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SHORT REPORT

Real-life study on the pharmacokinetic of remdesivir in ICU patients admitted for severe COVID-19 pneumonia

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Remdesivir is one of the most encouraging treatments against SARS-CoV-2 infection. After intravenous infusion, RDV is rapidly metabolized ($t_{1/2}$ = 1 h) within the cells to its active adenosine triphosphate analogue form (GS-443902) and then it can be found in plasma in its nucleoside analogue form (GS-441524). In this real-life study, we describe the remdesivir and GS-441524 concentrations at three time points in nine ICU patients, through a validated ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) method. The observed data confirmed the very rapid conversion of RDV to its metabolite and the quite long half-life of GS-441524. The mean C_{min}, C_{max} and AUC_{0-24}, were < 0.24 ng/mL and 122.3 ng/mL, 2637.3 ng/mL and 157.8 ng/mL, and 5171.2 ng*h/mL and 3676.5 ng*h/ml, respectively, for RDV and GS-441524. Three out of nine patients achieved a C_{max} > 2610 ng/mL and 140 ng/mL and AUC_{0-24} > 1560 ng*h/mL and 2230 ng*h/mL for RDV and GS-441524, respectively. The mean $t_{1/2}$ value for GS-441524 was 26.3 h. Despite the low number of patients, these data can represent an interesting preliminary report on the variability of RDV and GS-441524 concentrations in a real-life ICU setting.

KEYWORDS
COVID-19, ICU, pharmacokinetics, pneumonia, remdesivir, SARS-CoV-2

1 | BACKGROUND

Since the first cases were reported in December 2019, infection with the severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic.[1] The symptoms of SARS-CoV-2 infection vary widely, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome and, in some cases, requiring veno-venous extra corporeal membrane oxygenation (V-V-ECMO).[2,3]

In the absence of a proven effective therapy, current management consists of supportive care, and many patients have received off-label or compassionate-use therapies, including antivirals such as remdesivir (RDV), steroids or tocilizumab with inconclusive results.[4–6]

RDV is a prodrug of a nucleotide analogue (GS-441524) that is metabolized within the cells to an analogue of adenosine triphosphate (GS-443902), which inhibits viral RNA polymerases. RDV has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle

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The authors confirm that the Principal Investigator for this paper is Prof F.G. De Rosa, MD and that he had direct clinical responsibility for patients.

East respiratory syndrome coronavirus [MERS-CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses.[7,8] In vitro testing has also shown that RDV has activity against SARS-CoV-2 and data from the literature described the possible benefits of early initiation of RDV, especially within 10 days from clinical symptom onset, in terms of shorter time to recovery, along with low risk of side effects or adverse events compared to placebo or comparators.[9,10] Despite controversial data on the efficacy of RDV in the context of COVID-19 infection, RDV remains one of the main promising compounds in the setting of viral infections such as Ebola, Marburg or Mers-CoV viruses.[11,12]

RDV and GS-441524 PK parameters in plasma have been evaluated in single and multiple-dose studies in healthy human adult volunteers, showing a C_{max} of 2610 ng/mL and 140 ng/mL and AUC value of 1560 ng*h/mL and 2230 ng*h/mL for RDV and GS, respectively.[13]

Concerning its metabolism, Warren et al. demonstrated that, upon IV administration of a 10 mg/kg dose in rhesus monkeys, RDV exhibited a short plasma half-life ($t_{1/2} = 0.39$ h) with rapid systemic elimination followed by the appearance of transient systemic levels of a key intracellular intermediate alanine metabolite and more persistent levels of GS-441524 (which reaches the steady-state after 4 days with a once-daily administration).[14]

However, information about RDV pharmacokinetics (PK) in clinical practice is inadequate so far and no therapeutic or toxic ranges have been reported. In this report, we describe the pharmacokinetics of RDV and GS-441524 in a cohort of ICU patients hospitalized for severe COVID-19 pneumonia.

What is already known about this subject

- Remdesivir is a phosphoramidate prodrug of the cyano-derived adenosine analogue GS-441524 and is currently the only licensed antiviral agent for treatment of SARS-CoV-2.
- After intravenous infusion, RDV is rapidly metabolized ($t_{1/2} = 1$ h) within the cells to its active adenosine triphosphate analogue form (GS-443902) and, then, it can be found in plasma in its nucleoside analogue form (GS-441524).
- Although some PK data derived from studies in healthy volunteers are available in the literature, no PK data are available about the kinetics of this drug in intensive care units.

What this study adds

- This is a real-life study on the pharmacokinetics of remdesivir used to treat critically ill patients admitted to intensive care unit for severe COVID-19 pneumonia.
- Pharmacokinetics data of remdesivir in clinical practice will help to optimize treatment in COVID-19 patients, for which treatment options are scant and still under debate.

