SHORT COMMUNICATION

Remdesivir significantly reduces SARS-CoV-2 viral load on nasopharyngeal swabs in hospitalized patients with COVID-19: A retrospective case–control study

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Abstract

Remdesivir is a broad-spectrum antiviral agent able to inhibit the RNA polymerase of SARS-CoV-2. At present, studies focusing on the effect of remdesivir on viral load (VL) are few and with contrasting results. Aim of the present study was to evaluate the effect of remdesivir on SARS-CoV-2 VL from nasopharyngeal swabs (cycle threshold criterion) in a sample of patients treated with the drug, compared with patients who did not receive the antiviral treatment. This retrospective analysis evaluated patients with (1) real-time polymerase chain reaction (RT-PCR) confirmed COVID-19 diagnosis and (2) availability of at least two positive nasopharyngeal swabs analysed with the same analytic platform (ORF target gene, Ingenius ELITe, ELITechGroup, Puteaux, France). Upper respiratory specimens from nasopharyngeal swabs were collected at admission (T0) and 7–14 days after treatment, upon clinical decision. A total of 27 patients treated with remdesivir (Group A) met the inclusion criteria and were compared with 18 patients (Group B) treated with standard care, matched for baseline clinical characteristics. At baseline, both remdesivir-treated and nontreated patients showed comparable VLs (21.73 ± 6.81 vs. 19.27 ± 5.24, $p = 0.348$). At the second swab, remdesivir-treated patients showed a steeper VL reduction with respect to controls (34.28 ± 7.73 vs. 27.22 ± 3.92; $p < 0.001$). Longitudinal linear model estimated a mean decrease in cycle threshold equal to 0.61 (SE: 0.09) per day in remdesivir-treated versus 0.33 (SE: 0.10) per day in remdesivir nontreated patients (p for heterogeneity = 0.045). The present study shows that the administration of remdesivir in hospitalized COVID-19 patients significantly reduces the VL on nasopharyngeal swabs.

KEYWORDS

COVID-19, RT-PCR, corticosteroids, cycle threshold, viral load

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Annalucia Biancofiore and Antonio Mirijello are co-first, and Salvatore De Cosmo and Renato Lombardi are co-last authors.

1 | INTRODUCTION

Coronavirus disease-2019 (COVID-19) is characterized by an early viremic phase (e.g., presymptomatic and flu-like symptoms), followed by an inflammatory phase (e.g., fever, dyspnea, and hypoxemia) and a final stage characterized by complications (respiratory failure, multi-organ failure, and death).[1]

Remdesivir is a broad-spectrum antiviral agent able to inhibit the RNA polymerase of several viruses including coronaviruses, ebola and hepatitis C virus.[2] Given its possible effect in reducing the severity and progression of disease, remdesivir has received an emergency approval for the treatment of COVID-19.[3–6] Although remdesivir shows a significant in vitro activity in terms of reduction of viral load (VL) from respiratory specimens,[7] its effectiveness on clinical outcomes is still matter of debate.[8] In addition, evidences on the correlation between VL and clinical severity are controversial,[9–11] even if it has been shown that patients with more severe disease could present with a slower VL clearance.[7] At present, studies focusing on the effect of remdesivir on VL are few and with contrasting results.[9,12,13]

The aim of the present study was to evaluate the effect of remdesivir on SARS-CoV-2 VL from nasopharyngeal swabs in a sample of patients treated with the drug, compared with patients who did not receive the antiviral treatment.

2 | MATERIALS AND METHODS

This retrospective analysis was conducted in the COVID-19 Units of our 900-bed tertiary care research hospital. Criteria of inclusion were: (1) real-time polymerase chain reaction (RT-PCR) confirmed COVID-19 diagnosis; (2) availability of at least two positive nasopharyngeal swabs analysed with the same analytic platform. The study was approved by the Ethics Committee (COVID-19-CSS, n. 46/2020) and was conducted in agreement with the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practice guidelines.

The primary endpoint was the evaluation of VL measured by the cycle threshold (CT) criterion on nasopharyngeal swabs. Secondary endpoints were: need for noninvasive ventilatory support, admission to ICU, and death.

