



Potential Cardiotoxic Effects of Remdesivir on Cardiovascular System: A Literature Review

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Abstract

Corona disease 2019 (COVID-19) pandemic continues to spread around the world with no efficacious treatment. Intravenous remdesivir is the only authorized drug for treatment of COVID-19 disease under an Emergency Use Authorization. Remdesivir is a 1'-cyano-substituted adenosine nucleotide prodrug which inhibits viral RNA synthesis. This metabolite is an adenosine analog but with a significantly longer half-life than adenosine. Adenosine is a powerful vasodilator that can cause profound hypotension which is followed by the compensatory release of catecholamines. It can also shorten atrial action potential and refractoriness and lead to atrial fibrillation (AF). These effects may also occur in ventricular cells and predispose patients to ventricular fibrillation. Remdesivir can also induce significant cytotoxic effects in cardiomyocytes that is considerably worse than chloroquine cardiotoxic effects. Remdesivir-induced cardiotoxicity is due to its binding to human mitochondrial RNA polymerase. On the other hand, remdesivir can increase field potential duration with decreased Na⁺ peak amplitudes and spontaneous beating rates in a dose-dependent manner that might induce prolonged QT interval and torsade de point. There are some reports of sinus bradycardia, hypotension, T-wave abnormalities, AF, and a prolonged QT interval and few cases of cardiac arrest and complete heart block following remdesivir infusion. It seems remdesivir have some cardiotoxic and proarrhythmic effects that are especially more pronounced in patients with previous cardiovascular diseases. The current safety profile of remdesivir is still not completely known and further prospective clinical trials are needed to assess its safety profile and potential adverse cardiovascular effects.

Keywords Corona virus · COVID-19 · Remdesivir · Bradycardia · QTC prolongation · Cardiovascular

Introduction

Corona disease 2019 (COVID-19) is an infectious disease which continues to spread around the world with no efficacious treatment [1]. It has become a pandemic disease that has manifested itself as the most important health catastrophe of the century. Several medications including chloroquine/hydroxychloroquine, favipiravir, lopinavir/ritonavir,

azithromycin, and remdesivir have been used in clinical trials and have shown some beneficial effects [2]. Among these drugs, intravenous remdesivir is the only authorized drug for treatment of COVID-19 disease under an Emergency Use Authorization [3]. It is an investigational antiviral drug which was initially used in patients with the Ebola virus [4]. Remdesivir is a 1'-cyano-substituted adenosine nucleotide prodrug which inhibits viral RNA synthesis [2]. Indeed, it works as an adenosine analog by incorporating itself into viral RNA. This leads to premature chain termination and inhibition of viral replication [1]. COVID-19-infected patients with underlying cardiovascular disease seem to have an adverse outcome. Furthermore, a decreased potassium level occurs commonly in patients with COVID-19, which may lead to electrocardiographic changes such as prolonged QT interval and can increase the risk of adverse medical side effects [5]. Therefore, understanding the cardiovascular risks of potential medications is of particular importance. Given that remdesivir is the most important drug in the treatment

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of patients admitted with COVID-19, we decided to perform a literature review about its potential side effects on cardiovascular system.

Mechanism

Remdesivir molecule is similar to adenosine. Its active form is nucleoside triphosphate remdesivir and remdesivir (GS-441524) which is accessible in cytoplasm without ability to diffuse back to extracellular matrix. The active form is used by cell viral RNA-dependent RNA polymerase instead of the adenosine during replication of viral genome. This process can interrupt viral replication which is irreversible and unable to repair. The FDA Emergency Use Authorization recommends a loading dose of 200 mg (5 mg/kg) intravenous infusion once on the first day and 100 mg for the following days (for 5 to 10 days) [6, 7]. Its initiation is generally recommended when oxygen saturations fall below 94% [1].

Adverse Non-cardiac Side Effects

The most common adverse side effects of remdesivir are anemia, infusion site reactions, increased liver enzymes, cutaneous rash, kidney injuries, and hypotension [1]. Also,

worsening or respiratory failure, pyrexia, hyperglycemia, diarrhea, multiple organ failure, hypoalbuminemia, hypokalemia, hypernatremia, thrombocytopenia, and septic shock occurred more frequently in remdesivir than control group [6].

