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Remdesivir-induced bradycardia in patients hospitalized with SARS-CoV2 infection: a possible vagally-mediated mechanism

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Abstract

Recently, case series studies on patients with SARS-CoV-2 infection reported an association between remdesivir (RDV) administration and incidental bradycardia. However, the phenomenon has not yet been described in detail. We conducted a retrospective case–control study to evaluate the occurrence of RDV-related bradycardia in patients hospitalized for SARS-CoV2 pneumoniae. We retrospectively evaluated 71 patients, hospitalized in six internal medicine wards of the Milan area, affected by mild-to-moderate COVID-19 who received RDV (RDV group) and 54 controls, matched for sex, age and disease severity on admission (CTR group). The mean heart rate value recorded during the first two days of hospitalization was considered as baseline heart rate (HRb). Heart rate values relative to the 5-days treatment and the 5-days post-treatment were extracted for RDV group, while heart rate values relative to 10 days of hospitalization were considered for the CTR group. ΔHR values were calculated as maximum HR drop versus HRb. Possible associations between ΔHR and clinical-demographic factors were assessed through regression analysis. The RDV group experienced a significantly higher incidence of bradycardia compared to the CTR group (56% vs 33%, OR 2.6, 95% CI 1.2–5.4, p value = 0.011). Moreover, the RDV group showed higher ΔHR values than the CTR group. The HR progressively decreased with daily administration of RDV, reaching the maximun drop on day six (-8.6 ± 1.9 bpm). In RDV group, patients who experienced bradycardia had higher drop in HR, higher alanine aminotransferase (ALT) values at the baseline (bALT) and during the RDV administration period. ΔHR was positively associated with HRb ($\beta = 0.772$, $p < 0.001$) and bALT ($\beta = 0.245$, $p = 0.005$). In conclusion, our results confirmed a significant association between RDV administration and development of bradycardia. This effect was proportional to baseline HR and was associated with higher levels of baseline ALT, suggesting a possible interaction between RDV liver metabolism and a vagally-mediated effect on HR due to increased availability of RDV metabolites.

Keywords Autonomic nervous system · Vagal activity · Heart rate · COVID-19 · Remdesivir

Introduction

Since December 2019, SARS-CoV2 infection has gradually spread all over the world, becoming a pandemic. A lot of efforts have been made to manage this global emergency and to develop effective treatments for SARS-CoV2 infection [1]. Unfortunately, effective antiviral treatments in SARS-CoV2 patients remain limited [2, 3].

Remdesivir (RDV, Veklury®, 100 mg concentrate solution for infusion) was the first antiviral drug approved by the European Medicines Agency with specific indication for the "treatment of coronavirus disease 2019 (COVID-19) in adults and in adolescents (aged 12 years or older and

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weighing at least 40 kg) with pneumonia requiring supplemental oxygen therapy" [4].

Remdesivir (formerly GS-5734) is a monophosphoramidate nucleoside analog pro-drug that was originally developed in response to the Ebola outbreak in West Africa.

It has shown broad-spectrum activity against human and zoonotic coronaviruses in pre-clinical models and has been prioritized for inclusion in COVID-19 clinical trials [5].

The efficacy of RDV has been extensively investigated, although the associated adverse events (AEs) are not well-characterized. Since RDV has not been extensively used in clinical practice—other than in the treatment of Ebola virus (EBOV) disease and COVID-19—there is still limited evidence concerning adverse events. Safety studies reported rash, headache, nausea, diarrhea and transaminases elevation as the most common adverse effects, while hypotension and renal failure rarely occurred. Bradycardia was initially not mentioned as a potential adverse event. Nevertheless, since approval for clinical use, several cases of bradycardia have been reported during administration of RDV in COVID-19 patients [6–10]. In particular, two studies analyzed the incidence of bradycardia with discordant results. In the study by Attena and colleagues, the incidence of bradycardia detected on the fifth day of observation was 21% in the RDV group, while in the control group it was 3% [11]. They found that the group of patients who developed bradycardia showed lower resting heart rate, higher D-dimer values and had a higher percentage of females than the no-bradycardia subgroup. In a subsequent study by Pallotto et al., this observation was confirmed, however the overall incidence of bradycardia was higher than in the Attena study (46.8% vs 27.8%) [12]. Another retrospective study on the etiology of bradycardia in COVID-19 patients reported that the use of RDV was not associated with cardiac events [13].

