IDCases 29 (2022) e01572

Contents lists available at ScienceDirect

IDCases

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

Case report

A case report on the association between QTc prolongation and remdesivir therapy in a critically ill patient

Shmeylan Al Harbi [a,b,c], Mashael AlFaifi [a,d], Hasan M. Al-Dorzi [b,e,f], Ohoud Aljuhani [g], Abeer A. Alenazi [i], Mai Alalawi [j], Khalid Al Sulaiman [a,b,c,h,*]

[a] College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[b] King Abdullah International Medical Research Center-King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[c] Pharmaceutical Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia
[d] Pharmaceutical Services Administration, King Saud Medical City, Riyadh. Saudi Arabia
[e] College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[f] Intensive Care Department, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[g] Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
[h] Saudi Critical Care Pharmacy Research (SCAPE) Platform, Riyadh, Saudi Arabia
[i] Pharmaceutical Care Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia
[j] Department of Pharmaceutical Sciences, Fakeeh College for Medical Sciences, Jeddah, Saudi Arabia

ARTICLE INFO

Keywords:
Remdesivir
QTc prolongation
Coronavirus disease 2019 (Covid-19)

ABSTRACT

Remdesivir is a direct-acting inhibitor of SARS-CoV-2 RNA-dependent RNA polymerase that is used to treat severe COVID-19 infections. We report a patient with severe COVID-19 pneumonia who experienced palpitations and syncope two days after starting remdesivir therapy. The QTc interval was prolonged on the Electrocardiogram (ECG) without any significant electrolyte abnormalities or concomitant use of medications with QTc prolongation. Although the cardiac side effects of remdesivir therapy have been well documented, the link between remdesivir therapy and QTc interval prolongation in patients with severe COVID-19 has only been observed in a few cases. Because this arrhythmia has the potential to result in sudden cardiac death, practitioners should be aware of the QTc interval prolongation associated with remdesivir therapy.

Introduction

Remdesivir is a direct-acting 1′-cyano-substituted adenosine nucleotide analog prodrug that inhibits viral RNA polymerase in primary human airway epithelial cells as nanomolar activity [1]. This strategy has also been proposed for COVID-19 and in vitro, shown potency against the Middle East respiratory syndrome (MERS-CoV) and SARS-CoV-2 [1,2]. A phase 3 trial of remdesivir showed that the treatment course of both ten days and five days shortened the recovery time and reduced mortality, and the need for mechanical ventilation in hospitalized patients with severe COVID-19 [3]. A recently published trial reported that patients at risk for COVID-19 who were not hospitalized had an 87 % lower risk of hospitalization or death than placebo when treated with a 3-day regimen of remdesivir [4].

IInfusion site reactions, skin rashes, diarrhea, and reversible elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are among remdesivir most frequent side effects [5]. There is little research on remdesivir's adverse cardiac consequences [5]. We describe a case of severe COVID-19 who had QTc prolongation during remdesivir treatment, which resolved after completthe course of therapy.

Case report

An 80-year-old Saudi female presented to the Emergency Department (ED) with dyspnea, and cough. Her medical comorbidities included obesity (body mass index = 36 kg/m^2), diabetes mellitus, dyslipidemia, hypertension, ischemic heart disease post percutaneous coronary intervention 2014, chronic kidney disease (CKD), old stroke, asthma, hypothyroidism, and osteoarthritis.

* Corresponding author at: King Abdulaziz Medical City (KAMC) - Ministry of National Guard Health Affairs (MNGHA), King Abdullah International Medical Research Center/King Saud bin Abdulaziz University for Health Sciences, PO Box 22490, 11426 Riyadh, Saudi Arabia.
E-mail address: alsulaimankh@hotmail.com (K.A. Sulaiman).

https://doi.org/10.1016/j.idcr.2022.e01572
Received 24 May 2022; Received in revised form 1 July 2022; Accepted 11 July 2022
Available online 15 July 2022

