Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 112 (2021) 254–257

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Safety and heart rate changes in Covid-19 patients treated with Remdesivir

Natale Daniele Brunetti, MD, PhD[a,*], Mariacristina Poliseno, MD[b], Irene Francesca Bottalico, MD[b], Antonio Centola, MD[c], Laura Montemurro, MD[b], Salvatore Sica, MD[d], Teresa Santantonio, MD[b], Sergio Lo Caputo, MD[b]

[a] Department of Medical & Surgical Sciences, University of Foggia, Italy
[b] Department of Clinical and Experimental Medicine, University of Foggia, Italy
[c] Cardiology Department, Policlinico Riuniti University Hospital, Foggia, Italy
[d] Infectious Diseases Unit Policlinico Riuniti University Hospital, Foggia, Italy

ARTICLE INFO

Article history:
Received 3 July 2021
Revised 11 September 2021
Accepted 15 September 2021

Keywords:
Remdesivir
Covid-19
Cardiovascular Toxicity
Heart Rate

ABSTRACT

Objectives: Limited data are available regarding the occurrence and the extent of cardiac rhythm disturbances in patients with COVID-19 treated with Remdesivir.
Methods: We present a case series of 52 patients who underwent daily electrocardiogram (ECG) examination after Remdesivir administration.
Results: Compared to baseline, a significant heart rate reduction was observed after initiation of Remdesivir; however, no case of severe bradycardia or arrhythmias leading to significant clinical complications or Remdesivir discontinuation occurred. Heart rate reduction was proportional to baseline heart rate values ($r=0.75$, $p<0.001$). By multivariate analysis, a less severe clinical presentation of Covid-19 (beta=0.47, $p<0.01$) was related to lower heart rate levels observed after Remdesivir administration.
Conclusions: Despite a significant reduction in heart rate observed after Remdesivir administration, no severe cardiovascular toxicity was observed in Covid-19 patients, even in the case of cardiovascular comorbidities.

Introduction

Remdesivir is the only antiviral drug currently approved under emergency use authorization to treat patients hospitalized for mild and moderate COVID-19 (Beigel et al., 2020). Isolated cases of cardiac rhythm abnormalities have been reported in patients on Remdesivir, including sinus bradycardia and QTc interval-prolongation (Gubitosa et al., 2020; Gupta et al. 2020), warranting close cardiac rhythm monitoring during Remdesivir administration.

Therefore, we aimed to prospectively assess, in a cohort of Covid-19 patients treated with Remdesivir, the occurrence of heart rate abnormalities and their potential clinical predictors through serial electrocardiogram examination.

Methods

From October 1, 2020, to February 28, 2021, 52 consecutive patients with COVID-19 treated with Remdesivir underwent serial electrocardiogram examination after antiviral administration. Electrocardiograms were recorded at baseline (T0), each day for the following five days (T1-T5), and at discharge (Td). Minimum, maximum, and heart rate changes over time were collected. The occurrence of bradycardia, symptomatic bradycardia, QTc prolongation, and cardiac rhythm abnormalities of any kind were reported.

Bradycardia was defined as a heart rate<60 bpm, following the definition of the National Institute of Health (Rijnbeek et al., 2014).

Symptomatic bradycardia was intended to associate a heart rate <60 bpm and the development of clinical manifestations of syncope or presyncope, transient dizziness or light-headedness, heart failure symptoms, or confusion states resulting from cerebral hypoperfusion attributable to slow heart rate (Kusumoto et al., 2019). The occurrence of bradyarrhythmias (sinus pause, sinus node ar-

* Corresponding author: viale Pinto 1, 71122, Foggia, Italy, tel +39 328 7660350
E-mail addresses: natale.brunetti@unifg.it (N.D. Brunetti), polisenomc@gmail.com (M. Poliseno), ibott4@gmail.com (I.F. Bottalico), centola.antonio79@gmail.com (A. Centola), laura.monty91@gmail.com (L. Montemurro), salvatoresica@libero.it (S. Sica), teresa.santantonio@unifg.it (T. Santantonio), sergio.locaputo@unifg.it (S. Lo Caputo).