Given these contradictory data, the aim of our study was twofold: (1) to evaluate the incidence of bradycardia in COVID-19 patients treated with RDV, hospitalized in internal medicine wards of two tertiary hospitals in Milan and (2) to investigate possible clinical and laboratory markers associated with the risk of RDV-induced bradycardia.

Materials and methods

We conducted a two-center, retrospective, case–control study. We screened all the patients consecutively admitted to the Internal Medicine Units of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and Ospedale Luigi Sacco in Milan (Italy), from 1st April 2020 to 31st May 2021. Both centers are two large city hospitals accounting each for about 60.000 admissions every year. The vast majority of patients in the Internal Medicine wards are admitted after an Emergency Department assessment.

Inclusion criteria included:

- confirmed mild COVID-19 infection defined as symptomatic patient without evidence of viral pneumonia or hypoxia or confirmed moderate COVID-19 infection defined as symptomatic patient with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including $SpO2 \geq 90\%$, in accordance with WHO Guideline Clinical management of COVID-19 patients [14];
- symptoms onset no longer than 10 days prior to hospitalization.

Exclusion criteria were the presence of a pacemaker, the absence of a stable sinus rhythm defined as the presence or development of any other rhythm during study period, need for mechanical ventilation, orotracheal intubation, extracorporeal membrane oxygenation (ECMO) and previous admission to an Intensive Care Unit during hospitalization.

We defined two cohorts of patients, those treated with RDV (RDV group) and a cohort of control subjects not treated with RDV (CTR group) matched for age, sex and COVID-19 disease severity.

According to the indications of the Italian Medicines Agency (AIFA), Remdesivir has been used for the treatment of hospitalized patients, over 12 years old, suffering from SARS-CoV2 pneumonia and requiring supplementary low-flow oxygen therapy.

All patients in the RDV group had to receive a 200 mg initial dose of Remdesivir intravenously and maintenance doses of 100 mg for the following 4 days, according to standard guidelines [4]. Any other RDV treatment protocol was not included in our analysis.

Two authors for each center (AF & AF and FC & GR) independently extracted data of interest from hospital electronic reports of screened patients.

Demographic data, past medical history, date of symptoms onset, clinical course data (e.g., death, transfer to intensive care unit) and concurrent therapies were included into the database. The Charlson Comorbidity Index was calculated for each patient. Creatinine and ALT serum level at the admission and during the first six days were included into the database. We chose to include creatinine and ALT measurements at admission as surrogates of basal kidney and hepatic function that are known to affect RDV metabolism.

For patients in the RDV group, the heart rate at baseline (HRb) was calculated as the average value between the morning HR of the day before the first RDV dose and the morning HR of the first day of RDV administration. The daily morning HR for the entire duration of RDV therapy and for the following 5 days were then considered and used for comparison with baseline conditions. For patients of CTR group, the baseline heart rate (HRb) was calculated

as the average value between the morning HR of the first and second hospitalization days. The daily morning HR of the following 10 days were considered for comparison with baselined conditions. All HR measurements were made through pulse oximeter devices and measured between 8 and 10 am.

For both groups, any HR below 60 bpm recorded during the observation period was accounted as a bradycardic episode and episodes of HR below 45 bpm as severe bradycardia. Patients with bradycardia before RDV measurement were excluded from analyses.

The maximum HR variation (ΔHR) was calculated as the difference between HRb and minimum HR achieved over the 10-day observation period.

We compared the incidence of bradycardia in CTR and RDV groups. Secondarily, we assessed the incidence of severe bradycardia within the patients who developed bradycardia. We also analyzed the difference in the mean heart rate variation between the two groups and the possible predictors for the development of bradycardia in RDV-treated group.

A total sample size of 121 patients was defined assuming an α error of 0.05 and a power of 80%. This would allow to highlight an effect size of 0.255 and a difference of ≥ 18% between the incidence of bradycardia in the two groups, as observed in a previous study [11].

