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.

Journal of Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection

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

Letter to the Editor

Remdesivir reduced upper respiratory tract SARS-CoV-2 viral RNA concentration in COVID-19 patients who developed pneumonitis

Dear Editor,

We read with great interest the article by Yoon et al. describing the significant reduction of viable SARS-CoV-2 shedding with remdesivir treatment despite a non-significant reduction in viral load approximated by the cycle threshold value of real-time reverse-transcriptase polymerase chain reaction (RT-PCR).[1] Remdesivir was the earliest antiviral approved by the United States Food and Drug Administration of the treatment of COVID-19. Large scale clinical trials focused mainly on its clinical efficacy[2,3] and mortality.[3,4] Data on the effect of remdesivir on viral load changes is scanty and conflicting.[5–7] Here, we report an observational study on the effectiveness of remdesivir in reducing viral load a in real-world setting.

We performed a single-center prospective observational study between February 4, 2020 and February 22, 2021. Adult patients (age ≥18 years) admitted to Prince of Wales Hospital with laboratory confirmed COVID-19 and pneumonitis as documented by chest X-ray or computed tomography were identified. Patients with at least one respiratory sample collected during the early and late period of illness were included. We collected serial respiratory specimens including combined nasopharyngeal and throat swabs (NPSTS), combined nasopharyngeal aspirate and throat swabs (NPATS), nasopharyngeal swabs (NPS), and self-collected deep throat saliva (DTS) until discharge from hospital. Flocked swabs (FLOQSwabs, Copan, Italy) were used for nasopharyngeal and throat swabs collection. SARS-CoV-2 were detected using two separate RT-PCR platforms targeting different gene regions, and confirmed by the local reference laboratory.[8] The COVID-19 treatment strategy evolved over time and included the use of lopinavir, ribavirin, interferon-beta-1b, and remdesivir. For the purpose of analysis in this study, patients were classified into three different groups according to COVID-19 treatment regimens: (1) Remdesivir group who had received remdesivir as the only anti-COVID treatment, with a sub-group of early remdesivir treatment defined as remdesivir treatment started within 7 days after symptoms onset, (2) Other treatment group included those who had received lopinavir/ritonavir-based therapy, interferon-based therapy, or interferon-based therapy followed by remdesivir therapy, and; (3) No treatment group. Clinical severity was classified as mild (no pneumonitis), moderate (with pneumonitis), severe (required oxygen supplement), and critical (required mechanical ventilation) as previously described.[9] The longitudinal measurements of viral load were compared between treatment groups in a log scale. Univariate analyses were performed with chi-square test or fisher exact test for categorical variables as appropriate. Analysis of variance (ANOVA) was used for comparing the age between groups. *T*-test was used for comparing the change in viral load between treatment groups and adjusted with Benjamini-Hochberg procedure for multiple comparisons.

We recruited 208 patients, 30 (14.4%) received remdesivir alone, 17 of whom received remdesivir within 7 days after symptom onset, 114 (54.8%) received other treatments, and 64 (30.8%) had no specific therapeutic interventions. The mean (±standard deviation [SD]) age of the entire cohort was 55.8 (±16) years, and 92 (44.2%) were male. 138 (66.3%) had moderate, 38 (18.3%) had severe, and 32 (15.4%) had critical disease. Seven patients did not survive the hospital admission with one from remdesivir group, and six from other treatment group. For patients who had received remdesivir treatment, those with moderate severity received remdesivir earlier (mean 6.67, SD: 2.82 days) than those with severe (mean 9.52 SD: 2.96 days) and critical disease (mean 8.94: SD 4.37), respectively ($P < 0.001$ for both comparisons). The duration of remdesivir treatment was significantly longer in patients with critical disease (mean 6.4, SD 2.73 days) as compared to patients with moderate (mean 4.80, SD 2.32 days) and severe disease (mean 4.67, SD 1.85) ($P = 0.013$). A total of 849 samples collected from 208 patients, with a median of 4 (IQR: 2–5) samples from each patient (Fig. S1). The median collection time was 1 (IQR: 1–3) day from admission for baseline samples and 9 (IQR: 6–13) days from admission for follow up samples with no significant difference observed between treatment groups. The baseline viral load for the three treatment groups were not significantly different from each other (Table 1, Fig. 1A). The median log transformed viral load for early remdesivir group dropped from 6.77 copies/ml (IQR 6.28–8.59) at day 2–4, to 6.12 copies/ml (IQR 4.92–7.30) at day 5–7, and to 4.00 copies/ml (IQR 3.21–4.34) at day 8 onwards. We found a significant difference in viral load decrease in early remdesivir group as compared to patients who had received other treatment ($P = 0.029$), but not to patients with no treatment at day 8 onwards (Fig. 1A). A similar result was observed when using day from onset instead of day from admission, though differences were not statistically significant (Fig. 1B). Patients with moderate severity had a significantly faster decrease in viral load from baseline when compared to patients with severe disease ($P = 0.018$) and critical disease ($P = 0.039$) respectively at days 5–7 from admission. The difference remained significant from day 8 onwards for those with severe disease ($P = 0.003$) (Fig. S2).

