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Original Article

Remdesivir for the Treatment of SARS-CoV-2 Infection in Patients Admitted in ICU: A Case Series

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Abstract

The treatment of COVID-19 represents a challenge for the worldwide scientific community and, nowadays, a definitive antiviral treatment does not exist. Remdesivir (RDV), initially developed for Ebola virus disease, showed in-vitro efficacy against SARS-CoV-2 and a positive feedback in the COVID-19 patient. Because of potentially fatal nature of the illness and the absence of other treatments, clinicians started to use RDV as "compassionate" drug for the treatment of COVID-19. We report our clinical experience with RDV administered as compassionate drug in COVID-19 patients admitted to ICU at Monaldi Hospital-Italy.

Four male patients with confirmed SARS-CoV-2, requiring invasive mechanical ventilation, received RDV. They, previously treated with other antivirals, received a 200 mg loading dose, followed by 100 mg daily intravenously for up to 10 days. One patient experienced a torsade de pointes requiring cardiac resuscitation and one died due to acute pulmonary embolism. Three patients experienced both ALT and AST increase. Lymphocyte count increased in all patients soon after starting RDV. Nasopharyngeal swab SARS-CoV-2 RNA became negative in three of four patients after 3 days of therapy.

In conclusion, RDV can reduce the viral load persistently in critically COVID-19 patients, but it is unclear if this effect can improve outcomes. The clinicians should be alerted about the development of serious adverse events related to RDV administration. In particular, strict monitoring of cardiac rhythm and liver function is crucial. Further well-designed clinical trials, evaluating RDV benefit-risk ratio for COVID-19 patients, are needed.

Keywords: COVID-19; Intensive Care Unit; Remdesivir; SARS-CoV-2

Introduction

In late December 2019, patients with severe pneumonia and acute respiratory distress syndrome [1], requiring hospital admission, were confirmed to be infected with a novel coronavirus (2019-nCoV) in Wuhan, China. Subsequently, infection diffused worldwide and the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a public health emergency of international concern.

At present, there is no antiviral treatment with confirmed effectiveness for COVID-19. Available drug options that come from the clinical experience of treating severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and other previous influenza virus have been used for the treatment of COVID-19 patients.

The most commonly used antiviral was Lopinavir/ritonavir association (LPV/r), a protease inhibitor in the treatment of HIV infection: it has an antiviral activity by inhibiting the replication of coronavirus *in vitro* [2-4] but a randomised, controlled, open-label trial involving hospitalised adult patients showed that LPV/r was not effective in severe COVID-19 [5]. Remdesivir (GS-5734, RDV) is a new nucleoside analogue and has been recognised as a potential and promising antiviral drug against a wide array of RNA viruses, including SARS/MERS-CoV. It is currently under clinical development for the treatment of Ebola virus infection. It is a phosphoramidate prodrug that, once metabolised into its active form (GS-441524), interferes with viral RNA dependent RNA polymerase (RdRp) stopping RNA synthesis. This drug has shown potent inhibitory activity against RdRp with a low level of resistance to target mutations [6] and in-vitro efficacy against coronaviruses, including SARS-CoV-2 [7].

Holshue et al. [8] reported for the first time the use of RDV intravenous infusion to treat a COVID-19 patient. During the treatment patient's clinical condition improved and no adverse events were observed. Based on in-vitro studies and this first clinical experience, RDV could be considered as a potential therapeutic option for the therapy of COVID-19.

Since then, because of potentially fatal nature of the illness and the absence of other treatments, clinicians started to use RDV as "compassionate" drug for the treatment of COVID-19. Meanwhile, clinical

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trials to determine its safety and effectiveness are ongoing [9]. We report our clinical experience with RDV administered as compassionate drug in some COVID-19 patients admitted in ICU.

Materials and Methods

Four patients with confirmed SARS-CoV-2 infection (positive reverse-transcriptase polymerase chain reaction testing on nasopharyngeal swab) requiring mechanical ventilation with tracheal intubation, admitted to the ICU at Monaldi Hospital (AORN Ospedale dei Colli, Naples Italy) in March 2020, were treated with RDV. RDV treatment was given in the context of a compassionate use program: 200 mg i.v. loading dose on Day 1, followed by 100 mg i.v. once-daily maintenance dose for 10 days overall. Local ethics committee (University of Naples "Luigi Vanvitelli") approved this analysis (AOC/8468/2020). No consent was obtained from patients because they were in an unconscious state but their relatives were informed by telephone.

