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Review of Cardiotoxicity of Remdesivir in COVID-19 Treated Patients

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ABSTRACT

Remdesivir was one of the first antiviral medications approved for use in emergency situations when the global COVID-19 pandemic demanded quick therapeutic responses. Although it has been shown to be effective in shortening recovery times, questions have been raised about its cardiovascular safety profile. Bradycardia and other cardiac problems in COVID-19 patients are the main topic of this research, which examines the cardiotoxic adverse drug events (ADEs) linked to remdesivir. Bradycardia was found to be the most prevalent cardiac ADE after a thorough examination of clinical trials, cohort data, and pharmacovigilance databases, including WHO and FDA reports. Arrhythmias, cardiac arrest, and QT/QRS prolongation are further consequences that have been described. Notably, the adverse chronotropic and dromotropic effects of remdesivir's metabolite, an analogue of adenosine triphosphate, may account for these cardiac consequences. The results show that remdesivir is mostly safe, although individuals with heart problems should be closely watched while they are being treated.

Keywords: COVID-19, Remdesivir, Adverse Drug Events, FDA, WHO, Cardiotoxicity.

INTRODUCTION

Early in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused novel coronavirus infectious disease (COVID-19) first appeared in Wuhan, China[1,2]. It then quickly spread to other parts of the world [3]. On January 30, 2020, the WHO declared the COVID-19 outbreak to be a pandemic Public Health Emergency of International Concern[2].

The seventh coronavirus reported to infect humans is SARS-CoV-2. It is a brand-new single-stranded enclosed RNA virus. The primary route of entry for SARS-CoV-2 is the respiratory tract, which shows up as clinical signs like fever and dry cough in 88% and 67% of patients, respectively. However, many patients initially present with anosmia (loss of smell) or ageusia (loss of taste), which are brain processes related to the olfactory bulb[1].

According to their clinical characteristics, almost all SARS-CoV-2 patients experience pneumonia to some extent, and those who have more severe cases get acute respiratory distress syndrome (ARDS). Respiratory failure brought on by significant lung injury may be the primary cause of death in SARS-CoV-2 infected patients[2].

More investigation has shown that SARS-CoV-2 affects not just the lungs but also the heart, brain, kidneys, liver, and eyes. Patients with underlying cardiovascular disease are

more commonly impacted by the transmission of SARS-CoV-2, according to an emerging pattern. Clinical data demonstrate that SARS-CoV-2 infection results in cardiac issues such as heart failure, arrhythmias, and raised blood troponin I levels, an indication of cardio-myocyte death. The sudden rise in COVID-19 patients and the high death rate make it harder to diagnose the illness early and keep it under tight control. The development of efficient medications for COVID-19 therapy and prevention has gained international attention[4].

Clinical trials for COVID-19 have examined numerous currently approved medications, including hydroxychloroquine, antiviral medications, glucocorticoids, and neutralising antibodies[4]. Although some candidates have prior evidence supporting their activity against coronaviruses[5], other candidates are being repurposed for use against SARS-CoV-2 based on their capacity to obstruct SARS-CoV-2 viral replication in vitro. These include hydroxychloroquine, an autophagy inhibitor, and camostat, a lysosomal inhibitor of serine proteases[5].

Remdesivir, an already-approved drug candidate created by Gilead Sciences as part of an antiviral development effort, has also drawn attention as one of the first clinical candidates with initial findings against the Ebola virus (EBOV) were reported in 2015[5].

REMDESIVIR & COVID-19

Remdesivir (GS-5734)[6] is an analogue of adenosine triphosphate that was originally mentioned in the literature as a possible Ebola therapy in 2016. According to its mode of action, Remdesivir has wide antiviral activity, and in vitro tests have demonstrated its efficacy against the Paramyxoviridae, Arenaviridae, Flaviviridae, and Filoviridae, Pneumoviridae, and Coronaviridae virus families(7). After remdesivir's first demonstration of action against the Coronaviridae family in 2017, there has been a lot of interest in remdesivir as a potential COVID-19 therapy.