In this single-center prospective observational study, we found patients receiving early remdesivir monotherapy had a faster reduction in viral load as compared to those receiving other treatment, suggesting remdesivir may be effective in reducing SARS-CoV-2 viral load in upper respiratory tract of COVID-19 patients when prescribed early in the disease course. There are however limitations in our study. Firstly, in this observational study, there could be treatment assignment bias. This is reflected by our find-

https://doi.org/10.1016/j.jinf.2022.08.031

Table 1
Patient characteristics.

	Overall (n = 208)	Remdesivir Group (n = 30)	Other treatment Group (n = 114)	No treatment Group (n = 64)	P value
Age, mean (SD) years	55.8 (16.0)	62.1 (13.3)	59.1 (14.9)	47.0 (15.6)	**<0.001**
Sex					**0.045**
Male	92 (44.2%)	12 (40.0%)	59 (51.8%)	21 (32.8%)	
Female	116 (55.8%)	18 (60.0%)	55 (48.2%)	43 (67.2%)	
Co-morbidities	140 (67.3%)	25 (83.3%)	83 (72.8%)	32 (50.0%)	**<0.001**
Received steroids treatment	66 (31.4%)	14 (46.7%)	50 (43.9%)	2 (3.1%)	<0.001
Log10 viral load on admission, mean (SD) in copies/ml	7.22 (2.17)	8.61 (1.55)	7.26 (2.07)	6.75 (2.40)	0.054
Severity					**<0.001***
Moderate	138 (66.3%)	14 (46.7%)	61 (53.5%)	63 (98.4%)	
Severe	38 (18.3%)	8 (26.7%)	29 (25.4%)	1 (1.6%)	
Critical	32 (15.4%)	8 (26.7%)	24 (21.1%)	0 (0.0%)	
Symptom					
Fever	136 (65.4%)	19 (63.3%)	88 (77.2%)	29 (45.3%)	**<0.001**
Cough	124 (59.6%)	24 (80.0%)	65 (57.0%)	25 (54.7%)	0.060
Sputum	64 (30.8%)	15 (50.0%)	32 (28.1%)	17 (26.6%)	0.055
Diarrhoea	46 (22.1%)	6 (20.0%)	26 (22.8%)	14 (21.9%)	0.940
Sore throat	45 (21.6%)	10 (33.3%)	20 (17.5%)	15 (23.4%)	0.162
Malaise	40 (19.2%)	5 (16.7%)	25 (21.9%)	10 (15.6%)	0.578
Shortness of breath	37 (17.8%)	10 (33.3%)	21 (18.4%)	6 (9.4%)	**0.021**
Myalgia	36 (17.3%)	8 (26.7%)	17 (14.9%)	11 (17.2%)	0.331
Runny nose	35 (16.8%)	4 (13.3%)	17 (14.9%)	14 (21.9%)	0.377
Headache	29 (13.9%)	4 (13.3%)	14 (12.2%)	11 (17.2%)	0.641*
Outcomes					0.261
Discharged	149 (71.6%)	21 (70.0%)	84 (73.7%)	44 (68.9%)	
Death	7 (3.4%)	1 (3.3%)	6 (5.3%)	0 (0.0%)	
Transferred to other hospital for convalescence care	52 (25.0%)	8 (26.7%)	24 (21.1%)	20 (31.2%)	
Sample collection time, mean (SD) days					
Days from admission to first sample collection	1 (1–3)	1 (1–2.75)	1 (1–2)	1 (1–3)	0.819
Days from onset to first sample collection	2 (5–8)	6 (4–8)	4.5 (2–7)	5.5 (3–8.25)	0.65
Days from admission to subsequent samples collection	9 (6–13)	9 (6–13)	9 (6–14)	8.5 (5–12)	0.253
Days from admission to last sample collection	13 (9–17)	13 (10–16.8)	13 (8–17)	12 (9–17)	0.826

Age and timing of sample collection were reported in the format of mean (SD). Hemoptysis (n = 1) and Vomiting (n = 7) were removed from the list because of too few samples. Timing of sample collection was reported in the format of median (IQR). P-values in bold indicate the significant difference among groups. chi-square test was used for proportional variables; ANOVA was used for age.

