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Remdesivir-associated bradycardia in COVID-19: a rapid review protocol

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ABSTRACT

Introduction Remdesivir is an antiviral medication that is used in the treatment of severe COVID-19. Research has highlighted the potential cardiac side effects of remdesivir, including the occurrence of remdesivir-associated bradycardia (RAB), but these findings have not been consistent. In addition, very little is known about the clinical implications and outcomes of RAB. The aim of this rapid systematic review is to determine the event rate of developing bradycardia while receiving remdesivir treatment compared with not receiving remdesivir in patients diagnosed with COVID-19.

Methods and analysis This study follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines and will include original papers related to COVID-19, remdesivir and bradycardia. Only English language papers published from 1 December 2019 to 31 December 2022 will be included. The following databases will be searched using keywords and controlled vocabulary: Ovid MEDLINE, Ovid EMBASE, Scopus, Cochrane, PubMed and Web of Science. Two reviewers will independently perform screening and data abstraction. Data will be synthesised qualitatively as well as quantitatively. A random-effects model will be used to calculate the pooled estimates.

Ethics and dissemination This review will systematically analyse the clinical studies available to help better characterise RAB. The results will support a retrospective study investigating RAB that is currently being conducted at the University Medical Center of Southern Nevada in Las Vegas, Nevada.

PROSPERO registration number This protocol has been submitted to and approved by PROSPERO (Protocol ID: CRD42022331614).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This rapid review will be the first to analyse the event rate of remdesivir-associated bradycardia, a phenomenon which has not been consistently characterised in the past.
⇒ Two reviewers will independently perform a detailed screening, study appraisal and data abstraction process and will be blinded at each step.
⇒ Retrospective observational studies that are included will be considered subjective and acknowledged as a limitation of data collection.

INTRODUCTION

SARS-CoV-2 is a single-stranded RNA virus that gives rise to COVID-19.[1] Recent research has shown the effect of COVID-19 on the cardiovascular system, which may result in acute myocardial injury and bradycardia.[2 3]

Remdesivir is the only drug approved by the Food and Drug Administration under the Emergency Use Act for COVID-19.[4] It is an antiviral adenosine nucleotide prodrug that is metabolised into its active nucleoside triphosphate form known as GS-441524.[4 5] The mechanism of action of GS-441524 involves blocking RNA-dependent RNA polymerase, which then inhibits viral RNA synthesis.[1 5]

Research into the use of remdesivir for COVID-19 has highlighted the potential cardiogenic side effects of remdesivir.[6] Touafchia *et al* reported that 302 out of 2603 cases of remdesivir side effects were cardiac related. Bradycardia comprised 31% of cardiac-related events, with 80% categorised as serious and 17% categorised as fatal.[6] However, these findings have not been consistent. For instance, some studies indicate that despite patients developing bradycardia following treatment with remdesivir, there were no significant effects on the rates of adverse events or incidence of symptomatic bradycardia.[3 7] Furthermore, a study by Bistrovic *et al* demonstrated that bradycardia occurring during remdesivir use may actually reflect a more positive disease course and prognosis for patients with COVID-19.[8]

The exact mechanism of remdesivir-associated bradycardia (RAB) is not known. It has been hypothesised that remdesivir causes bradycardia because the active form of the drug shares a similar chemical structure to adenosine, which is known to decrease cardiac pacemaker automaticity and heart rate. Given the use of remdesivir in patients with severe COVID-19, it is imperative to characterise the rate of bradycardia and to identify patient-centred outcomes related to RAB.

METHODS AND ANALYSIS

This protocol complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines (online supplemental additional file 1). The protocol has been submitted to and approved by the PROSPERO protocol registry (Protocol ID: CRD42022331614).[9]

Research question

This systematic review will aim to determine the event rate of developing bradycardia while receiving remdesivir treatment compared with not receiving remdesivir in patients diagnosed with COVID-19. This will be accomplished by performing a systematic review of studies that report the occurrence of RAB in adult patients (>18 years old) who were diagnosed and treated for COVID-19. The intervention will be remdesivir (brand name Veklury), and will be compared with placebo and/or the standard of care as it is defined in each study included for analysis. The primary outcome measured will be the event rate of bradycardia.

Patient and public involvement

Patients were not involved in the design of this review.

Eligibility criteria

Case series, observational studies, interventional experimental studies and randomised controlled trials reporting the occurrence of RAB will be included. Case reports will not be included. We will only examine studies where the participants are adult patients (>18 years old) who were diagnosed and treated for COVID-19. The search will be restricted to English language papers published from 1 December 2019 to 31 December 2022. Review articles, letters to the editor, editorials, abstract-only studies, systematic reviews and animal/plant studies will be excluded.