https://doi.org/10.1016/j.ijid.2021.09.036

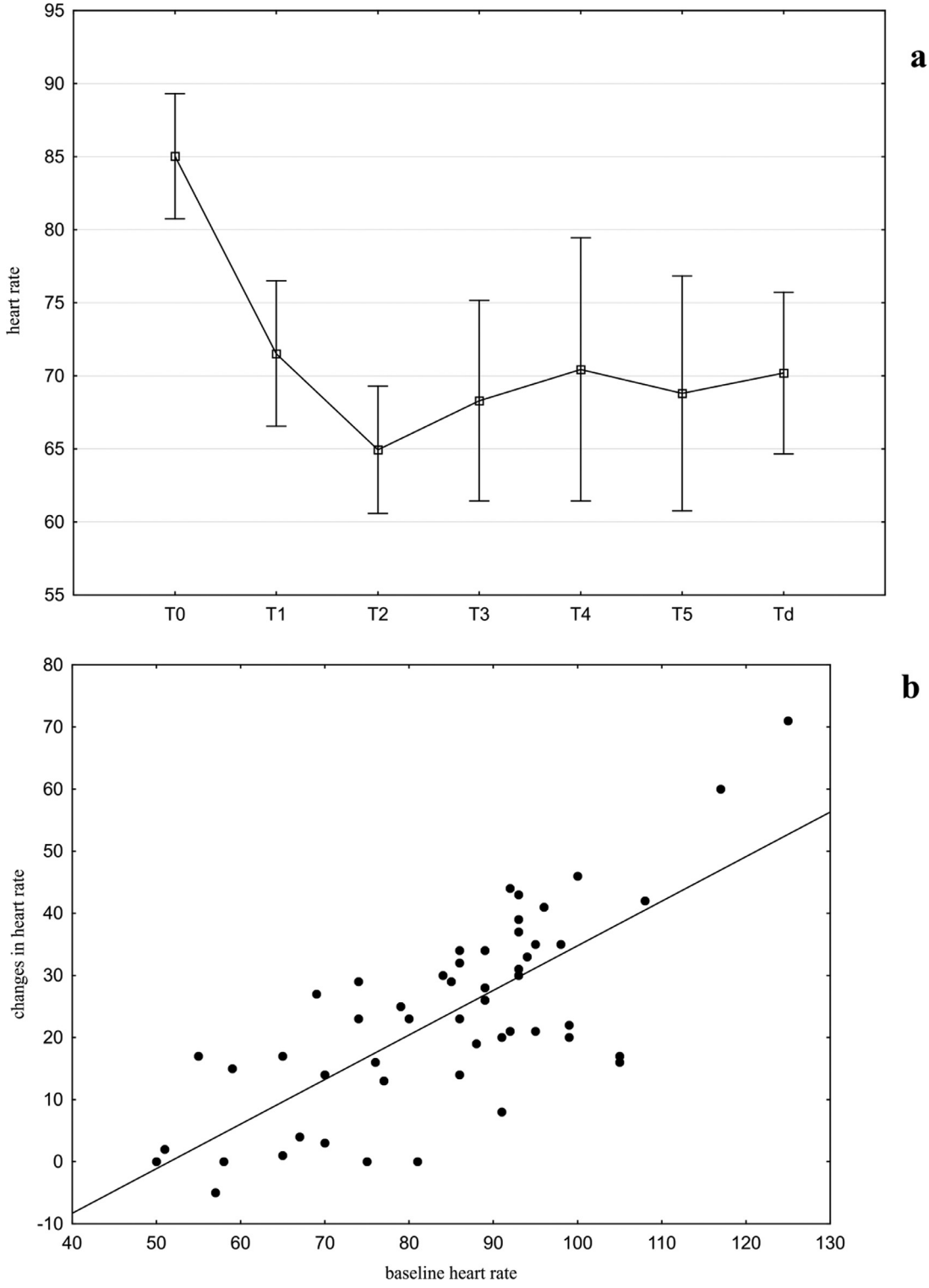

Figure 1. a) Heart rate changes (mean±95%CI) after Remdesivir administration (ANOVA $p<0.01$). b) Changes in heart rate after Remdesivir were proportional to baseline levels.

rest, tachycardia-bradycardia, atrioventricular block, atrial flutter, atrial fibrillation) was also noted.