Upon initial evaluation, she was hypoxic and had a temperature of 36.4 °C, a heart rate of 102 BPM, blood pressure of 106/58 mmHg, and respiratory rate of 31 breaths/min. Admission blood work showed elevated levels of C-Reactive Protein (108 mg/L; normal reference: 0–9 mg/L), procalcitonin (0.56 ng/ml; normal reference: 0–0.08 ng/ml) and D-dimer (3.87 ug/ml; normal reference: 0.27–0.5 ug/ml). The patient also had signs of acute kidney injury on top of CKD with creatinine 323 μmol/L (normal reference: 50–98 μmol/L), and blood urea nitrogen (BUN) 26.4 mmol/L (normal reference: 3.5–7.2 mmol/L). Electrolytes were within normal range except for potassium (5.9 mmol/L; normal reference: 3.5–5.1 mmol/L). In addition, her liver function tests were within normal limits.

On the first day of hospitalization, a chest X-ray revealed bilateral patchy airspace opacities that were mostly peripheral with blunting of the costo-phrenic angles (Fig. 1). On admission, the ECG indicated atrial fibrillation with QT/QTc intervals of 352/454 msec (Fig. 2), calculated based on Bazett's formula. Ejection fraction higher than 55 %, moderate tricuspid valve regurgitation, right ventricular systolic pressure greater than 60 mmHg, and moderate atherosclerotic plaque in the aortic arch were all found on an echocardiogram. The polymerase chain reaction test was positive for SARS-CoV-2 on a nasal swab.

She was admitted to the intensive care unit (ICU) and received non-invasive ventilation alternating with a high flow nasal oxygen to maintain her saturation over 92 %. She was treated with anti-hyperkalemic agents, intravenous (IV) furosemide, azithromycin 500 mg IV for 3 days, meropenem 500 mg IV every 12 h, dexamethasone 6 mg IV per day and tocilizumab 656 mg (8 mg/kg) once as intravenous infusion. Intravenous heparin infusion was given for the newly diagnosed atrial fibrillation. As the patient continued to require a high fraction of inspirated oxygen ($\geq$ 0.6), had worsening bilateral airspace opacities on Chest X-ray report, and the kidney function improved with GFR 38.07 ml/min/1.73 m^2 compared with baseline, remdesivir therapy was provided for five days. The patient experienced palpitations and dizziness leading to syncope two days after starting remdesivir therapy, but no hemodynamic instability. The electrocardiogram showed QTc prolongation (QT/QTc = 504/532 msec) as shown in Fig. 3. There were no significant concomitant serum electrolyte abnormalities (Table 1). Continuous monitoring of QT/QTc interval was performed with daily electrocardiograms, which showed no worsening of the QT prolongation. After the five-day course of remdesivir therapy, her QTc interval decreased to 429 msec (Fig. 4, Table 1). The patient eventually improved and was discharged home in good condition.

Discussion

A patient with severe COVID-19 developed QTc interval prolongation two days after starting remdesivir therapy for no apparent cause, according to our observation. In this patient, remdesivir exposure could have been a direct cause of QT interval prolongation. To the best of our knowledge, this is a rare occurrence.

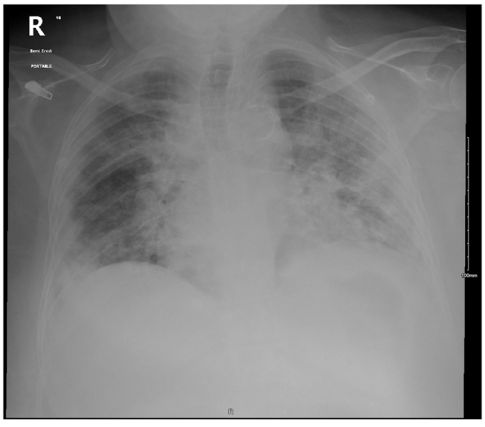

Fig. 1. Chest X-ray (during admission). There were bilateral patchy airspace opacities that were predominantly peripheral, with blunting of the CP angles.