Data were analyzed using SPSS Statistics 27 (IBM, Armonk, New York, United States). The Shapiro–Wilk test was used to evaluate the normal distribution of the data. Normally distributed parameters were expressed as mean and standard deviation (SD), whereas non-normally distributed data were expressed as median and interquartile range (IQR). Categorical variables were tested through χ^2 test or Fisher exact test. Continuous variables were tested through the Student t test when normally distributed and through the Mann–Whitney test when non-normally distributed. The difference in ΔHR between RDV and CTR groups correcting for age, sex, HRb and β-blockers assumption were assessed through ANCOVA analysis. The linear regression analysis was performed to assess the relationship between HR variation in RDV group and possible predictive factors (demographic and clinical data on the admission). HR variations during the 10-day monitoring were compared with respect to HRb through the Friedman test and significance values were adjusted by Bonferroni correction for multiple comparisons. *P* values < 0.05 were considered statistically significant.

Results

Through revision of hospital electronic reports between 1st April 2020 and 31st May 2021, we extracted data from 71 patients treated with RDV and 54 control patients matched for age, sex and COVID-19 disease severity (Fig. 1).

Characteristics of the enrolled groups are reported in Table 1. The two groups did not differ for age, sex, hospitalization outcome, assumption of β-blockers or amiodarone, comorbidities, HRb and ALT values at the baseline. No patients were on digoxin (Table 1). CTR group presented higher creatinine values and higher assumption of hydroxychloroquine (HCQ) at the baseline compared to RDV group. The impact of HCQ on HR is known [18] and in our observational study its frequency of administration is higher in the CTR group, corroborating our results.

Prevalence of primary and secondary outcomes are reported in Table 2. As for the assessment of the primary outcome, out of 71 patients treated with RDV, 40 subjects experienced at least one episode of bradycardia, whereas 18 of 54 patients experienced at least one episode of bradycardia in the CTR group, with a difference that reached statistical significance (56% vs 33%, OR 2.6, 95% CI 1.2–5.4, *p* value = 0.011). As for the assessment of the secondary outcomes, prevalence of severe bradycardia on the total bradycardia episodes was not significantly different in the two groups, even if it was higher in RDV group (10% vs 0%, OR 1.1, 95% CI 1.0–1.2, *p* value = 0.300). ANCOVA analysis highlighted a significant difference in ΔHR between CTR and RDV groups, with RDV group characterized by a higher drop in HR (15.7 ± 8.9 vs 20.6 ± 12.2, mean difference 4.9, 95% CI 2.0–7.7, *p* value = 0.001.

Six patients discontinued RDV treatment, three of them due to the onset of severe bradycardia during RDV treatment respectively after one, two and three RDV administrations. The fourth patient discontinued therapy after a single