2 | METHODS

2.1 | Patients

We included all ICU patients admitted to 'Città della Salute e della Scienza' Hospital in Turin (Italy) with acute respiratory distress syndrome (ARDS) due to SARS-CoV-2 and treated with RDV as compassionate use protocol. This hospital was in charge of the management of severe respiratory failure in the Piedmont Region of Italy and was the ECMO referral regional centre. All patients were tested positive for SARS-CoV-2 by real-time PCR on respiratory samples and transferred from peripheral hospital to our referral ICU centre.

Patients were eligible to receive compassionate RDV administration if they were a male or non-pregnant female aged ≥18 years, had SARS-CoV-2 infection confirmed by a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test of a respiratory tract sample and pneumonia confirmed by a chest X-ray or computed tomography (CT) scan, and were mechanically ventilated (i.e., intubated or tracheostomy). Patients were excluded if their alanine or aspartate aminotransferase level was more than five times the upper limit of the normal range and creatinine clearance was <30 mL/min.

Urgent approval for each eligible patient was obtained by our Ethics Committee and sent to Gilead together with the patient's clinical history. Written informed consent was obtained from all of the patients except those who were undergoing invasive mechanical ventilation, for whom the principle of urgency was applied. This study was approved by the Local Ethical Committee, compassionate use program (PROT.N. 0040388 23/04/2020). Principal investigator of the study was Prof. F.G. De Rosa, Chief of Infectious Diseases at AOU Città della Salute e della Scienza, Molinette Hospital, Turin, Italy.

In approved cases, the planned treatment was a 10-day course of RDV, consisting of a loading dose of 200 mg intravenously on Day 1, plus 100 mg daily for the following 9 days. Supportive therapy was to be provided at the discretion of the clinicians, according to clinical and routine laboratory tests. Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) mean score at ICU admission were calculated for all patients.

Information regarding demographics and clinical characteristics were collected for each patient, including days of hospitalization, length of stay in the unit and ICU mortality.

2.2 | Pharmacokinetic analysis

Plasma RDV and GS-441524 concentrations were determined at steady state 4 days after the beginning of therapy. The eligible time points for blood sampling were at the end of infusion, after 15 hours and before the next infusion (24 h). The C_{min} corresponds to concentration before administration (T_{24h}) and the C_{max} was considered as the concentration at the end of the infusion. Pharmacokinetic parameters were calculated using Phoenix WinNonlin software (ver. 8.1, Certara, NJ, USA). Due to the impossibility to perform intensive PK sampling on critical patients, the estimation of elimination $t_{1/2}$ for GS-441524 was based on two points (period between 15 and 24 h), assuming a constant $t_{1/2}$ at this late elimination timing, as reported in previous works.[13–15]

Blood samples were collected before the infusion, at the end of the infusion (1 h) and 15 hours after intravenous drug administration. Blood samples were collected in lithium heparin tubes (7 mL) and plasma was obtained by centrifugation at 1400*g* for 10 minutes at 4°C (ALC PK 130R refrigerated centrifuge; DJB Labcare Ltd., Newport Pagnell, UK). RDV and GS-441524 quantification was performed through a validated ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) method.[16] Limits of detection (LOD) were 0.24 ng/mL for RDV and 0.48 ng/mL for GS-441524, while the lower limit of quantification (LLOQ) was 0.98 ng/mL for both compounds.

The method was validated following Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines, showing contained bias and coefficients of variation (all <15% for both RDV and GS-441524) and good linearity (linear R^2 > 0.996).[13–15]

3 | RESULTS

Nine patients were enrolled in the study. The main clinical characteristics are described in Table 1. The majority of patients were male (6; 67%) with a median age of 56 years (SD ± 7.3). Patients had few comorbidities, mostly obesity, with a mean BMI of 30 (SD ± 5) and hypertension. SOFA, SAPS and APACHE II mean score at ICU admission were respectively: 8, 56 and 22, while mean MuLBSTA (multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age) score was 9. All patients were admitted to ICU due to ARDS caused by COVID-19 and were mechanically ventilated. Five out of nine patients were treated with V-V ECMO support.

RDV was administered after a mean of 25 days from the onset of COVID-19 symptoms and after a mean of 15 days from ICU admission. All patients were previously treated with combination therapy of hydroxychloroquine, steroids, antivirals (mostly darunavir/cobicistat) or tocilizumab. ICU mortality rate was 66% (6). Among those patients, only one died within 28 days (28 days ICU mortality 11%; 1). No side effects were reported during RDV administration.

The main RDV and GS-441524 PK parameters are reported in Table 2. The mean C_{min}, C_{max} and AUC_{0-24}, were 0 ng/mL and 122.3 ng/mL, 2637.3 ng/mL and 157.8 ng/mL, 5171.2 ng*h/mL and 3676.5 ng*h/mL, respectively. GS-441524 exhibited a quite flat PK profile, suggesting a delayed t_{max}.