Literature Review on Cardiac Side Effects

There are few studies focused on remdesivir and its adverse effects on the cardiovascular system.

Table 1 shows selected published studies that reported adverse effects of remdesivir on cardiovascular system. In 2020, Grein et al. conducted a study on 61 hospitalized patients with COVID-19 infection who had an oxygen saturation of 94% or less. Patients received intravenous remdesivir for 10 days and were followed up for 28 days. Any adverse event that lasted more than a day was considered a side effect. Besides more common non-cardiac adverse effects, four patients experienced hypotension and three patients revealed an atrial fibrillation (AF) rhythm. Adverse events were more prevalent in patients undergoing invasive ventilation. However, interpretation of these findings is not simply possible. It is due to small sample size, short duration of follow-up, some missing data, and the absence of a randomized control group [8]. In 2020, Gupta et al. evaluated two patients diagnosed with coronavirus infection who had

Table 1 Selected published studies that reported adverse effects of remdesivir on cardiovascular system

Authors	Study design	Year	The number of COVID-19 patients with an adverse event	Follow-up time	Side effects
Grein et al	Cohort	2020	7	28 days	Hypotension, AF rhythm
Gupta et al	Case presentation	2020	2	During hospitalization	Bradycardia, Prolonged QT interval, T-wave abnormality
Michaud et al	Pharmacological study	2021	Not applicable	Not applicable	Prolonged QT interval, Torsade de point
Mulangu et al	A randomized, controlled trial	2019	1	During hospitalization	Hypotension, cardiac arrest
Wang et al	A randomized, double-blind, placebo-controlled, multi-center trial	2020	1	During hospitalization	Cardiac arrest
Gubitosa et al	Case presentation	2020	1	During hospitalization	Sinus bradycardia and QRS widening
Bistrovic et al	Pilot study	2021	10	During hospitalization	T-wave rightward axis deviation
Rafaniello et al	Meta-analysis	2021	Twofold increased risk	During hospitalization	Adverse cardiac event
Sanchez-Codez et al	Case presentation	2021	1	During hospitalization	Sinus bradycardia
Selvaraj et al	Case presentation	2021	1	During hospitalization	Complete heart block
Barkas et al	Case presentation	2021	1	During hospitalization	Sinus bradycardia
Chow et al	Case presentation	2021	1	During hospitalization	Sinus bradycardia

AF atrial fibrillation

experienced worsening respiratory condition and received antibiotics including ceftriaxone and azithromycin, corticosteroids, and remdesivir. First patient was a 26-year-old African American female. She experienced sinus bradycardia with a heart rate of 40–50 beats per minute (bpm), prolonged corrected QT interval of 555 ms, and T-wave abnormality after receiving third dose of remdesivir. After discontinuation of remdesivir, all changes were returned to normal. Her serum potassium was within the normal range, indicating potassium did not have a significant role. Azithromycin discontinued shortly before remdesivir initiation that made it as a possible contributing factor for prolongation of the QT interval. Second patient was a 77-year-old Caucasian female who developed sinus bradycardia with a heart rate of 48 bpm on day three after remdesivir administration. The patient's heart rate returned to baseline on the following days after discontinuation of remdesivir. Sinus bradycardia had been seen in both of these patients within 20–40 min of infusion time (at peak dose) [1]. In 2021, Michaud et al. performed a study about the risk of drug-induced long-QT syndrome associated with COVID-19 medications by comparing them with 23 well-known torsadogenic and 10 low torsadogenic-risk compounds. Pharmacokinetic and pharmacodynamic data were computed to measure affinity for blocking the rapid component of the delayed rectifier cardiac potassium current and tendency toward a prolonged cardiac repolarization and torsade de pointes. The results of this study showed that remdesivir can significantly increase the risk of QT prolongation and torsade de point, especially with an elevated plasma concentration following intravenous administration. Therefore, they recommended close monitoring on the QT interval during remdesivir therapy [4]. In 2020, Davies et al. performed a systematic benefit–risk assessment to determine the overall benefit–risk of the use of remdesivir in comparison with placebo or other therapies. They suggested that remdesivir may have a favorable benefit–risk profile in comparison with placebo in severe COVID-19 infection. They pointed out that cardiovascular outcomes including hypotension and arrhythmias were documented with use of remdesivir [9]. Hypotension was reported in one patient with Ebola virus during remdesivir infusion that was followed by a cardiac arrest, although authors declare that this death might also be due to underlying fulminant Ebola virus [10]. Wang et al. did a randomized, double-blind, placebo-controlled, multicenter trial on 237 hospitalized patients with severe COVID-19 who were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo). They did not find any statistically significant clinical benefits with remdesivir. However, there was a reduction in time to clinical improvement in those treated earlier with remdesivir compared with placebo. One patient in remdesivir group suffered from a cardiac arrest compared with no case in placebo group [11]. Gubitosa et al. reported a 54-year-old