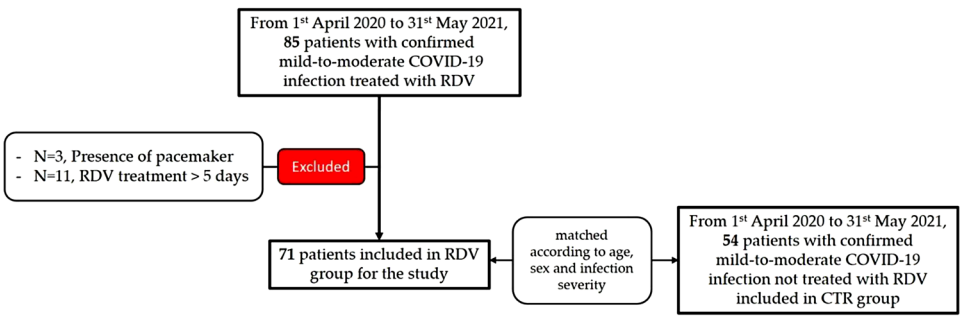

Fig. 1 Patient selection flowchart

Table 1 Demographic and clinical features of CTR and RDV groups

Characteristics	CTR group ($N=54$) Mean ± SD, median [IQR] $n°$ (%)	RDV group ($N=71$) Mean ± SD, median [IQR] $n°$ (%)	p
Age (years)	67.6 [54.9–81.2]	65.0 [54.6–75.7]	0.672
Sex (females)	18 (33%)	29 (41%)	0.390
Death	1 (2%)	2 (3%)	1.000
β-blockers assumption	12 (22%)	18 (25%)	0.685
Amiodarone	2 (4%)	3 (4%)	1.000
Hydroxychloroquine	12 (17%)	2 (4%)	0.001
Azithromycin	16 (30%)	20 (28%)	0.858
Comorbidities			
Cardiac disorders	32 (59%)	40 (56%)	0.743
Respiratory disorders	8 (15%)	12 (17%)	0.753
Hepatic disorders	6 (11%)	4 (6%)	0.264
Renal disorders	6 (11%)	10 (14%)	0.622
Gastro-intestinal disorders	10 (19%)	8 (11%)	0.253
Endocrine disorders	19 (35%)	15 (21%)	0.080
Immune disorders	3 (6%)	4 (6%)	0.985
Hematologic disorders	7 (13%)	4 (6%)	0.152
Oncologic disorders	3 (6%)	1 (1%)	0.192
Charlson Comorbidity Index	1.00 ± 1.55	0.73 ± 1.02	0.250
HRb (bpm)	77.8 ± 8.7	79.3 ± 13.1	0.442
Creatinine baseline (mg/dL)	1.02 [0.85–1.30]	0.90 [0.80–1.07]	0.013*
ALT baseline (U/L)	31.0 [18.5–45.5]	26.0 [18.0–41.0]	0.695

CTR group patients not treated with Remdesivir, *RDV group* patients treated with Remdesivir, *HRb* baseline; heart rate, *ALT* Alanine Aminotransferase, Δ*HR* heart rate maximum drop

*Significant p values < 0.05

Table 2 Bradycardia events in CTR and RDV groups

CTR group ($N=54$)		RDV group ($N=71$)		p
Characteristics	Mean ± SD, $n°$ (%)	Mean ± SD, $n°$ (%)	OR, mean difference (95% CI)	
Total Bradycardia	18/54 (33%)	40/71 (56%)	2.6 (1.2–5.4)	0.011*
Severe bradycardia	0/18 (0%)	4/40 (10%)	1.1 (1.0–1.2)	0.300
ΔHR (bpm)	15.7 ± 8.9	20.6 ± 12.2	4.9 (2.0–7.7)	0.001*

Total bradycardia, bradycardia events with HR below 60 bpm; severe bradycardia, severe bradycardia events with HR below 45 bpm

CTR group patients not treated with Remdesivir, *RDV group* patients treated with Remdesivir, Δ*HR* heart rate maximum drop

*Significant p values < 0.05

administration due to a marked increase in transaminases and the last two patients discontinued RDV for unknown cause.

Time course of HR daily variation, calculated as the difference between morning HR of each observation day and HRb, was analyzed in the two groups, showing significant difference from the baseline only for the RDV group. In particular, a progressive HR reduction was observed in the RDV group with the succession of daily RDV administrations (Fig. 2), reaching the significance at the end of the therapy (day 6, mean reduction − 8.6 ± 1.9 bpm, p value = 0.009). Subsequently, the HR progressively returned to baseline values.

RDV patients who developed bradycardia showed higher drop in HR than patients who did not develop bradycardia (ΔHR, 27.1 ± 1.0 bpm vs 12.9 ± 1.1 bpm respectively, $p < 0.001$). Moreover, RDV group with bradycardia presented higher ALT values at the baseline (ALT baseline, 43.1 ± 5.9 U/L vs 27.6 ± 3.0 U/L respectively, $p = 0.023$) and higher ALT values during the RDV administration period (ALT maximum, 70.8 ± 11.8 U/L vs 54.9 ± 6.5 U/L respectively, $p = 0.039$.