Three out of nine patients achieved a C_{max} > 2610 ng/mL and 140 ng/mL and AUC_{0-24} > 1560 ng*h/mL and 2230 ng*h/mL for RDV and GS-441524, respectively. The mean $t_{1/2}$ value for GS-441524 was 26.3 hours, in strict concordance with previous preclinical PK studies.[13–15]

4 | DISCUSSION

RDV is a prodrug of the C-adenosine nucleoside analogue GS-441524. Following intravenous administration, RDV is rapidly distributed in peripheral blood mononuclear cells and tissues, where it is rapidly activated to the nucleoside triphosphate (GS-443902). Several studies and clinical trials have investigated the use of RDV for the treatment of COVID-19 pneumonia showing clinical improvement, shortening time to recovery and a generally acceptable toxicity profile. These data generated a great deal of controversy, due to many limitations including the small sample size, the short duration of follow-up, missing data and the absence of a control group.[17–19]

In our real-life study, patients have few comorbidities, but BMI was high for the majority of them, supporting the association between obesity and severity of the disease and death among COVID-19 patients. Moreover, obesity may have affected PK parameters of RDV and GS-441524, leading to suboptimal concentration and distribution of the antiviral during treatment.[19] Further dedicated studies, including intensive PK sampling on obese volunteers, could be beneficial to better describe the specific impact of obesity on RDV PK.

RDV was administered after a mean of 25 days from clinical symptoms and 15 days after ICU admission, since the majority of patients were transferred to our referral hospital from other peripheral centres. The delayed time of RDV administration, compared to those reported in other studies, was mainly due to the time needed to receive the drug in compassionate setting as well as to the arrival of the patients from peripheral hospital to the regional ECMO ICU, and may have had a negative impact on the survival rate. In fact, preclinical studies suggest that RDV has little benefit when administered after the peak in viral replication and, although the precise timing of peak viral loads was not available for our patients, it may be unfair to attribute any outcome when RDV was given beyond 10–12 days from the initial symptoms.[20]

So far, few data are available about the PK parameters of RDV in the clinical setting, and especially in ICU patients, in which pathophysiological changes and invasive procedures (e.g. ECMO, continuous veno-venous haemofiltration [CVVH]) can affect the PK profile of drugs, leading to a suboptimal plasma concentration.[21–24] Despite the low number and heterogeneity of patients, our data suggested a high interpatient variability in PK parameters of RDV and GS, which led to 33% of patients obtaining C_{max} and AUC values comparable to those reported in healthy volunteers.[13] Of note, we evaluated RDV and GS-441524 plasma concentrations at three time points during

TABLE 1 Main clinical and demographic characteristics of ICU patients treated with RDV

ID	Age, sex	BMI	Comorbidities	VV-ECMO configuration	Transfusion*	MuLBSTA	SOFA	APACHE	SAPS II	ICU before RDV (days)
1	54 M	33	HTA obesity	F-F V 4.6 L Sw 1 FiO2 1	Y	14	10	17	56	28
2	52 M	26	HTA	-	N	13	11	-	-	17
3	41 M	40	Obesity	F-F-J V 4 L Sw 9 FiO2 1	Y	5	10	26	74	3
4	52 M	26	-	F-F V 5.2 L Sw 7 FiO2 1	Y	5	12	21	54	18
5	62 F	38	HTA obesity	F-F-J V 6 L Sw 6 FiO2 1	N	10	10	26	60	9
6	64 M	26	HTA smoke	-	N	14	2	16	40	4
7	59 M	24	-	-	N	5	3	24	52	32
8	67 F	31	Asthma obesity	-	N	7	8	21	54	5
9	55 F	30	Chron obesity	F-F V 3.5 L Sw 6 FiO2 1	Y	9	10	25	58	23

BMI body mass index; VV-ECMO, veno-venous extracorporeal membrane oxygenation; J, jugular; F, femoral; ECMO configuration: V, flow; Sg, sweep gas, FiO_2, inspired fraction of oxygen; MuLBSTA, multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; ICU, intensive care units; RDV, remdesivir; ClCr: creatinine clearance; AKI, acute kidney injury; CVVH, continuous veno-venous haemofiltration.

