir therapy, concomitant use of other hepatotoxic agents is discouraged [42].

Safety

Fortunately, remdesivir has proved to have an excellent safety profile for nearly all population groups. Moreover, having shown no*in-vitro* and *in-vivo* genotoxicity, remdesivir seems to be safe in pregnancy. However, close monitoring of LFTs is required because of potential hepatitis after remdesivir injection and its overlap with other causes of LFTs impairment during pregnancy. Besides, its use in nursing women is also safe. Being predominantly eliminated by the kidneys, remdesivir should be used cautiously in patients with creatinine clearance < 30 mL/min. However, the short duration of treatment makes it feasible to be used even in lower estimated glomerular filtration rates (eGFRs) [43], to the point that even it has been reported that in some trials, remdesivir was well tolerated by patients with end-stage kidney disease (ESRD) [44]. Moreover, although it seems that remdesivir should not be administrated for individuals with chronic liver diseases, such as chronic hepatitis, there have been case reports showing no difference in the pharmacokinetics of this drug in severe cirrhotic and non-cirrhotic patients [45]. Nonetheless, further studies are needed to validate the safety, efficacy, and required dose adjustment of remdesivir in COVID-19 patients with underlying chronic hepatic disorders. At present, it is recommended not to administer remdesivir for patients with baseline serum transaminases levels exceeding five times the upper limit of normal (ULN) since this medication per se can increase both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [46]. Thus, if ALT increases $> 5 \times$ ULN, and evidence of liver inflammation or elevating levels of conjugated bilirubin, alkaline phosphatase (ALP), or international normalized ratio (INR) is observed during remdesivir therapy, it should be promptly discontinued until ALT falls below $5 \times$ ULN [47]. Nonetheless, If necessary, remdesivir could be safely given in patients with increased baseline LFTs [48], in which close monitoring of LFTs is needed to prevent further liver damage.

Increasing evidence has witnessed that COVID-19 is implicated in injuries of multiple organs, including lung, liver, gastrointestinal tract, heart, and kidney. Hence, distinguishing the underlying causes of adverse events during remdesivir treatment is complex. Moreover, the latest safety data from Grein et al.'s study on compassionate-use remdesivir which reported adverse events in 60% of the patients, and the RCT in China, which reported adverse events in 66% of remdesivir recipients versus 64% of placebo recipients, might be limited by the inclusion criteria, finite sample size and follow-up duration. Since the experience of remdesivir application in the newly emerging COVID-19 is still limited, adverse drug effects need to be paid much attention [49-51].

Efficacy and controversies

Several trials have been performed on the efficacy and benefits of remdesivir added to other agents in managing SARS-CoV-2-infected patients. Preliminary studies had highlighted the additive efficacy of remdesivir plus inhaled steroids in hypoxic COVID-19 patients [52]. However, it was later understood that systemic corticosteroids attain the most beneficial effect with or without remdesivir or any other antiviral agent [53, 54]. In addition, co-administration of remdesivir and dexamethasone has decreased the mortality rate and mechanical ventilation requirement in moderate-to-severe COVID-19 patients [55]. More recent trials have concluded that human monoclonal antibodies (mAb), such as baricitinib, a selective Janus kinase (JAK) 1 and 2 inhibitors, plus remdesivir, can be more effective than remdesivir alone in decreasing the time-to-recovery and clinical improvement, especially in patients needing supplemental oxygen therapy [56]. This beneficial effect may be due to alleviating immune response and inhibiting the hyperinflammatory phase by baricitinib. [57].

For remdesivir itself, there have been contradictory results reported by different trials. For example, some reported the absence of a statistically significant clinical benefit in reducing the time-to-improvement [18]. Moreover, some authorities even believe that remdesivir treatment neither can improve survival nor shorten hospitalization [58]. Whereas, results of other studies, including those performed by the World Health Organization (WHO), were different, revealing remdesivir as a beneficial agent in shortening the recovery time in hospitalized COVID-19 patients while having no impact on mortality rate [20, 22, 59, 60]. Accordingly, the lack of efficacy in reducing the overall mortality rate was recommended against remdesivir treatment [61]. Interestingly, most of the trials concluding the lack of efficacy of remdesivir had been carried out on the Asian population, highlighting that the Asian patients may show poorer outcomes after remdesivir therapy [62]. On the other hand, there have been trials acknowledging the positive role of remdesivir in decreasing the mortality rate of these patients [19, 63-65]. For this reason, other guidelines, except the WHO guideline, still recommend remdesivir, particularly in the early stages of the disease [66]. In general, while the patients requiring supplemental oxygen therapy may benefit the most from remdesivir, its application in those in need of high-flow oxygenation, noninvasive ventilation (NIV), or mechanical ventilation may not be helpful [20].

Hence, remdesivir administration has become quite challenging due to the disparities mentioned above. It is noteworthy that some have concluded that a 5-day course of remdesivir treatment, rather than a 10-day one, induced a relatively better outcome than standard care, despite having no significant difference [67]. It should be noted that these disparities may be the result of the heterogenicity of populations and study protocol in different clinical trials. Moreover, underlying disorders predisposing patients to more severe infection should also be considered another reason for the lack of favorable response and poor outcomes in some individuals [68]. Furthermore, the positive effect of concomitant corticosteroid administration in many hospitalized patients should also be considered before interpreting the favorable efficacy of remdesivir, leading to the overestimation of outcome improvement rates [69].

Conclusion

As discussed above, remdesivir is efficacious in COVID-19 patients, especially non-severe cases. Remdesivir has been used in many countries as an emergency medication for patients with COVID-19, and several patients showed better clinical outcomes. Also, this medication has little interaction with other medications, making it an ideal candidate for administration in these patients. Moreover, close monitoring of liver function tests (LFTs) and estimated glomerular filtration rate (eGFR) is mandated in patients undergoing remdesivir therapy, as hepatotoxicity and renal damage have been reported in such patients. Overall, as indicated in different guidelines worldwide, remdesivir could be a drug of choice in non-severe SARS-CoV-2-infected patients.

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Figure legends

Figure 1. The function of Remdesivir in the treatment of COVID-19 patients. The SARS-CoV-2 virus can enter host cells and activate the immune system through ACE2 and TMPRSS2 receptors. In patients with COVID-19, after entering the body, the virus translates its genome through the ribosome and produces RdRp. After administration, remdesivir (GS-5734) is activated, forming GS-441524, which in turn binds to RdRp and prevents virus RNA replication. **Abbreviation:**ACE2, Angiotensin-converting enzyme 2; TMPRSS2, Transmembrane Serine Protease 2; RdRp, RNA-dependent RNA polymerase.