Remdesivir is an adenosine analog with significant cardiovascular effects. Adenosine is a potent vasodilator that causes compensatory catecholamine release, shortening the atrial action potential and causing cardiac arrhythmia. Remdesivir, via binding to human mitochondrial RNA polymerase, can cause substantial cytotoxicity in cardiomyocytes. This could explain the related cardiovascular side effects, such as the QTc interval prolongation seen in our case report [5].

In a prospective cohort study of 2403 patients with COVID-19 admitted to 13 hospitals, 11.2 %, and 17.6 % had QTc $\geq$ 500 msec and ΔQTc $\geq$ 60 msec, respectively [6]. The study suggested that the risk of critical QTc prolongation and Torsades de pointes increased due to treatment with lopinavir/ritonavir, atazanavir/ritonavir, oseltamivir, favipiravir, and remdesivir alone or in combination with azithromycin [6]. Another article described two cases of bradycardia during treatment with remdesivir for COVID-19 [7]. The first patient had bradycardia with a heart rate of 40–50 beats/min and a prolonged QTc interval of 555 msec on the third day of treatment. The heart rate and QT interval returned to baseline in three days after discontinuation of remdesivir [7]. The second patient developed sinus bradycardia with a heart rate dropping from 80 bpm to 48 bpm on the third day of remdesivir treatment. The heart rate returned to baseline two days later after remdesivir was discontinued [7]. Remdesivir has been associated with atrial fibrillation [5]. However, our patient had atrial fibrillation before starting remdesivir. The QT interval varies from beat to beat during atrial fibrillation, with no consensus on how to measure QTc interval. Some clinicians suggest averaging the measured QT interval over 10 beats. Others suggest to measure the QT intervals that come after the shortest and longest R-R intervals and divide each by the square root of the R-R interval preceding it. The average of these intervals would be the QTc interval [8].

Prolongation of QT interval, which represents prolonged ventricular repolarization, can predispose to Torsade de Pointes, malignant arrhythmias, and cardiac arrest. Hence, vigilance is needed during remdesivir treatment, especially in patients at risk. A prolonged QTc interval represents 27 % of patients and was associated with older age, comorbidities, specifically hypertension, diabetes mellitus, ischemic heart disease, and elevated troponin and D-dimer concentrations [9]. Apart from medications used for COVID-19, the viral infection itself due to an interaction of SARS-CoV-2 with the renin–aldosterone system, leads to the development of hypokalemia and other electrolyte abnormalities, such as hypomagnesemia and hypocalcemia, which might lead to QTc interval prolongation and arrhythmias [10,11]. Furthermore, moderate to severe COVID-19 infection cases develop a multi-system inflammatory response responsible for the incidence of hypoxemia, myocardial injury, and myocarditis, as well as elevated troponin concentrations and prolonged QTc interval [12,13]. Appropriate caution and continuous ECG monitoring should be utilized in all patients as the safety of remdesivir remains uncertain. Even closer surveillance for patients with pre-existing heart disease is warranted when using remdesivir. This supports the need for better powered and more high-quality studies [14–16].

Conclusions

We describe a case of QT interval prolongation following the initiation of remdesivir therapy that reversed after finishing the treatment course. Continuous monitoring may be needed especially in high-risk patients. This possible adverse effect needs further evaluation in randomized controlled trials or observational cohorts studies.