Upper respiratory specimens from nasopharyngeal swabs were collected at admission (T0) and 7–14 days after treatment, upon clinical decision. Samples have been processed using the reverse transcriptase RT-PCR (rtRT-PCR) molecular technique. Since the availability of the whole SARS-CoV-2 genome from Wuhan, several target genes sequences have been identified for genome detection using RT-PCR (e.g., Nucleocaspid [N] gene, RNA-dependent RNA polymerase [RdRp] gene, Envelope [E] gene, Spike [S] gene, Helicase [H] gene, Hemagglutinin-esterase [HE] gene and open reading frame [ORF] gene cluster).[14] At our hospital, a total of seven different RT-PCR platforms have been used to analyse nasopharyngeal swabs during the COVID-19 pandemic. For the present study we selected those patients who had at least two positive swabs confirmed by one of the seven available platforms, using the ORF target gene (Ingenius ELITe, ELITechGroup, Puteaux, France). The CT is defined as the number of amplification cycles required for the viral RNA signal to be detected by the analyser system. It represents a reliable, semi-quantitative, indicator of the presence viral genetic material inversely correlated to VL.[10] The cut-off value of CT was 35 (e.g., ≤35 positive/>35 negative) according to manufacturer indications. However, the results of the test were analysed automatically and interpreted by the instrument software with the parameters included in the Assay Protocol.[15]

A total of 27 patients treated with remdesivir during the second pandemic wave (October 2020–March 2021) (Group A) met the inclusion criteria and were compared with 18 patients (Group B) treated with standard care (without remdesivir) during the first pandemic wave (March–May 2020), matched for baseline clinical characteristics. Remdesivir was administered for 5 days (200 mg loading dose on Day 1 then 100 mg/day for 4 days).

Demographic and clinical baseline patients' characteristics were reported as mean and SD or frequency and percentage for continuous and categorical variables, respectively. Group comparisons (remdesivir treated vs. nontreated) were carried out using Mann–Whitney U-test for continuous variables and Pearson chi-squared test for categorical variables. Patients' VL measured at baseline and at a variable follow-up was analysed using a longitudinal linear model for repeated measurement with a spatial power covariance matrix, the last accounts for unequally spaced follow-up times. A $p < 0.05$ was considered as statistically significant.

3 | RESULTS

Table 1 shows baseline characteristics of patients, both as overall sample, and as comparison between groups. As expected, groups were comparable, excepted for the use of antibiotics (higher in Group B), corticosteroids and oxygen supplementation (higher in Group A). Moreover, the follow-up period (time from 1st to 2nd swab) was similar (14.81 ± 9.52 vs. 17.83 ± 9.84 days, $p = 0.10$). At baseline, both remdesivir-treated and nontreated patients showed comparable VLs (21.73 ± 6.81 vs. 19.27 ± 5.24, $p = 0.348$) (Table 1 and Figure 1). At the second swab, remdesivir-treated patients showed a steeper VL reduction with respect to controls (34.28 ± 7.73 vs. 27.22 ± 3.92; $p < 0.001$) (Table 1 and Figure 1). Longitudinal linear model estimated a mean decrease in CT equal to 0.61 (SE: 0.09) per day in remdesivir-treated versus 0.33 (SE: 0.10) per day in remdesivir nontreated patients (p for heterogeneity = 0.045) (Figure 2). No differences in secondary outcomes have been observed between the two groups.

4 | DISCUSSION

The present study shows that the administration of remdesivir in hospitalized COVID-19 patients significantly reduces the VL on nasopharyngeal swabs. This result is in line with the recent literature