Multiple linear regression analysis was performed to find associated factors to ΔHR in RDV group, considering age, sex, β-blockers assumption, HRb and ALT values at the admission ($R^2 = 0.605$, $p < 0.001$). We observed a significant positive relationship between ΔHR and HRb ($\beta = 0.772$, $p < 0.001$) and between ΔHR and ALT values

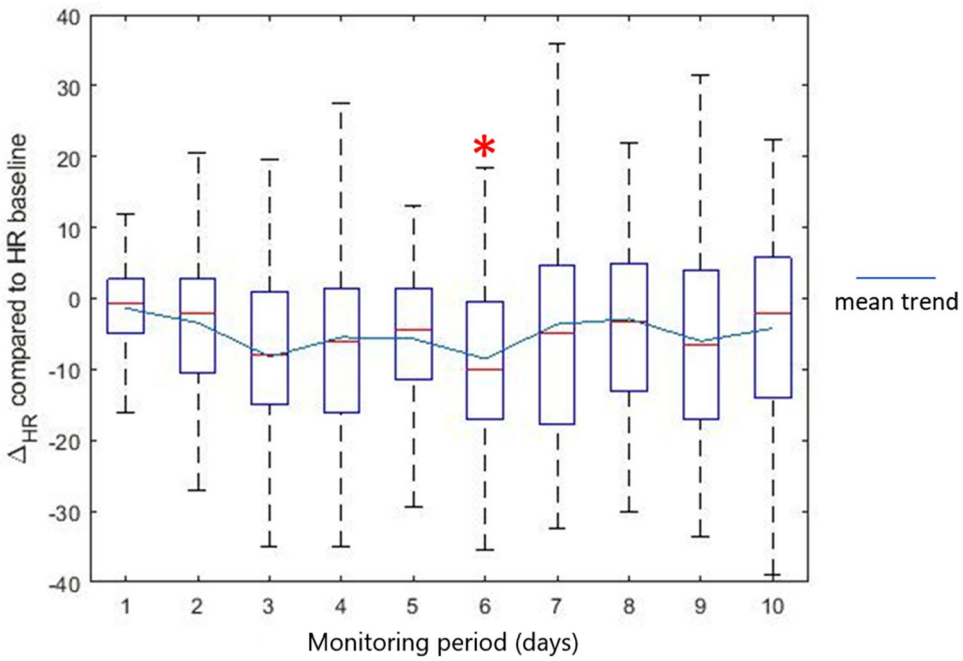

Fig. 2 Changes in morning HR with respect to HRb during the 10 days of the monitoring period. *Significant *p* values < 0.05 with respect to HRb

at the admission ($\beta = 0.295$, $p = 0.001$), as shown in Fig. 3a and b respectively.

Discussion

The major findings of our study on are: (1) patients with mild-to-moderate COVID-19 treated with RDV experienced a significantly higher incidence of bradycardia and had a higher drop in HR during the 10 days of observation compared to CTR group; (2) in RDV group, the HR progressively decreased with daily administration of remdesivir, reaching the nadir on the day 6; (3) higher drop in HR was positively associated with higher HR at the baseline and higher ALT values at the admission; (4) patients from the RDV group who presented bradycardia had higher ALT values during the RDV administration period.

At difference with another study [13], where no correlation was found between RDV administration and bradycardia, in our analysis the occurrence of bradycardia was statistically greater in RDV-treated patients compared to the CTR group. This observation suggests a possible causal association between RDV administration and the occurrence of bradycardia, which could not be totally explained by SARS-CoV-2 infection or hospital stay. The discrepancy with our finding could be due to the different patient selection criteria since the study by Umeh et al. [13] was not specifically focused on RDV treatment, but on all the causes of bradycardia in COVID-19 patients, therefore patients treated with RDV and control patients