* Fisher exact test was used.

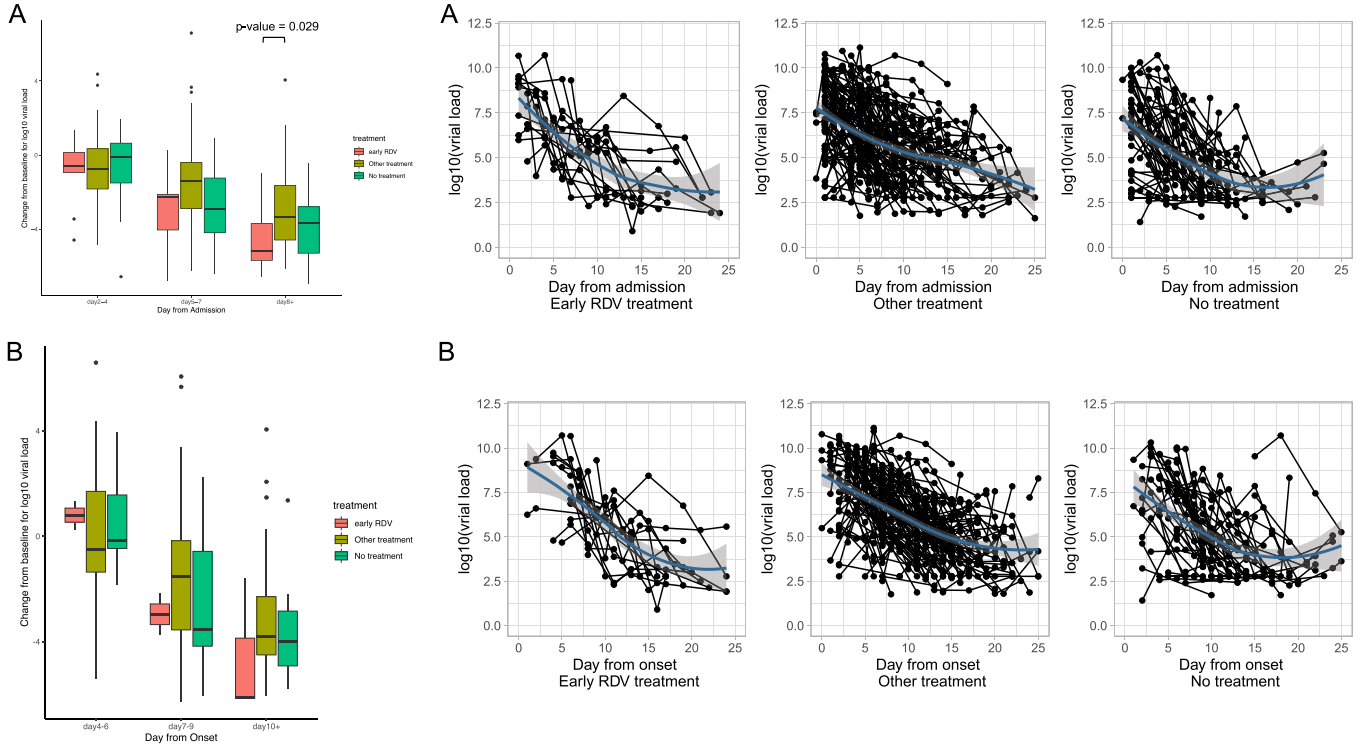

Fig. 1. Comparison of viral load response between treatment groups. (A) Comparison by treatment group and day from admission. Left panel: Box plot for change of log10 viral load (in copies/ml) from baseline to day 2–4, day 5–7, and day >7. t-test was used for comparing of the viral load change between early remdesivir group and other treatment group. Right panel: Change of log10 viral load (in copies/ml) over time. Each black dot represents a single sample. Early RDV, early remdesivir group. Other treatment, other treatment group. No treatment, no treatment group. (B) Comparison by treatment group and day from onset. Left panel: Box plot for change of log10 viral load (in copies/ml) from baseline to day 2–4, day 5–7, and day >7. Right panel: Change of log10 viral load (in copies/ml) over time. Each black dot represents a single sample. Early RDV, early remdesivir group. Other treatment, other treatment group. No treatment, no treatment group.

ings that patients who received no treatment were younger, with less comorbidities, less presented with fever, and with less severe disease. However, the two groups received remdesivir or other treatments were similar and did not differ significantly. Secondly, we could not use the length of hospital stay as a clinical end point, since during the first year of COVID-19 pandemic, hospitalization also served the purpose of isolation. Thirdly, the study spanned over 12-months and the treatment protocol evolved over time as more evidence emerged. In conclusion, we found early treatment with remdesivir for hospitalized patients could accelerate the decline in SARS-CoV-2 viral concentration in upper respiratory tract, supporting further investigations to maximize the clinical benefits of remdesivir administration.