TABLE 1 Patients' baseline demographical and clinical characteristics

	Total (N = 45)	Group A Remdesivir yes 1 (N = 27)	Group B Remdesivir no 0 (N = 18)	p value
Age				0.88
Mean (SD)	62.42 (11.45)	62.15 (10.70)	62.83 (12.80)	
BMI				0.326
Mean (SD)	26.65 (5.25)	25.99 (3.94)	27.64 (6.76)	
Gender				**0.004**
F	14 (31.1%)	4 (14.8%)	10 (55.6%)	
M	31 (68.9%)	23 (85.2%)	8 (44.4%)	
Onset of symptoms at admission				0.874
≥10 days	8 (17.8%)	5 (18.5%)	3 (16.7%)	
<10 days	37 (82.2%)	22 (81.5%)	15 (83.3%)	
Comorbidities				0.071
None	6 (13.3%)	5 (18.5%)	1 (5.6%)	
Diabetes	13 (28.9%)	11 (40.7%)	2 (11.1%)	
Cardiovascular disease	13 (28.9%)	6 (22.2%)	7 (38.9%)	
Cancer	4 (8.9%)	1 (3.7%)	3 (16.7%)	
Others	9 (20.0%)	4 (14.8%)	5 (27.8%)	
Tocilizumab				0.076
0	43 (95.6%)	27 (100.0%)	16 (88.9%)	
1	2 (4.4%)	0 (0.0%)	2 (11.1%)	
Antibiotics				**0.042**
0	6 (14.0%)	6 (22.2%)	0 (0.0%)	
1	37 (86.0%)	21 (77.8%)	16 (100.0%)	
Heparin				0.215
0	1 (2.2%)	0 (0.0%)	1 (5.6%)	
1	44 (97.8%)	27 (100.0%)	17 (94.4%)	
Glucocorticoids				**0.002**
0	8 (17.8%)	1 (3.7%)	7 (38.9%)	
1	37 (82.2%)	26 (96.3%)	11 (61.1%)	
Oxygen supplementation				**0.028**
0	10 (22.2%)	3 (11.1%)	7 (38.9%)	
1	35 (77.8%)	24 (88.9%)	11 (61.1%)	
Noninvasive ventilatory support				0.464
0	35 (77.8%)	22 (81.5%)	13 (72.2%)	
1	10 (22.2%)	5 (18.5%)	5 (27.8%)	
Invasive ventilatory support (ICU)				0.807
0	42 (93.3%)	25 (92.6%)	17 (94.4%)	
1	3 (6.7%)	2 (7.4%)	1 (5.6%)	
Deaths				0.521
0	41 (91.1%)	24 (88.9%)	17 (94.4%)	
1	4 (8.9%)	3 (11.1%)	1 (5.6%)	

TABLE 1 (Continued)

	Total (N = 45)	Group A Remdesivir yes 1 (N = 27)	Group B Remdesivir no 0 (N = 18)	p value
Follow-up (days)				0.099
Mean (SD)	16.02 (9.65)	14.81 (9.52)	17.83 (9.84)	
T0 viral load (CT)				0.348
Mean (SD)	20.75 (6.28)	21.73 (6.81)	19.27 (5.24)	
Follow-up viral load (CT)				< 0.001
Mean (SD)	31.46 (7.31)	34.28 (7.73)	27.22 (3.92)	