Information sources and search strategy

Articles will be selected for inclusion based on all published studies of COVID-19 treated with remdesivir in which bradycardia was an outcome. This will be accomplished using search strings with keywords and registry-specific controlled vocabulary that use the following terms: 'COVID-19', 'bradycardia' and 'remdesivir' (online supplemental additional file 2). Database searches of Ovid MEDLINE, Ovid EMBASE, Scopus, Cochrane, PubMed and Web of Science will be conducted.

Screening and data collection

Detailed screening of selected articles will be performed using Rayyan Systems, an online tool that facilitates article selection for systematic reviews.[10] After compiling the articles obtained from the above online databases, two reviewers will independently perform title and abstract screening followed by full-text screening via a blinded review process. A senior reviewer will serve as a tie breaker and resolve any discrepancies. The reasons for article exclusion will be recorded at each step.

A double data extraction method in which two reviewers extract the data independently will be used. If the need arises, the entries will be verified by a third reviewer. Abstracted variables will include demographics (age, gender, race/ethnicity); study type (case series, observational study, randomised trial); study size; COVID-19 severity; and the event rate of bradycardia. The effect size (ORs/relative risks), corresponding 95% CIs and covariates adjusted will be included in the statistical analysis. For studies that report several multivariable-adjusted effect estimates, we will select the one that adjusts for more potential confounding variables. Data will be recorded into an encrypted, password-protected Excel spreadsheet.

Quality assessment

Two trainees will independently perform a study appraisal process using standardised collection forms available from the Joanna Briggs Institute and the National Institutes of Health.[11 12] The quality assessment of the original articles will be re-examined and adjudicated independently by the additional reviewer, in case of disagreements with the first two reviewers. The inter-rater agreement will be reported as Cohen's kappa coefficient.

Data analysis

If the pooled estimates of the final included studies (randomised or quasirandomised controlled trials) are adequate, we will use a meta-analysis approach. The most up-to-date publication for each outcome will be used in studies with multiple publications. We will provide a narrative synthesis of the findings from the included studies structured around the type of intervention (eg, remdesivir, standard of care), target population characteristics (eg, age, gender, comorbidities) and type of outcome (eg, length of hospitalisation, death). We will provide summaries of intervention effects for each study by calculating the risk ratios for dichotomous outcomes or standardised mean differences for continuous outcomes. We will pool the results using a random-effects meta-analysis, with standardised mean differences for continuous outcomes and risk ratios for binary outcomes, and calculate 95% CIs and two-sided p values for each outcome. In studies where the effects of clustering have not been considered, we will adjust the SDs for the design effect.

Heterogeneity between the studies in effect measures will be assessed using both the I^2 test and the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity.[13] If enough studies are available in subgroups, then further analyses based on moderator variables, such as quality rating, logistics of intervention provision and demographic factors, will be conducted. Sensitivity analysis will be conducted to identify studies which may severely affect the pooled estimate. Funnel plot and Egger statistics will be used to assess the publication bias.[14]

The main outcome reported will be the event rate of RAB. Additional outcomes considered will be rates of mortality secondary to RAB, length of hospitalisation

(in days) and other cardiovascular complications (eg, myocardial infarction, heart failure). Summative descriptive statistical analysis for case series and retrospective studies will also be provided.

ETHICS AND DISSEMINATION

Remdesivir has become a mainstay therapy in the treatment of severe COVID-19. However, little is known about the clinical outcomes of the drug's adverse cardiac event profile in relation to bradycardia.[4] Further investigation is urgently needed given the increased risk in morbidity and mortality that may be associated with RAB.[6]

Our study will systematically evaluate and analyse the clinical studies available to help better characterise this cardiac phenomenon. Given the inconsistent reporting of cardiac side effects of remdesivir, however, several limitations exist that are worth noting. First, retrospective studies (observational, case series and case reports) will be considered subjective and will be acknowledged as a limitation of data collection in our final written report. Next, we will assess for evidence of publication bias by searching for unpublished studies that report similar outcomes. Finally, there are many factors that confound the clinical outcomes of patients diagnosed with COVID-19, including the cardiac effects of the illness itself. We acknowledge that further study will be required to determine a true association between bradycardia and the use of remdesivir to treat severe COVID-19.

We will publish our findings in a peer-reviewed academic journal. In addition, our findings will support an ongoing study investigating RAB that is being conducted at the University Medical Center of Southern Nevada in Las Vegas, Nevada. If this review demonstrates an increase in risk, it may raise a clinical suspicion for an understated but potentially harmful adverse event of remdesivir.

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