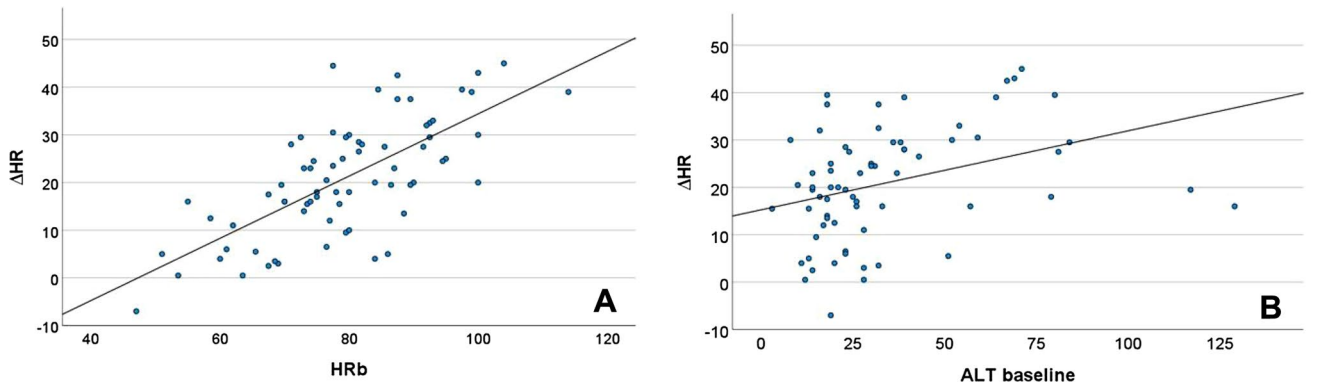

Fig. 3 **a** Regression plot of maximum HR drop in RDV group and HRb. **b** Regression plot of maximum HR drop in RDV group and ALT values at the baseline. Δ*HR* maximum heart rate drop, *HRb* baseline heart rate, *ALT* Alanine Aminotransferase

were not matched. Our results are instead in agreement with two previous case–control studies [11, 12], which reported an increased incidence of bradycardia in the group of patients treated with RDV although with different percentages probably due to the different HR monitoring methods: Attena et al. [11] considered the HR at the day of the hospitalization and at day fifth of RDV therapy, while Pallotto et al. [12] considered the days of RDV treatment, as we did, however, without considering the following five day.

RDV is a prodrug of an adenosine analog and it is metabolized in host cells to form the pharmacologically active nucleoside triphosphate metabolite. RDV triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural substrate for the incorporation into nascent RNA chains by SARS-CoV-2 RNA polymerase, causing the delayed chain termination during viral replication [15]. The pharmacodynamic mechanism for RDV-induced bradycardia is still unknown. One of the main hypotheses about how RDV can induce sinus node dysfunction is based on its active metabolite triphosphate that structurally resembles adenosine 5′-triphosphate (ATP). It is known that ATP and metabolites exert negative chronotropic and dromotropic effects on the automatism of the sinoatrial node and on the conduction of the atrioventricular node. Adenosine activates purinergic A1 receptors, inducing activation of potassium current and also inhibiting adenylyl-cyclase via inhibitory G protein [6, 7]. This is the reason why it is used as first-line treatment for paroxysmal supraventricular tachycardia. Furthermore, adenosine it is well known to have a direct effect on the central autonomic structures, namely increasing vagal activity in a dose response-manner [16].

It can be hypothesized that the RDV metabolite may exert the same effects. In particular, the link observed in our study on the occurrence of higher HR drop in RDV patients with higher values of HR at baseline suggests the establishment of an accentuated antagonism. It is known that vagal deceleration effects are augmented with increased sympathetic background levels [17].

The major drop in HR observed on day 6 at the end of RDV treatment, could be explained by the pharmacokinetics of the antiviral drug. Although remdesivir does not accumulate in the organism, by contrast its metabolite GS-441524 (nucleoside monophosphate) reaches steady state around day 4 and accumulates by ~ twofold after multiple once daily dosing [5]. Moreover, data showed a higher HR drop when baseline ALT values were elevated and RDV patients that developed bradycardia presented higher ALT values during the 6-day monitoring period. Considering a 50% renal—50% hepatic excretion of GS-441524, we could speculate that even a subclinical impairment of the hepatic function, may determines a slower elimination of the antiviral drug metabolite with a consequent increase in the serum availability of the metabolite, leading to an increased effect on both sinus node and vagal activity, thus inducing bradycardia. However, our data as well as current knowledge, do not allow one-sided interpretation and further studies are needed to clarify the interactions between RDV pharmacokinetics and possible cardiac side effects.

