DOI: 10.1002/jmv.26898

JOURNAL OF MEDICAL VIROLOGY WILEY

LETTER TO THE EDITOR

Potential remdesivir-related transient bradycardia in patients with coronavirus disease 2019 (COVID-19)

To the Editor,

Coronavirus disease 2019 (COVID-19) is still a global concern with elevated morbidity and mortality.[1–3] Several drugs were evaluated, but, until now, only remdesivir (RDV), an inhibitor of the viral RNA-dependent RNA polymerase, was approved for COVID-19 therapy.[4,5] Although RDV treatment was quite well described,[4–6] the knowledge about RDV-related adverse events is still scarce and mostly limited to case reports describing hepatotoxicity and skin reactions.[7] Here, we describe our experience about COVID-19 treatment with RDV focusing on possible RDV-related cardiologic adverse events.

We retrospectively evaluated all the patients consecutively admitted to our ward with a confirmed diagnosis of COVID-19 from September 14th to October 14th, 2020. The study population was divided into two groups, according to RDV administration (cases treated with RDV were defined as patients, whereas cases who did not receive RDV were defined as controls). We collected data about demographic and clinical characteristics, treatments, and adverse events; heart rates (HRs) were collected three to six times per day according to patients' clinical status. Clinical characteristics and laboratory data were collected using an ad hoc case report form. Data selection was based on a previous work of this group about risk factors for severe illness in COVID-19 patients.[2] In the patients' group, we compared median HR during RDV administration with the median HR of the 3 days before RDV administration and the median HR of the 3 days after RDV administration. Moreover, we compared incidence of bradycardia between patients and controls. RDV was administered according to the indications of the European Medicines Agency (EMA)[8] as follows: 200 mg as loading dose on Day 1 and 100 mg on Days 2–5. Hyperimmune plasma was administered in the context of a specific trial, the TSUNAMI Study. A positive outcome was defined as clinical healing and/or discharge independent of microbiological status, whereas a negative outcome was defined as exitus.

Forty-six patients were observed in the study period, 20 patients and 26 controls. Table 1 describes patients' and controls' clinical characteristics at admission and outcomes. In

TABLE 1 Patients' and controls' characteristics at admission and outcomes

	Study population $n = 46$	Patients $n = 20$	Controls $n = 26$	p
Female sex, *n* (%)	21 (45.7)	7 (35)	14 (53.8)	>.1
Age (years), median (IQR)	64 (48.25–73.25)	66 (58–70.25)	58 (47–75.5)	>.1
CCI, median (IQR)	2 (1–4)	2.5 (1.75–4)	2 (0–4.75)	>.1
CVD[a], *n* (%)	25 (54.6)	15 (75)	10 (38.5)	**.019**
Beta-blockers, *n* (%)	12 (26.1)	5 (25)	6 (23.1)	>.1
Days onset–admission, median (IQR)	5 (3.25–7)	5 (4.75–7)	5.5 (3–7)	>.1
$T \geq 38°C$, *n* (%)	6 (13)	3 (15)	3 (11.5)	1
$PaO_2/FiO_2 < 300$, *n* (%)	15 (32.6)	11 (55)	4 (15.4)	**.01**
C-RP > 5 mg/dl, *n* (%)	25 (54.6)	16 (80)	4 (15.4)	**.003**
Lymphocytes < 800/mm^3, *n* (%)	17 (37)	8 (40)	9 (34.6)	>.1
IL-6 (pg/ml), median (IQR)	17.85 (6.75–54.475)	23.45 (8.75–63.375)	13.85 (4.575–49.975)	>.1
D-dimer > 1000 ng/ml, *n* (%)	13 (28.3)	5 (25)	8 (30.8)	>.1
Bradycardia, *n* (%)	18 (39.1)	12 (60)	6 (23.1)	**.016**
Exitus, *n* (%)	5 (10.9)	1 (5)	4 (15.4)	>.1

Note: Bold values indicate statistically significant values.

Abbreviations: CCI, Charlson comorbidity index; CVD, cardiovascular diseases; Days onset–admission, days from disease onset to hospital admission; *T*, temperature; C-RP, C-reactive protein; IL-6, interleukin 6.

[a]Hypertension in 14 patients while Pt 3 had heart failure NYHA II; hypertension in 10 controls.