CRediT authorship contribution statement

All authors contributed to data collections, analysis, drafted, revised,

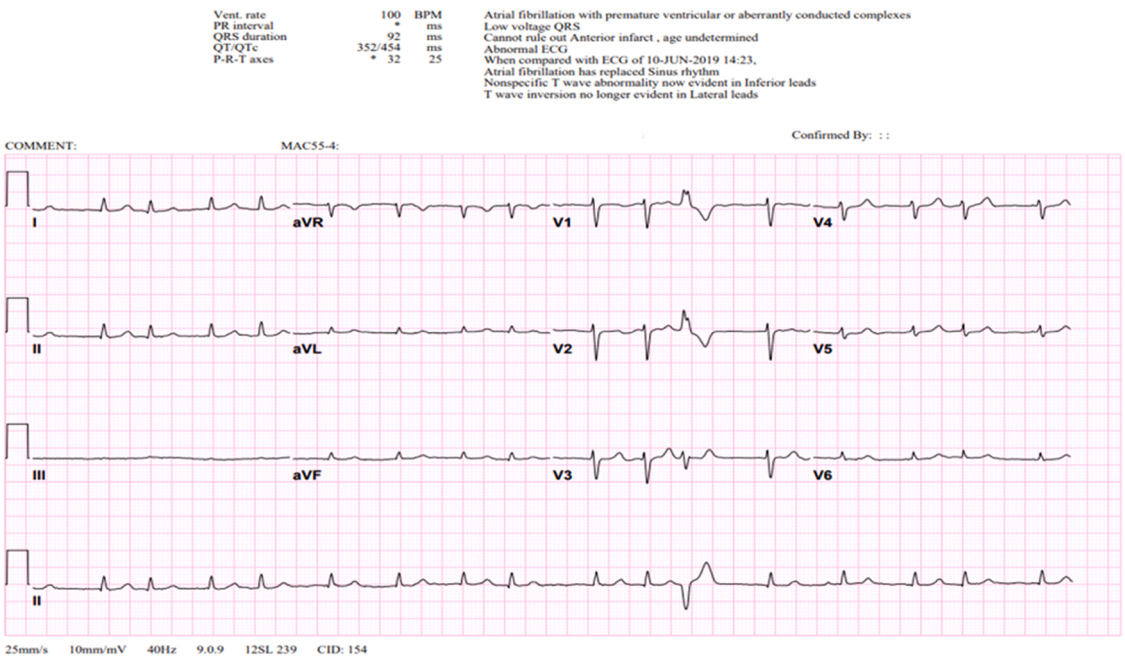

Fig. 2. Electrocardiogram (Day1).

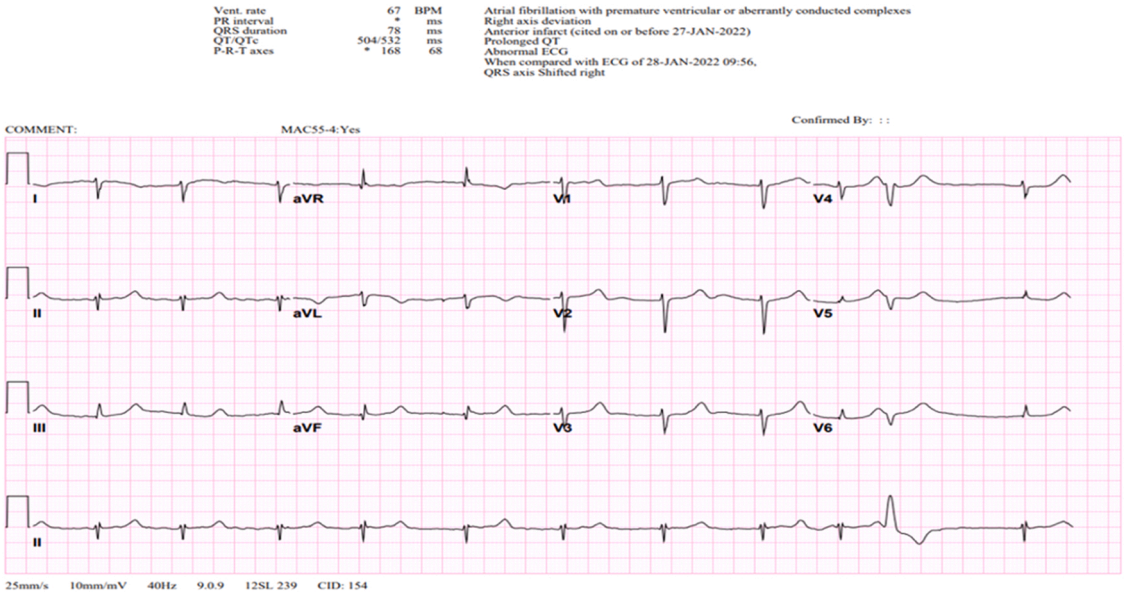

Fig. 3. Electrocardiogram (Day 7).

and approved the manuscript's final version. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Funding

None.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia (Reference No. RC22R/211/04). Throughout the study, participants' confidentiality was rigorously preserved by utilizing an anonymous unique serial number for each individual and confining data to just the investigators.