Other currently available antiviral agents for COVID-19 also include Nirmatrelvir/ritonavir and Molnupiravir.

Nirmatrelvir mechanism of action is different from RDV, it is a peptidomimetic inhibitor of the SarS-CoV2 main protease, which leads to the prevention of viral replication while ritonavir serves to slow the metabolism of nirmatrelvir via cytochrome enzyme inhibition, thereby increasing the circulating concentration of the main drug. Until now no effect on cardiac rate have been reported. On the other hand, Molnupiravir, which is antiviral drug proven effective against influenza A virus, Venezuelan equine encephalitis virus, Ebola virus, SARS-CoV, and more recently given emergency use authorization for treatment of COVID-19, has a similar mechanism of action as RDV, since it is a prodrug metabolized and posphorylated into host cells to form the pharmacologically active ribonucleoside *N*-hydroxycytidine triphosphate (NHC-TP). NHC-TP can substitute for either cytidine triphosphate or uridine triphosphate, resulting in an accumulation of mutations in the viral genome leading to inhibition of replication. Thus, it doesn't have similarities to adenosine and no effect on cardiac rate have been reported until now. Concerning monoclonal antibodies, they target different epitopes of the receptor binding domain of the spike(s) protein of SARS-CoV-2 consequently blocking cellular entry and SARS-CoV-2 infection, known adverse reactions only account for infusion-related reactions (e.g., nausea, headache, tachycardia, hypotension, rash and shortness of breath).

Taking into account the hypothesized mechanism of action of RDV on cardiac rate, we expect this to be a drug-specific effect, due to RDV metabolite similarity to adenosine.

Conclusion

Through our retrospective case–control study, we reported the experience on RDV-induced bradycardia of six internal medicine units from two large hospitals of Milan. We highlighted a significant difference in the incidence of bradycardia in patients affected by mild-to-moderate COVID-19 treated with RDV with respect to a group of patients matched of age, sex and disease severity not treated with RDV. This effect was proportional to baseline HR and was associated with higher levels of baseline ALT, suggesting a possible interaction between RDV liver metabolism and a vagally-mediated effect on HR due to increased availability

of RDV metabolites. In our experience, bradycardia did not induce any clinically relevant consequences, thus it can be considered as a minor side effect of RDV administration. Furthermore, since fully vaccinated patients admitted to hospital with COVID-19 present lower disease severity than unvaccinated patients for all the variants, RDV could still represent a valid treatment strategy in a contest of non-critical disease. However, since RDV is currently making its way as a forefront treatment in the early stage of COVID-19, the healthcare workers should be aware of the potential cardiac effect and use the drug with caution.

Author contributions Literature search: AF (Annalisa Filtz), AC, AF (Annalaura Fasiello); conceptualisation: NM, ET; data collection: AF (Annalisa Filtz), AF (Annalaura Fasiello), LB, RL, FC, GR; data curation: AF (Annalisa Filtz), AC, AF (Annalaura Fasiello), FC, GR; data analysis: AF (Annalisa Filtz), AC, AF (Annalaura Fasiello); data interpretation: AF (Annalisa Filtz), AC, AF (Annalaura Fasiello), NM, ET; supervision: EC, ALF, CH, CC (Chiara Cogliati), CC (Ciro Canetta), FP, NM, ET; writing original draft: AF (Annalisa Filtz), AC, AF (Annalaura Fasiello); writing—review & editing: LF, CB, NM, ET. All authors have read and agreed to the published version of the manuscript.