For each patient, the duration of the QT interval at every ECG was recorded on the case report form. Corrected QT (QTc) was calculated in relation to heart rate according to Bazett's formula (Bazett, 1920). QTc prolongation was defined as the detection of values above the normal range (440 msec for men, 460 msec for women) (Crotti, 2013).

Remdesivir was discontinued in the case of i) clinical signs of symptomatic bradycardia (as defined above) or ii) laboratory findings of worsened kidney and/or liver function noticed by the attending physician. A global evaluation of the patient's condition

that kept age, the severity of disease, comorbidities, comedications into account was also requested.

Patients were enrolled in the study under the condition of having at least three ECGs performed in the course of Remdesivir, besides those recorded the days of admission and discharge.

Demographics and clinical data were recorded. The clinical severity of Covid-19 was assessed according to NIH Coronavirus Disease 2019 (Coronavirus Disease 2019 COVID-19 treatment guidelines, 2020) (https://www.covid19treatmentguidelines.nih.gov/.).

Statistical analysis

Data are presented as frequency (%) for categorical variables. For continuous variables, results are reported as means ±standard deviation or as median (Inter Quartile Range, IQR), according to their parametric or non-parametric distribution, respectively. The Student's t-test and the Mann–Whitney U-test were used to compare continuous variables with normal and non-normal distributions. The Chi-squared test or Fisher's exact test were used to compare categorical variables. Linear correlation was evaluated by Pearson's test. Repeated measures were compared with the ANOVA test. Multiple stepwise forward regression analysis was used to assess the bias of possible principal confounders. A p-value <0.05 was considered statistically significant.

Results

Mean hospital stay was 18±9 days, 56% of patients enrolled were male, 76% were >50-year old, 53% had at least one major cardiovascular comorbidity, 57% were hypertensive, 24% diabetic, 7% had ischemic heart disease, and 77% (N 40) a severe clinical presentation of Covid-19. All but one of the patients were discharged alive; one patient died from septic shock.

A median of five ECGs (IQR 2) per patient was overall recorded in the study population.

Compared to baseline, a significant reduction of heart rate was observed after administration of Remdesivir (ANOVA $p<0.05$, **Figure 1a**) from 85±16 bpm at baseline to 70±18 bpm at discharge; heart rate reduction was already statistically significant on the first day of treatment (ANOVA $p<0.001$). No case of symptomatic bradycardia or arrhythmias leading to clinical complications or Remdesivir discontinuation was observed. No case of QTc prolongation occurred.

Mean lowest heart rate recorded was 61±11 bpm, mean heart rate reduction observed was 24±16 bpm: mean heart rate reduction was higher in men than in women (28±16 bpm vs. 18±14 bpm, $p<0.05$). Heart rate reduction was proportional to baseline heart rate values ($r=0.75$, $p<0.001$, Figure 1b).

The result of a multivariate analysis including age, gender, cardiovascular risk factors, presence of ischemic heart disease, atrial fibrillation, baseline heart rate, troponin, renal function values, cardiovascular therapy (beta-blockers, amiodarone), and need for ventilation, showed that the only factor significantly related to lower heart rate levels observed after Remdesivir administration was a less severe clinical presentation of Covid-19 (beta=0.47, $p<0.01$)

Discussion

Cardiovascular implications of Sars-COV-2 infection have been widely documented and associated with poor prognosis, which can be worsened by underlying cardiovascular diseases (Azavedo, 2021).

Assessing potential adjunctive drug-related cardiovascular toxicity is thus crucial, especially in the absence of data regarding the cardiovascular toxicity of some of the few therapeutic options available such as Remdesivir, an antiviral prodrug polymerase with inhibitory activity against the viral RNA-dependent, RNA polymerase of the SARS-CoV virus (Beigel et al., 2020). Studies *in vitro* demonstrated a pronounced affinity of Remdesivir for human cardiomyocytes, with higher local concentrations and activity (Choi et al., 2020), partly explaining the reported pro-arrhythmic activity of Remdesivir.