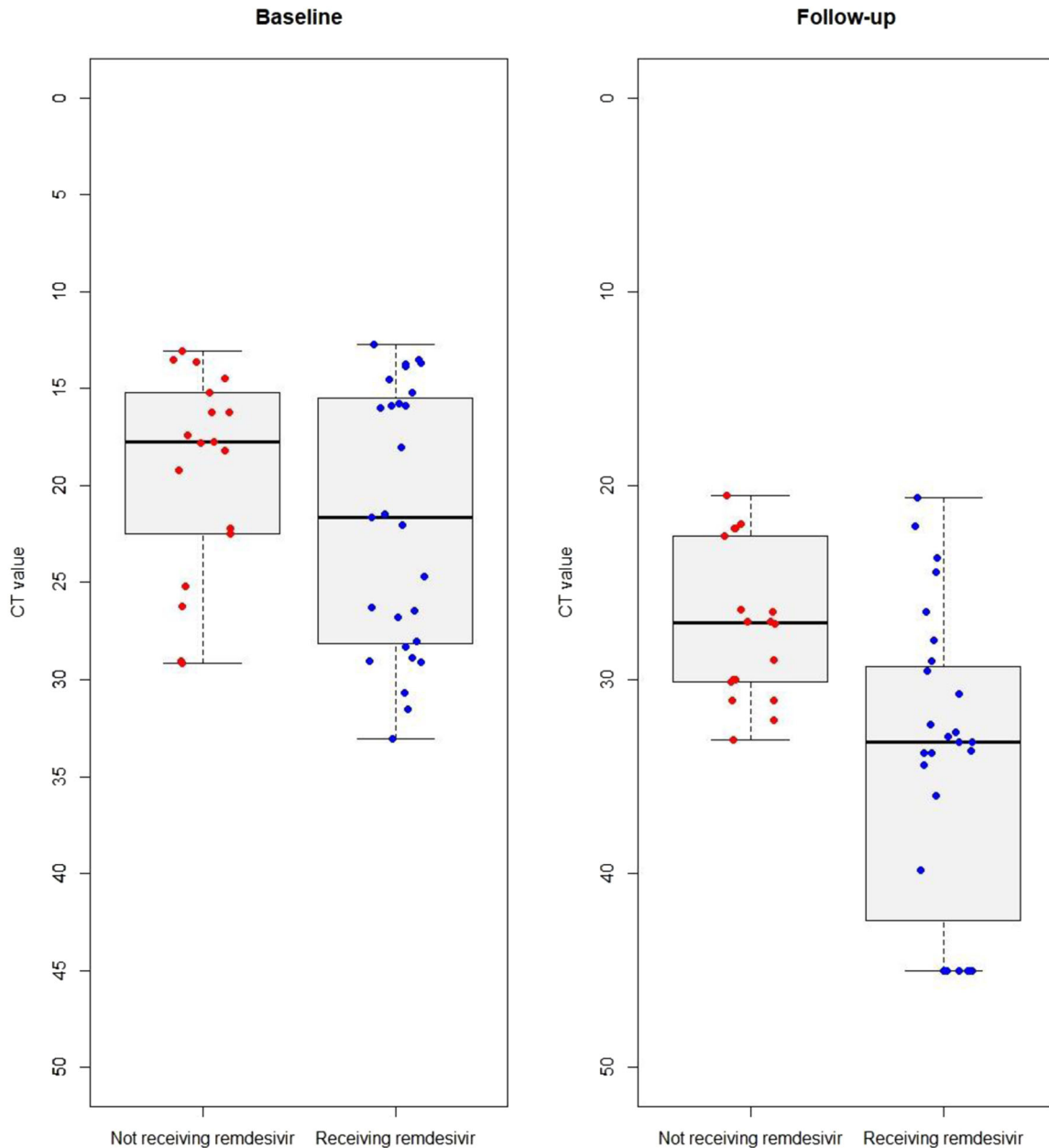Abbreviations: CT: cycle threshold; ICU: intensive care unit.

FIGURE 1 Boxplots and observed individual CT values in patients untreated versus treated with remdesivir at baseline (*p* = 0.348) and at follow-up (*p* < 0.001), separately
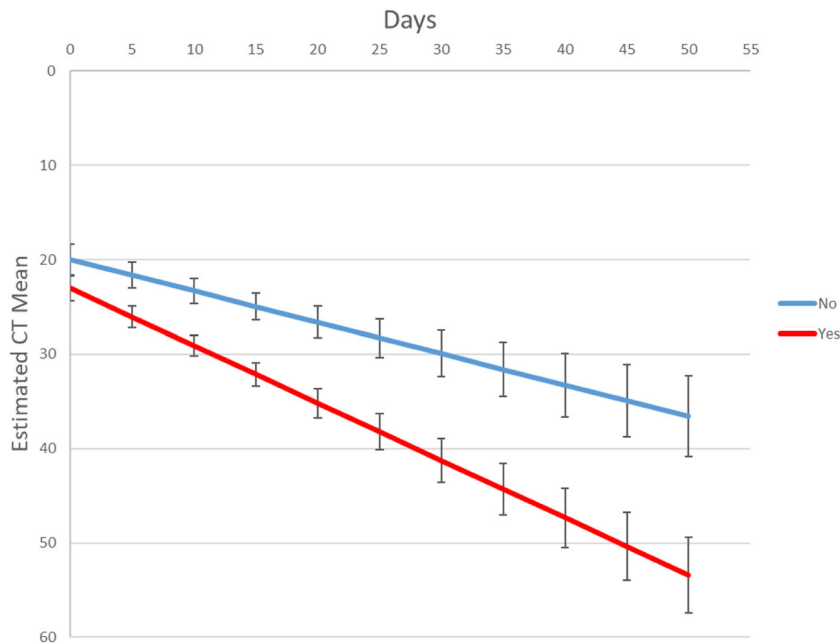
FIGURE 2 Estimated (by longitudinal linear model) CT mean through follow-up for patients receiving (Yes) and not receiving (No) remdesivir (p for heterogeneity = 0.045)