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TABLE 2 Patients' treatment, HR, and outcomes

Patient (gender-age)	Therapy (+RDV)	HR before RDV median (IQR)	HR during RDV median (IQR)	p^a	HR after RDV median (IQR)	p^b	Days to			Outcome
							Apyrexia	Stop O_2 therapy	Discharge[c]	
Pt 1 (M-74)	DXM, HP, LMWH	60 (60–61)	52.5 (50–55)	**.049**	60 (54.5–70.75)	**.025**	1	7	7 (14)	Pos
Pt 2 (M-69)	DXM, LMWH	81 (79–85)	68 (64.5–70.5)	**<.01**	70 (65–73)	>.1	1	18	19 (27)	Pos
Pt 3 (M-65)	DXM, LMWH	60.5 (58–64.5)	55 (55–62)	>.1	69 (65.75–70.75)	**<.01**	0	9	10 (13)	Pos
Pt 4 (M-54)	DXM, LMWH	63 (56.75–65.5)	67 (56.5–72)	>.1	69.5 (62.5–70.75)	>.1	1	13	13 (17)	Pos
Pt 5 (M-47)	DXM, HP, LMWH[d]	81.5 (67.25–84)	62.5 (49.5–70.25)	**.011**	65 (59.5–68.5)	>.1	7	25[d]	16 (25)	Pos
Pt 6 (M-82)	DXM, LMWH[d]	80.5 (78.5–81.75)	71 (59.5–75)	**<.01**	73 (62.75–81.75)	>.1	1	13[d]	13 (13)	Pos
Pt 7 (F-59)	DXM, LMWH	65 (64–72)	59.5 (56–62.75)	**<.01**	69 (64.25–72)	.055	4	15	13 (17)	Pos
Pt 8 (M-88)	DXM, LMWH	85 (81–88)	65 (59–67)	**<.01**	69.5 (63.25–73.75)	>.1	3	11	5 (24)	Pos
Pt 9 (M-69)	DXM, LMWH[d]	65 (63–71.5)	50 (48–57)	**.026**	79 (75–84)	**<.01**	7	43[d]	33 (43)	Pos
Pt 10 (M-69)	DXM, LMWH	77 (75.5–77)	65 (56.5–68)	**.016**	63 (58–66.5)	>.1	1	16	16 (16)	Pos
Pt 11 (M-59)	DXM, LMWH	55 (54–63)	56 (52–60.5)	>.1	54 (53–57)	>.1	2	14	12 (15)	Pos
Pt 12 (F-74)	DXM, LMWH	55 (55–65)	63 (55–65.5)	>.1	60 (58–66.5)	>.1	1	25	17 (28)	Pos
Pt 13 (F-55)	DXM, HP, LMWH	68.5 (63.25–73.75)	64 (62–69)	>.1	80 (79–88)	**<.01**	2	14	8 (16)	Pos
Pt 14 (F-64)	DXM, LMWH	74 (71.5–77.25)	71 (64.5–73.5)	>.1	68 (65.5–84.75)	>.1	0	9	6 (16)	Pos
Pt 15 (M-46)	DXM, LMWH	85 (78–89)	73 (68.5–78)	**.008**	76.5 (74.25–79.5)	>.1	1	8	4 (10)	Pos
Pt 16 (F-69)	DXM, HP, LMWH	73 (66.75–77.75)	65 (61.25–73)	>.1	72 (70–78)	>.1	1	10	9 (15)	Pos
Pt 17 (F-67)	DXM, LMWH	73 (71–74)	60 (57–65)	**.005**	60 (59–63)	>.1	0	12	10 (12)	Pos
Pt 18 (M-80)	DXM, LMWH	66.5 (63.75–71)	60 (57.75–62.5)	**.012**	48 (46.5–55)	**.012**	1	NA	17 (17)	Pos
Pt 19 (M-63)	DXM, LMWH[d]	74.5 (69.75–79.25)	80 (72–81.75)	>.1	71 (66–75)	>.1	2	NA[d]	19 (19)	Pos
Pt 20 (F-34)	DXM, LMWH	88 (76–92)	76 (70.5–82.5)	**.03**	85 (79.75–90.75)	.087	1	11	10 (12)	Pos

Note: Bold values indicate statistically significant values.

Abbreviations: CCI, Charlson Comorbidity Index; DEX, dexamethasone; F, female; HR, heart rate; LMWH, low-molecular-weight heparin; M, male; NA, not available (patients were discharged with the indication to continue O_2 therapy at home); neg, negative; pos, positive; Pt, patient; RDV, remdesivir.

[a]Difference between median HR before RDV administration and median HR during RDV administration.

[b]Difference between median HR during RDV administration and median HR after RDV administration.

[c]Length of hospital stay and between brackets, length of hospital + intermediate/low-care facility stay.

[d]Patients treated with continuous positive airway pressure (CPAP).