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical statements The study was reviewed and approved by the local Ethics Committee (Comitato Etico Milano Area 2, approval document number: 1084_2021) and it was developed in accordance with the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

Data availability The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

References

1. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S et al (2020) Remdesivir for the treatment of covid-19—final report. N Engl J Med 383:1813–1826. https://doi.org/10.1056/NEJMoa2007764
2. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M et al (2020) A trial of Lopinavir-Ritonavir in adults hospitalized with severe covid-19. N Engl J Med 382:1787–1799. https://doi.org/10.1056/NEJMoa2001282
3. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, Mourão MPG, Brito-Sousa JD, Baía-da-Silva D, Guerra MVF et al (2020) Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open 3:e208857. https://doi.org/10.1001/jamanetworkopen.2020.8857
4. EMA (2020) Veklury. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/veklury. Accessed 10 June, 2022
5. Jorgensen SCJ, Kebriaei R, Dresser LD (2020) Remdesivir: review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19. Pharmacotherapy 40:659–671. https://doi.org/10.1002/phar.2429
6. Gubitosa JC, Kakar P, Gerula C, Nossa H, Finkel D, Wong K, Khatri M, Ali H (2020) Marked sinus bradycardia associated with Remdesivir in COVID-19: a case and literature review. JACC Case Rep 2:2260–2264. https://doi.org/10.1016/j.jaccas.2020.08.025
7. Gupta AK, Parker BM, Priyadarshi V, Parker J (2020) Cardiac adverse events with Remdesivir in COVID-19 infection. Cureus 12:e11132. https://doi.org/10.7759/cureus.11132
8. Day LB, Abdel-Qadir H, Fralick M (2021) Bradycardia associated with remdesivir therapy for COVID-19 in a 59-year-old man. CMAJ 193:E612–E615. https://doi.org/10.1503/cmaj.210300
9. Barkas F, Styla C-P, Bechlioulis A, Milionis H, Liberopoulos E (2021) Sinus bradycardia associated with remdesivir treatment in COVID-19: a case report and literature review. J Cardiovasc Dev Dis 8:18. https://doi.org/10.3390/jcdd8020018
10. Touafchia A, Bagheri H, Carrié D, Durrieu G, Sommet A, Chouchana L, Montastruc F (2021) Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. Clin Microbiol Infect 27:791.e5-791.e8. https://doi.org/10.1016/j.cmi.2021.02.013
11. Attena E, Albani S, Maraolo AE, Mollica M, De Rosa A, Pisapia R, Fiorentino G, Parrella R, Severino S, Russo V (2021) Remdesivir-induced bradycardia in COVID-19: a single center prospective study. Circ Arrhythmia Electrophysiol 14:e009811. https://doi.org/10.1161/CIRCEP.121.009811
12. Pallotto C, Blanc P, Esperti S, Suardi LR, Gabbuti A, Vichi F, Mecocci L, Esposti AD, Pierotti P, Attala L et al (2021) Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19). J Infect 83:237–279. https://doi.org/10.1016/j.jinf.2021.05.025
13. Umeh C, Giberson C, Kumar S, Aseri M, Barve P (2022) A Multicenter retrospective analysis on the etiology of bradycardia in COVID-19 patients. Cureus 14:e21294. https://doi.org/10.7759/cureus.21294
14. Living guidance for clinical management of COVID-19 (2022) https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-clinical-2021-2. Accessed 10 June, 2022
15. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30:269–271. https://doi.org/10.1038/s41422-020-0282-0
16. da Silva VJD, Gnecchi-Ruscone T, Bellina V, Oliveira M, Maciel L, de Carvalho ACC, Salgado HC, Bergamaschi CM, Tobaldini E, Porta A et al (2012) Acute adenosine increases cardiac vagal and reduces sympathetic efferent nerve activities in rats. Exp Physiol 97:719–729. https://doi.org/10.1113/expphysiol.2011.063925
17. Uijtdehaage SHJ, Thayer JF (2000) Accentuated antagonism in the control of human heart rate. Clin Auton Res 10:107–110. https://doi.org/10.1007/BF02278013
18. Gasperetti A, Biffi M, Duru F, Schiavone M, Ziacchi M, Mitacchione G, Lavalle C, Saguner A, Lanfranchi A, Casalini G, Tocci M, Fabbricatore D, Salghetti F, Mariani MV, Busana M, Bellia A, Cogliati CB, Viale P, Antinori S, Galli M, Galiè N, Tondo C, Forleo GB (2020) Arrhythmic safety of hydroxychloroquine

in COVID-19 patients from different clinical settings. Europace 22(12):1855–1863. https://doi.org/10.1093/europace/euaa216