female diagnosed with corona virus who had experienced a worsening dyspnea, fever, and chills for more than 2-week duration. Other vital signs were within the normal ranges and oxygen saturation on the room air was 95%. The baseline heart rate was 60–70 bpm. The patient's past medical history revealed an unknown origin left bundle branch block, hypertension, and lymphoma. Remdesivir was initiated 2 days after admission. Patient developed a sinus bradycardia with a heart rate of 38 bpm with 24 h. Other vital signs and cardiac biomarkers were within normal limits. Her heart rate decreased to 34 bpm and she complained of dizziness and chest discomfort and developed hypotension in the next two days. An electrocardiogram was taken which revealed a QRS widening of 170 ms. Remdesivir was discontinued and atropine was administered. The patient's heart rate reverted to the baseline and QRS complex decreased to 168 ms and her related symptoms improved within the following days [12]. In 2021, Bistrovic et al. performed a pilot study on 14 consecutive patients with severe COVID-19 treated by remdesivir and dexamethasone. An electrocardiogram was recorded before and 2 h after infusion of remdesivir. A total of 10 patients experienced a statistically significant effect of remdesivir on the T-wave axis deviation including rightward axis deviation [13]. The T-axis deviation is a powerful risk factor of sudden cardiac death, cardiac death, and non-fatal cardiac events in aged individuals [14]. In 2021, Rafaniello et al. analyzed all Individual Case Safety Reports (ICSRs) collected in the Eudra Vigilance database focusing on cardiac adverse events that 1375 ICSRs related to remdesivir were retrieved. The most commonly reported adverse events were hepatic/hepatobiliary disorders (19.4%), kidney and urinary involvements (11.1%), and cardiac events (8.4%). Among 221 cardiac ICSRs, 69 patients experienced a fatal outcome. Data analysis revealed a twofold increased risk of an adverse cardiac event associated with remdesivir in comparison with hydroxychloroquine and azithromycin. The result of this study showed that remdesivir might increase the risk of adverse cardiac events [15]. Sanchez-Codez et al. reported a 13-year-old boy with a history of bronchial asthma who was admitted with severe bilateral pneumonia and hypoxemia by COVID-19 with a baseline heart rate of 80–90 bpm. He received oxygen therapy, dexamethasone, ceftriaxone, and remdesivir (a loading dose of 200 mg/day that was followed by 100 mg/day). He developed an asymptomatic and nonhemodynamically significant sinus bradycardia (a heart rate of 40 bpm) following the third dose of remdesivir. Remdesivir infusion was stopped which consequently resulted in normalization of the heart rate in the following day. Cardiac biomarker levels and echocardiographic variables were within the normal range. They claimed that bradycardia in this patient occurred due to the fact that remdesivir was an adenosine analog with a tendency to block the atrioventricular (AV) node [16]. Selvaraj

et al. reported a 72-year-old male with a previous history of AF, right bundle branch block, and pulmonary cancer who was hospitalized for COVID-19. Intravenous remdesivir and dexamethasone were initiated. He developed an AF with ventricular rates between 30 and 40 bpm following the first day of initiating remdesivir. On the fifth day of remdesivir treatment, patient developed a complete AV block. Patient remained asymptomatic and received full remdesivir regimen under close cardiac rhythm monitoring. The AV block resolved spontaneously within the next 48 h [17]. Barkas et al. reported a 36-year-old male hospitalized with severe COVID-19 symptoms, including prolonged fever, hypoxemia, myalgia, and hemoptysis. An electrocardiogram revealed a normal sinus rhythm with a heart rate of 92 bpm. He received oxygen, corticosteroid, remdesivir, and antibiotic therapy. An asymptomatic sinus bradycardia with a heart rate of 39 bpm developed on third day. Secondary causes of sinus bradycardia were ruled out based on laboratory and echocardiographic findings. The rhythm reverted to normal 9 days after discontinuation of remdesivir [18]. Chow et al. described a 16-year-old obese male with COVID-19 disease hospitalized with fever, respiratory distress, dry cough, headache, and gastrointestinal symptoms. The patient's baseline heart rate was more than 90 bpm. He had mild hypoxia and the treating physicians decided that the patient should not receive corticosteroids. Remdesivir treatment was initiated on the second day of hospitalization. This was followed by a decrease in heart rate ranged between 40 and 60 bpm over the next 4 days. Patient was not hypotensive and echocardiography revealed normal left ventricular size and systolic function. Two days after discontinuation of remdesivir, the patient's heart rate reverted to the baseline value [19].