The potential effect of a five-day treatment regimen with Remdesivir on cardiac rhythm has been already highlighted. Besides isolated reports of transient bradycardia, detected by clinical observation or with a single ECG performed in the course of antiviral treatment (Barkas et al., 2021, Gubitosa et al., 2020), in several cohort studies, heart rate has been monitored by waist pulse before and during Remdesivir administration (Pallotto et al., 2021) or, just two ECGs were collected before and after antiviral treatment (Attena et al., 2021).

In this paper, data collected from a cohort of patients who underwent daily ECG monitoring in the course of Remdesivir administration are presented.

Our data seem to confirm previous observations on heart rate reduction after Remdesivir administration, although never associated with bradycardia, symptomatic bradycardia, or significant QTc prolongation leading to Remdesivir discontinuation.

Notably, higher heart rate reduction was observed in subjects with higher baseline heart rate, thus supporting the hypothesis that the principal driver in heart rate reduction was not Remdesivir but, presumably, the improvement in baseline clinical conditions responsible for tachycardia (fever, hypoxia, inflammation, anxiety). Moreover, the phenomenon was mainly observed in patients with a less severe clinical presentation, a finding that may further reassure clinicians about the absence of contraindications about the use of Remdesivir in critical patients, at least regarding cardiac function.

As well, no significant correlation was observed with age, cardiovascular risk factors, comorbidities, cardiovascular drugs, or troponin levels.

The limited number of subjects and the absence of a Remdesvir-free control arm are the main limitations of this study.

Nevertheless, as far as can be observed in our sample, Remdesivir showed a favorable toxicity profile even though associated with a significant heart rate reduction. Further research is needed to confirm this preliminary observation on a larger number of subjects.

Conclusions

Despite a significant reduction in heart rate observed after Remdesivir administration, no severe cardiovascular toxicity was observed in Covid-19 patients, even in the case of cardiovascular comorbidities.

Conflict of Interest

None to disclose.

Funding Source

No funding was received.

Ethical Approval

This is an observational study waived from ethics committee approval. All participants gave written informed consent.

References

Attena E, Albani S, Maraolo AE, et al. Remdesivir-induced Bradycardia in COVID-19: a single-center prospective study. Circ Arrhythm Electrophysiol 2021;14.

Azevedo RB, Botelho BG, Hollanda JVG, et al. Covid-19 and the cardiovascular system: a comprehensive review. J Hum Hypertens 2021;35:4–11.

Barkas F, Style CP, Bechlioulis A, et al. Sinus Bradycardia associated with Remdesivir treatment in COVID-19: a case report and literature review. J Cardiovasc Dev Dis 2021;8:18.

Bazett JC. An analysis of time relations of electrocardiograms. Heart 1920;7:353–70.

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383:1813–26.

Choi SW, Shin JS, Park SJ, et al. Antiviral activity and safety of remdesivir against SARS-CoV-2 infection in human pluripotent stem cell-derived cardiomyocytes. Antiviral Res 2020;184.

Crotti L, Dossena C, Mastantuono E, et al. Condizioni cliniche associate ad anomalie dell'intervallo QT: implicazioni cliniche [Clinical conditions associated with abnormal QT interval: clinical implications]. G Ital Cardiol 2013;14:55–65.

Gubitosa JC, Kakar P, Gerula C, et al. Marked Sinus Bradycardia associated With Remdesivir in COVID-19: a case and literature review. J Am Coll Cardiol Case Rep 2020;2:2260–4.

Gupta A K, Parker B M, Priyadarshi V, et al. Cardiac adverse events with Remdesivir in COVID-19 infection. Cureus 2020;12:e11132.

Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with Bradycardia and Cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:932–87.

Pallotto C, Blanc P, Esperti S, et al. Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19). J Infect 2021;83:237–79.

Rijnbeek PR, van Herpen G, Bots ML, et al. Normal values of the electrocardiogram for ages 16-90 years. J Electrocardiol 2014;47:914–21.

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) treatment guidelines. National Institutes of Health; 2020 Available at https://www.covid19treatmentguidelines.nih.gov/.