TABLE 3 Univariate analysis and multivariate logistic regression assessing risk factors for transient bradycardia

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Female sex	3.467 (0.969–12.398)	.056	3.655 (0.708–18.876)	.122
Age > 65 years	**5 (1.393–17.943)**	**.014**	**18.618 (2.339–148.171)**	**.006**
CVD	0.923 (0.281–3.034)	.895	9.472 (0.779–115.107)	.078
Beta-blockers	2.368 (0.544–10.317)	.251	2.119 (0.232–19.384)	.506
$T \geq 38°C$	3.714 (0.604–22.867)	.157		
Lymphocytes < 800/mm^3	0.773 (0.224–2.668)	.683		
C-RP > 5 mg/dl	3.467 (0.969–12.398)	.056	2.973 (0.449–19.665)	.258
D-dimer > 1000 ng/ml	0.7 (0.19–2.58)	.592		
RDV therapy	**5 (1.393–17.943)**	**.014**	**6.915 (1.007–47.499)**	**.049**
PaO_2/FiO_2 < 300	2.057 (0.575–7.364)	.268		

Note: Bold values indicate statistically significant values.

Abbreviations: CI, confidential interval; C-RP, C-reactive protein; CVD, cardiovascular diseases, OR, odds ratio; RDV, remdesivir; *T*, temperature.

particular, 15 patients and 10 controls had one cardiovascular disease and 5 patients and 6 controls were chronically under treatment with low-dose beta-blockers; no cardiac rhythm alterations nor other electrocardiograms (ECG) abnormalities were detected in the whole study population. Table 2 shows treatments, HR, and outcomes of the patients. Moreover, all the patients and the controls received low-molecular-weight heparin according (LMWH) to the local standards, whereas 4 patients and 1 control and 2 patients and 20 controls were also administered hyperimmune plasma and dexamethasone, respectively. It is observed that in 12/20 patients, median HR significantly decreased during RDV administration, and in 2 of them (Pt 1 and Pt 9), HR significantly increased after its suspension. In all but Pt 4, Pt 11, Pt 12, and Pt 19, at least a tendency of HR reduction was reported in association with RDV administration. No further cardiologic alterations, especially ECG or blood pressure significative modifications, or other clinically relevant conditions were observed. Patients remained completely asymptomatic. Only Pt 6 had a negative outcome.

As shown in Table 1, bradycardia appeared to be more frequent in the patients' group (60% vs. 23%, $p = .016$). To better understand this finding, a univariate and a multivariate logistic regression was managed (Table 3). Both at univariate and multivariate analysis, age > 65 years and RDV treatment were significantly associated with bradycardia.

RDV was shown to reduce the recovery time from COVID-19, with no effect on mortality rates,[9] and it was recently approved by EMA.[8] Although some studies were published on this field and many others are ongoing, our knowledge about RDV tolerability is still scarce; hepatotoxicity and skin reactions were the only adverse events described at the moment.[7] On the contrary, such events were not observed in our study. Moreover, we noticed a tendency to develop bradycardia during RDV treatment. Bradycardia tended to resolve after RDV discontinuation. These HR variations reached the threshold of statistical significance in some cases (Table 2). Moreover, incidence of bradycardia was higher in the patients' group and its association with RDV administration was confirmed also by multivariate logistic regression.

In our experience, bradycardia did not induce any consequences of clinical relevance: patients were asymptomatic, blood pressure remained in the normal range, and no ECG alterations were observed. However, this phenomenon appeared to be worthy of consideration, especially in patients who were chronically under treatment with bradycardia-inducing drugs such as beta-blockers.

To the best of authors' knowledge, this is the first report of potential RDV-related bradycardia. As a consequence, we are not able to provide a full "pathogenetic" explanation.

This study has some limitations, such as the limited sample size and its observational design. Nevertheless, it pointed out a new aspect of RDV treatment that could be of clinical interest.

In conclusion, a potential—at least time—association between bradycardia and RDV administration was observed. Clinicians should be aware of this potential RDV side effect. More extensive studies are necessary to clarify this finding.

CONFLICT OF INTERESTS

Carlo Pallotto has received funds for speaking at symposia organized on behalf of Merck, Angelini, and Bristol Myers Squibb.

AUTHOR CONTRIBUTIONS

Carlo Pallotto, Andrea Gabbuti, and Lorenzo Mecocci conceived the study. Carlo Pallotto, Lorenzo R. Suardi, and Sara Esperti collected data. Carlo Pallotto drafted the manuscript. Carlo Pallotto, Andrea Gabbuti, Lorenzo Mecocci, and Pierluigi Blanc revised the manuscript. Carlo Pallotto and Pierluigi Blanc supervised the study. All Authors approved the final version of the manuscript to be submitted.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jmv.26898

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Patients provided their consent for data analysis and submission

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