favouring the administration of remdesivir in patients with lower respiratory tract involvement due to COVID-19.[3–6] We did not observe any difference in secondary outcomes between the two groups. However, this probably occurred because the small sample size of the study was underpowered for exploring clinical outcomes.

At present, available data on the effect of remdesivir on in vivo VL are few, often anecdotal, and with contrasting results. The first double-blind RCT evaluating the effectiveness of remdesivir in patients with COVID-19 pneumonia did not show any effect on VL, even if the length of mechanical ventilation was shorter among treated patients.[6] However, the emergency approval of remdesivir for the treatment of COVID-19 was mainly based on clinical outcomes. The first evidence of an increased viral decay in patients treated with remdesivir compared to those nontreated with the drug was showed by Regan and colleagues in a sample of 51 patients, 18 of whom treated with remdesivir.[13] Even Dubert and colleagues published a case series reporting that remdesivir was able to reduce viral load in four out of five treated patients.[16] In addition, a case control study by Joo and colleagues evaluating 86 severe COVID-19 patients (48 receiving remdesivir) showed a faster decrease of VL in treated-patients, as well a reduced length of mechanical ventilation with respect to controls. However, these results did not affect the clinical recovery at 14-days nor at 28-days.[9] On the contrary, Goldberg and colleagues evaluating 142 COVID-19 patients, 29 of them treated with remdesivir, did not find any difference on VL between the two groups.[12] Moreover, a retrospective propensity score matched cohort study evaluating 1699 patients (352 treated with remdesivir) evidenced a significant effect on the reduction of VL, length of hospital stay and death rate.[17] Finally, Barrat and colleagues evaluated 181 patients, 42 of whom treated with remdesivir, compared to 52 treated with hydroxychloroquine and 87 with standard care. No differences in terms of VL decay and mortality rate were found among the three groups.[18]

In our sample, the reduction of VL over time was about doubled in remdesivir-treated patients with respect to nontreated patients despite the concomitant treatment with glucocorticoids (Figure 2). With this regard, it should be underlined that during the first pandemic wave, caution for the administration of corticosteroids in COVID-19 patients has been suggested due to the possible suppression of immune response leading to a potential increase of VL.[19] Our observation confirms the activity of remdesivir in favouring viral elimination even when associated with glucocorticoids. Although our findings support the use of glucocorticoids, at least in patients with need for oxygen supplementation, given their benefit in reducing COVID-19 mortality,[20,21] the design of the study and the sample analysed does not allow us to explore the effect of remdesivir administration on clinical outcome.

The main limitation of the present study is represented by the small sample size. However, selecting patients evaluated by a single analytical method strengthen the results.

There are still open challenges for future studies. First, the optimal timing for remdesivir administration to prevent disease progression and complication is still under evaluation.[1] Moreover, the identification of early predictors for severe disease (i.e., low admission eGFR)[22] could help in the risk stratification to choose the best treatment strategies (i.e., high-dose glucocorticoids treatment or other immunomodulating drugs).[21,23]

AUTHOR CONTRIBUTIONS

Annalucia Biancofiore, Antonio Mirijello, Salvatore De Cosmo, and Renato Lombardi planned the study, wrote and revised the paper. Annalucia Biancofiore and Maria A. Puteo collected data. Maria P. Di Viesti worked on data revision and methodology. Maria Labonia performed microbiological analyses. Massimiliano Copetti analyzed and interpreted data. Authors of the CSS-COVID-19 Group participated in the clinical management of patients. All the authors have approved the final version of the paper, had full access to all the data

in the study, including statistical reports and tables, and can take responsibility for integrity of data and accuracy of data analysis.

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DATA AVAILABILITY STATEMENT

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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