Consent

Informed consent was not required due to the research method, which followed the policies of the governmental and local research institutes.

Table 1
Electrolytes and QTc interval.

Day	QTc interval	Potassium normal reference: 3.5-5.1 mmol/L	Magnesium normal reference: 0.66-1.07 mmol/L	GFR ml/min/1.73 m2
Day 2	454 ms	5.9	0.95	11.43
Day 3		5.1	1.17	13.30
Day 4		4.4	1.07	18.77
Day 5		4	1.03	38.07
Day 6		4.8	0.95	32
Day 7	532 ms	4.1	1.15	31.22
Day 8		4.4	1.13	32.24
Day 9		3.9	0.97	31
Day 10		4.7	0.87	31.68
Day 11		4.2	0.82	38
Day 12	429 ms	4.4	1.03	33.82

Shaded rows represent the days when remdesivir was given.

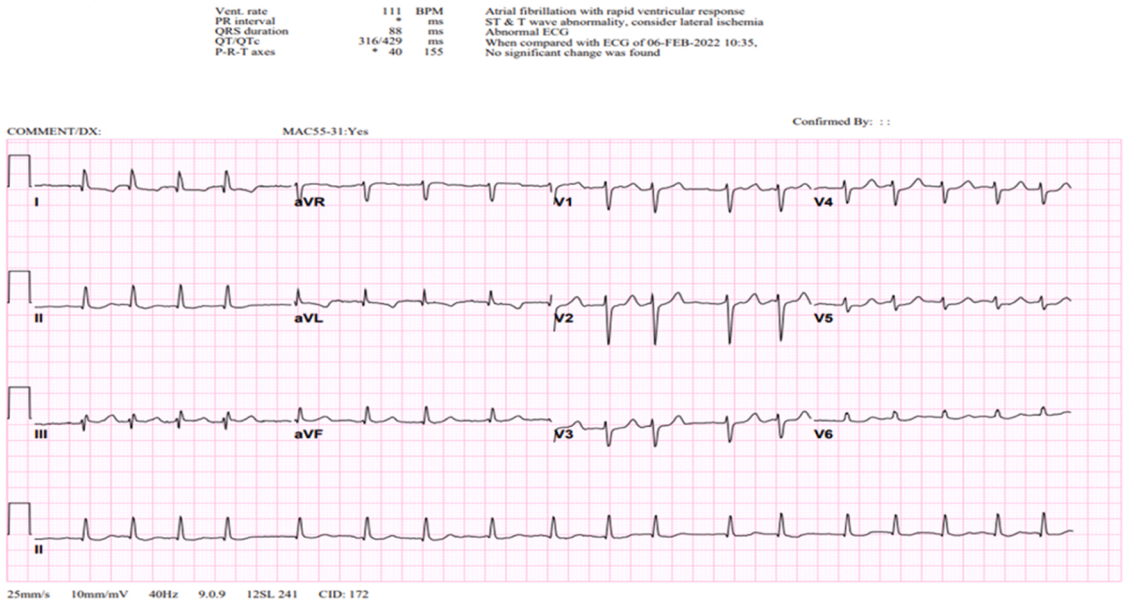

Fig. 4. Electrocardiogram (Day 12).

Conflict of interest

No author has a conflict of interest in this study.

Acknowledgments

We would like to acknowledge all the investigators in the Saudi critical care pharmacy research (SCAPE) platform who participated in this project.

