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LETTER TO THE EDITOR

Plasma concentrations of remdesivir metabolite in a critical COVID-19 patient needing continuous venovenous haemodialysis

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Remdesivir is the first small molecule against SARS-CoV-2 approved for use in hospitalized patients with coronavirus disease 2019 (COVID-19) [1]. Pharmacokinetic (PK) data have demonstrated that the remdesivir main metabolite (GS-441524) is predominantly eliminated renally [2, 3]. Actually, remdesivir is not recommended in adults with an estimated glomerular filtration rate (eGFR) less than 30 mL/min [2]. The evaluation of the safety and efficacy of remdesivir treatment for patients with COVID-19 kidney impairment and/or on haemodialysis is an important clinical need given that these patients are at higher risk of mortality [4].

We describe the concentrations of remdesivir and GS-441524 in a COVID-19 patient affected by type 2 diabetes mellitus and chronic kidney disease (CKD) during cycles of continuous renal replacement therapy (CRRT) with continuous venovenous haemodialysis (CVVHD).

A 59-year-old female patient was on treatment with lopinavir/ritonavir and dexamethasone. She received two cycles of tocilizumab and was on helmet continuous positive airway pressure (clinical data are available as Supplementary Information). In June 2020, the clinical condition rapidly deteriorated, and she was transferred to the intensive care unit (ICU) of the Spallanzani National Institute for Infectious Disease. Here, she became anuric and started CRRT with CVVHD (information on CVVHD equipment and flow used is available in Supplementary Information). Two weeks after admission to the ICU, remdesivir was started with intravenous (IV) infusion of 200 mg (day 1). Subsequently, on days 2, 4, 7, 9, 13, 16, 21, 24, and 27, remdesivir 100 mg was administered in 1-h IV infusions (for a total of 10 doses) [2, 3]. During the same period (from day 3 to day 27), the patient received CVVHD cycles (day 3, 5, 8, 10, 14, 18, 22, 25) with duration ranging between 24 and 48 h based on both eGFR and hemodynamic stability.

To evaluate the impact of CVVHD on drug plasma concentration, remdesivir and GS-441524 were measured using a validated ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) method [5]. PK samples were collected 24 h after remdesivir IV infusion ($C_{pre\text{-}CVVHD}$) and after CVVHD sessions ($C_{post\text{-}CVVHD}$).

As expected, remdesivir was undetectable in all plasma samples evaluated (<1.96 ng/mL) [3, 6]. The values of GS-441524 plasma concentration were analysed and are shown in Fig. 1. Twenty-four hours after the second dose (day 3), $C_{pre\text{-}CVVHD}$ GS-441524 was 420 ng/mL, about sixfold higher than the mean C24-h post-dose (C_{24}) GS-441524 reported by Gilead after multiple 100-mg IV administration of remdesivir in healthy donors (mean = 69.2 ng/mL, CV = 18.2), and even higher than in COVID-19 patients with normal kidney function [3, 6].

After 24 h of CVVHD (day 4), $C_{post\text{-}CVVHD}$ of GS-441524 was 194 ng/mL, a 54% decrease. A decrease in the remdesivir metabolite of 50–54% and 70–75% was observed after CVVHD cycles of 24 or 48 h, respectively. Of note, the $C_{post\text{-}CVVHD}$ GS-441524 values were

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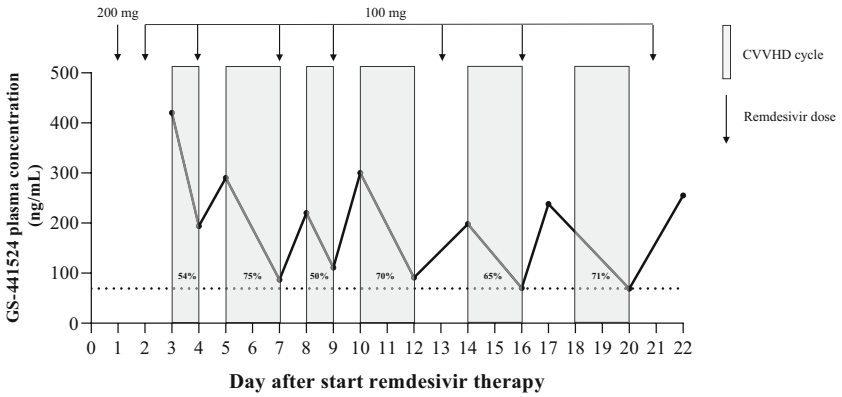

Fig. 1 Plasma concentrations of main remdesivir metabolite (GS-441524) 24 h after intravenous remdesivir therapy in a critically ill patient undergoing CVVHD cycles. Remdesivir IV infusions (arrows) were performed after each single CVVHD session (grey boxes). Each box shows the GS-441524 decrease. Dashed line represents the mean C_{24} of GS-441524 found in healthy adult subjects [3]

similar to C_{24} drug levels reported in healthy adults [3]. During remdesivir treatment, no signs of any drug-related toxicity were reported (biochemical parameters are available as Supplementary Information). One day after treatment completion, SARS-CoV-2 RNA was cleared in bronchoalveolar washing. In contrast, the nasopharyngeal swab was persistently positive. Six days later, the patient died from sepsis associated with pulmonary aspergillosis.

Patients with comorbidities resulting in low eGFR are also at higher risk for severe COVID-19, and thus adequate and safe antiviral prescription in this population is of major concern [4]. Recent PK reports have described the safety of remdesivir treatment during haemodialysis in SARS-CoV-2-positive patients [7–9].

In our COVID-19 patient, long CVVHD sessions (24–48 h) were able to maintain remdesivir metabolite plasma concentrations similar to C_{24} found in subjects without kidney dysfunction. Further evaluations of intracellular remdesivir active metabolite can be helpful in better defining the PK in CKD patients. Clinical studies on a wider population are needed to define the protocol in critically ill COVID-19 patients experiencing end-organ failure.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-021-03128-7.

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Availability of data and material All data are available in the text and in the supplementary materials.

Declarations

Ethics approval The study was conducted in accordance with the Declaration of Helsinki as well as with national and institutional standards. The study was approved by the Local Ethical Committee (approval 9/2020).

Consent to participate Informed consent was obtained.

Conflicts of interest/competing interests The authors declare no conflict of interest.

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