Pharmacologically, Remdesivir is a prodrug of a phosphoramidite of a 1'-cyano-substituted adenosine nucleotide analogue that competes with ATP for incorporation into newly synthesized viral RNA by the matching RdRp complex (RNA-dependent RNA polymerase)(8) or it is a mono phosphoramide nucleoside prodrug that undergoes intracellular metabolism to become remdesivir triphosphate, which is the drug's active form. When remdesivir is activated, RNA-dependent RNA-polymerase incorporates it into the viral RNA, terminating the RNA chain and preventing viral reproduction[4].

Remdesivir has been tested in a number of COVID-19 clinical trials and has been found to be a non-obligate chain terminator of RdRp from SARS-CoV-2 and the associated SARS-CoV and MERS-CoV. According to subsequent randomized placebo-controlled trials (RCTs) and open-label trials, Remdesivir treatment reduced the median recovery time for COVID-19 patients, with some trials also showing a decrease in mortality.(8)

On May 1st, 2020, the FDA approved the use of remdesivir in severe hospitalised COVID-19 patients under an emergency use authorization (EUA)(9,10), based on the findings of the national institute for allergy and infectious diseases (NIAID) and SIMPLE studies. Finally, On October 22, 2020, the US Food and Drug Administration (FDA) approved Remdesivir as the first medication to treat COVID-19 based on this supporting evidence[6].

Remdesivir generally has a good safety profile, with nausea and transaminase increases being the most frequent side effects. Several post-marketing studies have observed severe bradycardia with remdesivir usage. Bradycardia may result in negative health effects, such as reduced functional ability and the triggering of heart arrhythmias[4].

There is little evidence of its adverse effects (ADR), especially on the cardiovascular system. The studies which are available are primarily focused on hepatic, renal, and

dermal adverse drug reactions of the drug. Phlebitis, constipation, headache, ecchymosis, nausea, pain in the extremities, and a brief rise in liver enzymes were the most prevalent ADRs in these trials and in a controlled trial with patients with the Ebola virus disease(11).

Therefore, the objective of this review was to find the precise relationship between Remdesivir and adverse cardiac effects that may cause bradycardia and other cardiac issues in COVID-19 patients using this drug.

MATERIALS & METHODS

Using a variety of specific keywords, such as "COVID 19" and "Remdesivir" or "SARS COV 2," we conducted an extensive search of the PubMed and various online databases such as Google Scholar etc., and retrieved all articles written in English that discussed the effectiveness, safety, clinical outcomes, and pharmacology of the drug remdesivir in COVID-19 patients.

S.NO.	Study & Year	Study Design	Sample Size & Age	Findings
1	ALSOWAIDA et al (2022)[4]	RETROSPECTIVE COHORT STUDY	N - 1635	In this 606 people developed the cardiac ADEs in the form of Bradycardia and categoried into Mild (437), Moderate (158) & Severe (11) Bradycardia
2	Devgun et al. (2022)[10]	COHORT STUDY	TOTAL SAMPLE SIZE - 760 & NO. OF PEOPLE IN REMDESIVIR GROUP - 342	Out of 342 people in Remdesivir Group, 220 people developed Bradycardia While other Cardiotoxic ADEs are QRS & OT prolongation - 1.1 %, Sinus pause & V-tach - 0.5 % & Cardiac arrest - 1.1%
3	RAFANIELLO (2021)[12]	COHORT STUDY (EUDRA Vigilance Database)	N - 1375	No. of people who got cardiac disorders - 266 (8.4%) includes - Cardiac arrythmia (230), coronary artery disease - 16, heart failure - 10, Other - 10
4	HAJIMORADI et al(2022)[11]	PROSPECTIVE LONGITUDINAL STUDY	N - 177 and Age Group - 49 ± 15	Out of all the people 27% of the people got bradycardia after administration of the Remdesivir
5	CHARAN et al (2020)[13]	REVIEW (WHO Database)	No. of ICSR - 439 & ADEs - 1088	It reported various Adverse Drug events and the no of cardiac disorder ADEs - 51. The Cardiac Disorder invloves - Cardiac Arrythmia - 26, Cardiorespiratory arrest - 17 & Pulseless Electrical Activity - 5