References

[1] Kaka AS, MacDonald R, Greer N, Vela K, Duan-Porter W, Obley A, et al. Major update: remdesivir for adults with COVID-19: a living systematic review and meta-analysis for the American College of Physicians practice points. Ann Intern Med 2021;174:663–72.
[2] Aggarwal G, Henry BM, Aggarwal S, Bangalore S. Cardiovascular safety of potential drugs for the treatment of Coronavirus disease 2019. Am J Cardiol 2020; 128:147–50. https://doi.org/10.1016/j.amjcard.2020.04.054.
[3] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - Final Report. N Engl J Med 2020;383 (19):1813–26. https://doi.org/10.1056/NEJMoa2007764.

[4] Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med 2022;386(4):305–15.
[5] Nabati M, Parsaee H. Potential cardiotoxic effects of remdesivir on cardiovascular system: a literature review. Cardiovasc Toxicol 2021:1–5.
[6] Haghjoo M, Golipra R, Kheirkhah J, Golabchi A, Shahabi J, Oni-Heris S, et al. Effect of COVID-19 medications on corrected QT interval and induction of torsade de pointes: Results of a multicenter national survey. Int J Clin Pract 2021;75:e14182.
[7] Gupta AK, Parker BM, Priyadarshi V, Parker J. Cardiac adverse events with remdesivir in COVID-19 infection. Cureus 2020;12.
[8] Dash A, Torado C, Paw N, Fan D, Pezeshkian N, Srivatsa U. QT correction in atrial fibrillation - measurement revisited. J Electrocardiol 2019;56:70–6. https://doi.org/10.1016/j.jelectrocard.2019.06.009.
[9] Mohamed Ali S, Musa A, Omar Muhammed K, Javed S, Al Raqabani M, Adnan Baradie B, et al. Prolonged corrected QT interval in hospitalized patients with coronavirus disease 2019 in Dubai, United Arab Emirates: a single-center, retrospective study. J Int Med Res.. 2021. https://doi.org/10.1177/03000605211056834.
[10] Sandhu AT, Kohsaka S, Lin S, Woo CY, Goldstein MK, Heidenreich PA. Renin-angiotensin-aldosterone system inhibitors and SARS-CoV-2 infection: an analysis from the veteran's affairs healthcare system: Sandhu. ACEI, ARB, and association with COVID. Am Heart J 2021;240:46–57. doi:10.1016/j.ahj.2021.06.004.
[11] Henry BM, Benoit JL, Rose J, de Oliveira MHS, Lippi G, Benoit SW. Serum ACE activity and plasma ACE concentration in patients with SARS-CoV-2 infection. Scand J Clin Lab Invest 2021;81:272–5. https://doi.org/10.1080/00365513.2021.1926536.
[12] McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the inflammatory response to severe COVID-19 illness. Am J Respir Crit Care Med 2020;202:812–21. https://doi.org/10.1164/rccm.202005-1583oc.
[13] Maeda T, Obata R, Rizk D, Kuno T. Cardiac injury and outcomes of patients with COVID-19 in New York city. Heart Lung Circ 2021;30:848–53. https://doi.org/10.1016/j.hlc.2020.10.025.
[14] ClinicalTrials.gov [Internet]. Daewoong Pharmaceutical Co. LTD.: National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT04713176, Efficacy and Safety of DWJ1248 With Remdesivir in Severe COVID-19 Patients; 2021 January 19 [cited 2022 May 22]; [about 4 screens]. Available from: ⟨https://clinicaltrials.gov/ct2/show/study/NCT04713176⟩.
[15] ClinicalTrials.gov [Internet]. Gilead Sciences: National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT04292899, Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19); 2020 March 3 [cited 2022 May 22]; [about 4 screens]. Available from: ⟨https://clinicaltrials.gov/ct2/show/record/NCT04292899⟩.
[16] ClinicalTrials.gov [Internet]. Fadoi Foundation: National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT05239988, Observational Study in COVID-19 Patients Treated With Remdesivir (RECOVER); 2022 February 15 [cited 2022 May 22]; [about 4 screens]. Available from: ⟨https://clinicaltrials.gov/ct2/show/NCT05239988⟩.