Ethical statement

All patients provided a written consent, and the study was approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. (CREC Ref. No.: 2020.076).

Financial support

The study was supported by the Health and Medical Research Fund - Commissioned Research on the Novel Coronavirus Disease (COVID-19) (reference no. COVID190107 and COVID19F06) from the Food and Health Bureau, Hong Kong SAR Government.

Declaration of Competing Interest

All authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.08.031.

References

[1]. Yoon JG, Yoo JS, Lee J, Hyun HJ, Seong H, Noh JY, et al. Viable SARS-CoV-2 shedding under remdesivir and dexamethasone treatment. *J Infect* 2022;**84**(6):834–72 Jun. doi:10.1016/j.jinf.2022.03.022.
[2]. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. ACTT-1 study group members. remdesivir for the treatment of COVID-19 - final report. *N Engl J Med* 2020;**383**(19):1813–26 Nov 5. doi:10.1056/NEJMoa2007764.
[3]. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. GS-US-540-9012 (PINETREE) investigators. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med* 2022;**386**(4):305–15 Jan 27. doi:10.1056/NEJMoa2116846.
[4]. W.H.O. Solidarity Trial Consortium Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet* 2022;**399**(10339):1941–53 May 21. doi:10.1016/S0140-6736(22)00519-0.
[5]. Joo EJ, Ko JH, Kim SE, Kang SJ, Baek JH, Heo EY, et al. Clinical and virologic effectiveness of remdesivir treatment for severe coronavirus disease 2019 (COVID-19) in Korea: a nationwide multicenter retrospective cohort study. *J Korean Med Sci* 2021;**36**(11):e83 Mar 22. doi:10.3346/jkms.2021.36.e83.
[6]. Goldberg E, Ben Zvi H, Sheena L, Sofer S, Krause I, Sklan EH, et al. A real-life setting evaluation of the effect of remdesivir on viral load in COVID-19 patients admitted to a large tertiary centre in Israel. *Clin Microbiol Infect* 2021;**27**(6):917.e1–917.e4 Jun. doi:10.1016/j.cmi.2021.02.029.
[7]. Biancofiore A, Mirijello A, Puteo MA, Di Viesti MP, Labonia M, Copetti M, et al. CSS-COVID-19 Group. Remdesivir significantly reduces SARS-CoV-2 viral load on nasopharyngeal swabs in hospitalized patients with COVID-19: a retrospective case-control study. *J Med Virol* 2022;**94**(5):2284–9 May. doi:10.1002/jmv.27598.
[8]. Lui G, Ling L, Lai CK, Tso EY, Fung KS, Chan V, et al. Viral dynamics of SARS-CoV-2 across a spectrum of disease severity in COVID-19. *J Infect* 2020;**81**(2):318–56 Aug. doi:10.1016/j.jinf.2020.04.014.
[9]. Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu province: a multicenter descriptive study. *Clin Infect Dis* 2020;**71**(15):706–12 Jul 28. doi:10.1093/cid/ciaa199.

Christopher KC Lai[1]
Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, 1/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, N.T., Shatin, China Hong Kong Special Administrative Region

Grace CY Lui[1]
Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, China Hong Kong Special Administrative Region
Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, China Hong Kong Special Administrative Region

Yuchen Wei[1], Ka Chun Chong
School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, China Hong Kong Special Administrative Region

Zigui Chen
Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, 1/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, N.T., Shatin, China Hong Kong Special Administrative Region

Lowell Ling
Department of Anaesthesia and Intensive Care, Faculty of Medicine of Medicine, The Chinese University of Hong Kong, China Hong Kong Special Administrative Region

Rita WY Ng, Siaw SS Boon, Wendy CS Ho, Apple CM Yeung
Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, 1/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, N.T., Shatin, China Hong Kong Special Administrative Region

David SC Hui
Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, China Hong Kong Special Administrative Region
Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, China Hong Kong Special Administrative Region

Paul KS Chan*
Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, 1/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, N.T., Shatin, China Hong Kong Special Administrative Region
Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, China Hong Kong Special Administrative Region

*Corresponding author at: Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, 1/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, N.T., Shatin, China Hong Kong Special Administrative Region.
E-mail address: paulkschan@cuhk.edu.hk (P.K. Chan)
[1] These author contributed equally to this work.