Discussion

Remdesivir is a nucleotide analog prodrug that is activated to a nucleoside triphosphate metabolite (GS-443902). This metabolite is an adenosine analog but with a significantly longer half-life than adenosine with an elimination half-life of 11 h. Also, there is another dephosphorylated nucleoside metabolite (GS-441524) that has a half-life of 20–25 h [13, 17]. Adenosine has been documented to have antiarrhythmic effects in AV re-entrant tachycardias by inducing transient AV nodal block. However, it may be proarrhythmic in patients with structural heart disease [13]. Adenosine is a powerful vasodilator that can cause profound hypotension which is followed by the compensatory release of catecholamines. These events can lead to ventricular tachycardia or even degenerate into ventricular fibrillation (VF). It can also shorten atrial action potential and refractoriness and lead to AF. These effects may also occur in ventricular cells

and predispose patients to VF. On the other hand, adenosine may lead to VF by inducing spatially and temporally inhomogeneity in ventricular refractoriness [20]. Remdesivir is structurally similar with adenosine, but with a longer half-life. Therefore, its adverse cardiovascular effects are not unexpected.

Choi et al. generated human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) from human embryonic stem cells and human-induced pluripotent stem cells to determine the potential cardiovascular risk associated with remdesivir treatment in COVID-19-infected hPSC-CMs. This study revealed that remdesivir can induce significant cytotoxic effects in cardiomyocytes that is considerably worse than chloroquine cardiotoxic effects [3]. Remdesivir-induced cardiotoxicity is due to its binding to human mitochondrial RNA polymerase [16]. Furthermore, longer duration of remdesivir treatment (48 h) considerably decreased viability of CMs in comparison with shorter treatment time (24 h) that was suggestive of a potential accumulative toxicity with remdesivir treatment. Remdesivir-induced cardiotoxicity in hPSC-CMs occurred with 50% cytotoxic concentration (CC_{50}) values close to its estimated peak plasma concentration (C_{max} 9 μ M) as have been reported in the literature. On the other hand, remdesivir dose dependently increased field potential duration with decreased Na^+ peak amplitudes and spontaneous beating rates that lead to complete cessation of spontaneous beating at higher concentrations. These findings showed that overdose or drug accumulation might induce serious adverse cardiac effects. This means that a remdesivir concentrations at a level higher than the estimated peak plasma concentration (C_{max} 9 μ M) is associated with the potential risk of QT prolongation. Therefore, close monitoring of the electrocardiogram and QT interval is advisable during remdesivir medication, especially in patients with structural heart disease or severe COVID-19-infected individuals [3].

Conclusion

Some patients with COVID-19 infection on remdesivir may develop sinus bradycardia, hypotension, T-wave abnormalities, AF, and a prolonged QT interval. Also, few cases of cardiac arrest and complete heart block following remdesivir infusion have been reported. It seems remdesivir have some cardiotoxic and proarrhythmic effects that are especially more pronounced in patients with previous cardiovascular diseases. Continuous cardiac rhythm monitoring is recommended in patients undergoing remdesivir treatment. It is especially advisable in individuals with any known cardiac diseases or electrolyte disturbances. Furthermore, we should be more cautious about additive cardiovascular adverse effects when other drug classes are used in addition

to remdesivir treatment. It is due to the fact that their combination may increase the risk of potential fatal ventricular arrhythmias or cardiac arrest. The current safety profile of remdesivir is still not completely known. Further prospective clinical trials can assist us to know more about its safety profile and potential adverse cardiovascular effects.

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