TABLE 1 (Continued)

ID	ECMO before RDV (days)	Symptoms before RDV (days)	ClC	AKI	CVVH	Previous treatment	ICU mortality	28-day mortality
1	16	33	43	Y	N	Hydrox Dar/cob steroids	Yes	No
2	-	28	41	Y	N	Hydrox Dar/cob	Yes	Yes
3	0	10	-	Y	Y*	Hydrox	No	No
4	15	23	64	N	N	Hydrox Dar/cob steroids	Yes	No
5	7	35	97	N	N	Hydrox Toci steroids	Yes	No
6	-	13	144	N	N	Oseltamivir Hydrox toci	No	No
7	-	40	150	N	N	Dar/cobi Hydrox Toci steroids	No	No
8	-	13	145	N	N	Hydrox Toci steroids	Yes	No
9	10	38	68	N	N	Hydrox Toci steroids	Yes	No

BMI body mass index; VV-ECMO, veno-venous extracorporeal membrane oxygenation; J, jugular; F, femoral; ECMO configuration: V, flow; Sg, sweep gas, FiO_2, inspired fraction of oxygen; MuLBSTA, multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; ICU, intensive care units; RDV, remdesivir; ClCr: creatinine clearance; AKI, acute kidney injury; CVVH, continuous veno-venous haemofiltration.

TABLE 2 Main PK/PD characteristics of RDV and GS in ICU patients

	RDV (ng/ml)	GS 441524 (ng/ml)	RDV (ng/ml)	GS 441524 (ng/ml)	RDV (ng/ml)	GS 441524 (ng/ml)	AUC RDV	AUC GS 441524
P.	C_{min}		C_{max}		T_{15}		h*ng/mL	h*ng/mL
1	<0.24	200	1390	230	<0.24	278	3140	5922
2	<0.24	40	605	69	<0.24	49	1528	1274
3	<0.24	39	7855	50	<0.24	52	14 670	1168
4	<0.24	26	5454	56	<0.24	33	10 560	915,4
5	<0.24	364	1353	402	<0.24	525	3066	10 850
6	<0.24	204	6964	226	<0.24	345	13 160	6651
7	<0.24	33	43	69	<0.24	41	182	1137
8	<0.24	31	50	82	<0.24	37	203	1153
9	<0.24	164	22	236	<0.24	168	32	4018
Mean	<0.24	122.3	2637.3	157.8	<0.24	169.8	5171.2	3676.5
SD (±)	<0.24	118.4	3246.6	122	<0.24	176.8	5925.6	3499.5

RDV, remdesivir; GS, nucleotide analogue GS-441524. Undetectable results for RDV were reported as lower than the limit of detection (0.24 ng/mL for RDV).

administration and, as expected, we found a low level of prodrug and high level of GS-441524.

The very low level of C_{min} for RDV in all patients can be explained by its rapid transformation (half-life [$t_{1/2}$], 1 h) within the cells, into GS-443902 and, in plasma GS-441524. On the other hand, the wide variability in the observed concentrations could be related to the capillary leak syndrome and related endothelial damage could have an impact in predicting the PK characteristics of RDV and its metabolite.[25] Moreover, in patients 7–9, very low RDV C_{max} could be related to the degradation of RDV by plasma esterases: this process could be increased by a delayed processing (e.g., delayed transport from the ICU to the laboratory).

Our study has several limitations: first of all, the sample size, as well as the timing of treatment, which was deferred compared to the values of previous studies. From a PK perspective, we probably overestimated the AUC of RDV (its C_{min} could be reached after as little as 2–3 hours) and probably underestimated the AUC of GS-441524 (delayed T_{max} would be expected, due to metabolism of RDV), due to the lack of intermediate time points between T_1 and T_{15}. On the other hand, the description of C_{min} for GS-441524, as well as its observed half-life, despite the poor number of data for its calculation (15–24 h), can be considered reliable: considering the fast conversion of the prodrug and the quite long half-life, GS-441524 could be the most practical and reliable marker of exposure and antiviral effect retrievable in plasma, also considering experience from other prodrugs of antiviral nucleosides (e.g., anti-HCV sofosbuvir).[26,27]

Moreover, since the plasma PK characteristics for an intracellular metabolized prodrug such as RDV could have a limited correlation with its activity (e.g., anti-HIV tenofovir-alafenamide),[28] a thorough description of the intracellular concentrations of the active triphosphate analogue GS-443902 would provide useful information about the activity of this drug, particularly in the ICU setting.

In conclusion, this is the first real-life report describing some preliminary PK data on RDV in an ICU setting, showing a high interpatient variability with slow attainment of PK parameters reported in healthy volunteers, supporting the possible future relevance of therapeutic drug monitoring (TDM) in this setting. These data may provide useful information to better define the best strategy to care for these challenging patients and may also provide a framework for much-needed future research about the management of these patients. Our experience seems to suggest, in fact, the need for strict TDM at least in the first days of RDV therapy for critically ill COVID-19 patients.

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COMPETING INTERESTS

There are no conflicts of interest to declare.

CONTRIBUTORS

F.D.R., S.C. and A.D. conceived the study. S.S., S.M.P., F.C., G.M. and C.B. collected samples and clinical data. V.A., J.C. and A.D. performed the analysis. All authors wrote the manuscript and reviewed the data.

DATA AVAILABILITY STATEMENT

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

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