RESULT

We summarized the data from the various published articles regarding the cardiotoxic adverse drug events of the Remdesivir. Some of the article[4] found out that the most common ADEs associated with the Remdesivir Drug Administration were the Bradycardia. While some studies[9,10] found out the other cardiotoxic effects were such as QT/QRS prolongation, Cardio-respiratory arrest, Pulseless Electrical activity, Sinus pause, Ventricular Tachycardia etc.

Most of the study which has been done were the Cohort Study which were either prospective or retrospective in nature. It has also been found in the study that the bradycardia is the most common cardiotoxic adverse drug event which can also be categorized in the mild, moderate or severe type[4]. Also, the most common age group associated with it were either the 18-64 & above 70 which might be due to the associated co-morbidities such as hypertension or diabetes mellitus.

We also included study which reviewed the WHO Vigibase database[13] which included the Individual Case Safety Reports (ICSRs) which reported around 1088 ADEs from the 439 patients. The no. of Cardiac Disorder ADEs were 51 having most common adverse effect was Cardiac arrhythmia followed by Cardiorespiratory arrest and pulseless electrical activity.

DISCUSSION

The goal of this present study was to review the Cardio-toxic adverse drug event associated with the Remdesivir Drug Administration in Covid-19 patients. Studies published since the COVID-19 and data from the FDA FAERS were utilized in this review so as to only account for the most recent information in the field, which might be a strength or limitation of the study.

Evidences from the total studies and database which were included in the review, there is one study [9,10] which identified the Bradycardia following Remdesivir administration through the US food & Drug Administration American college of medical toxicology COVID-19 toxic pharmaco-vigilance report. They identified that out of 342 people, 220 people developed the bradycardia and 42% people got serious bradycardia. The other effects that found were the QRS/QT prolongation, sinus pause, V-tachycardia & Cardiac Arrest. While there is other study showed that there was less cardiac disorder than other adverse drug events such as hepatic and renal impairments.

Similarly, there is one more retrospective cohort study[4] having sample size of around 1635 people and they found at that 606 developed the bradycardia as an adverse drug event due to remdesivir administration. They categorized the Bradycardia in their types depending on the severity such as mild, moderate and severe with more people developed the mild bradycardia (437) followed by moderate (158) and then severe[11]. Notably, in this study the author postulated that an analogue of adenosine triphosphate is the active metabolite of remdesivir. It is well known that Adenosine triphosphate suppresses the firing of cardiac pacemakers at the sinoatrial node and the conduction of the heart at the atrioventricular node, resulting in negative chronotropic and dromotropic effects. And therefore, Remdesivir-associated bradycardia may therefore be a result of the adenosine triphosphate cardiac effects mediated by remdesivir tri-phosphate[4].

One of the studies also reviewed the WHO database which identifies the Individual Case Safety Reports and they found out that more ADEs were from the other systems of the body such as hepatic and renal system. They identified the cardiac disorders such as Cardiac arrhythmia, Cardiac arrest, pulseless electrical activity in the study as the Adverse Drug Events. It was observed that the majority of ADEs were reported from male subjects and those aged 45 years or greater[13].

CONCLUSION

This study was an effort to add to the information about the safety of remdesivir reported so far from published clinical studies in patients with COVID-19 given potential concerns. According to the FDA's product information, the most significant adverse drug events (ADEs) linked to cardiac disorders included bradycardia, cardiac arrest, sinus bradycardia, and others. These findings call for greater monitoring of cardio markers such as Heart rate, Blood Pressure etc., during treatment, building on existing guidance, with the potential for dose adjustments, as well as monitoring cardiac function before and during treatment with remdesivir. Greater guidance can also be given by the authorities as more knowledge becomes available including potential doses of remdesivir in patients with COVID-19 with existing cardiac impairment or poor cardiac function.

Declaration by Authors

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