On admission, the four patients, with severe COVID-19 respiratory disease, were already intubated and mechanically ventilated; they performed arterial blood gas analysis and blood chemistry tests: cell-blood count, coagulation (aPTT, PT, INR, D-dimer), liver (AST, ALT, bilirubin), kidney (urea, creatinine), heart markers (troponin I, CK-MB), inflammation and infectious markers (PCR, IL-6, procalcitonin). These tests were daily performed or repeated based on patients' clinical changes and therapeutic adjustments. A 12-derivations ECG was performed and reviewed by an intensivist. Heart rate, invasive blood pressure, SpO_2, body temperature and diuresis were monitored continuously. All four patients were sedated by continuous infusion of propofol (2-4 mg/kg/h) or dexmedetomidine (0.8-1.5 mcg/Kg/h) and/or remifentanil (0.1-0.5 mcg/kg/min), and were connected to mechanical ventilator (Evita Drager). The infusion rates could then be adjusted stepwise to achieve the desired level of sedation. In case of mismatch to the ventilator, prone ventilation, or high plateau pressures, we used deep sedation plus neuromuscular blockade (continuous infusion of rocuronium, 0.4-0.7 mg/Kg/h after iv bolus 0.7 mg/kg).

Based on PaO_2/FiO_2 and pulmonary compliance (PaO_2/FiO_2 < 150 mmHg and compliance <50 mL/cm H_2O), we followed a protocol of protective ventilation strategy [10,11] with low tidal volumes (6 mL/kg of predicted body weight), plateau pressures (P_{plat}) ≤ 30 cm H_2O, high PEEP values titrated to maintain low driving pressures (<15 cm-H_2O) and prone ventilation cycles.

About fluid management, we performed a conservative fluid strategy, obtaining a daily negative balance, to avoid an increase in "lung water", evaluated by ultrasound (B-lines, white lung). We also carried out an echocardiographic examination every day to diagnose and promptly treat cardiac complications in COVID-19 patients.

About specific SARS-CoV-2 infection treatment, all patients received hydroxychloroquine (HCQ, 200 mg twice daily po) and LPV/r (400/100 mg twice daily po) for a variable number of days. All four patients had to switch, for a few days, from LPV/r to darunavir/cobicistat (DRV/c) (800/150 mg once daily po) due to shortage of the former drug. Of note, before RDV was initiated, all other antivirals were stopped. RDV protocol was the following: intravenous infusion lasting one hour of 200 mg loading dose on Day 1 and then of 100 mg once daily maintenance dose for a total of 10 days. However, HCQ was restarted in combination with RDV in all patients.

Moreover, monoclonal antibodies as tocilizumab (TCZ, a single dose of 8 mg/kg, iv, with the possibility of repeating a second administration dose after 24 hours) were administered.

Because SARS-CoV-2 infection caused endothelial disfunction, related to high risk of thromboembolic complications [12], all patients received low weight molecular heparin (enoxaparin sc).

Data collected were:

- Age, sex, weight, height, body mass index (BMI), and previous comorbidities
- On admission: PaO_2/FiO_2, HR, systolic and diastolic blood pressure, ECG/Echo pattern (normal or pathologic)
- Administration of HCQ, antiviral drugs (LPV/r or DRV/c), monoclonal antibodies (TCZ)
- LOS and mortality.

We also reported the changing in nasal swab SARS-CoV-2 RNA results and lymphocyte count after RDV administration, and the development of drug-related adverse events. We presented the data on the table.

Results

Among 22 patients admitted to the ICU at Monaldi Hospital (AORN Ospedale dei Colli, Naples Italy), four male patients (18%) received RDV in March 2020. The low number of patients treated with RDV depended on the scarce availability of the drug so that patients under the age of 65, with few comorbid factors and unresponsive to the other treatments were chosen in this "compassionate therapy program". Table 1 reported data and clinical characteristics of patients treated with RDV.

Clinical characteristics of patients treated with remdesivir				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Demographic data				
Age (years)	57	50	55	26
Weight (Kg)	65	80	70	82
Height (cm)	160	175	170	175
BMI (Kg/m2)	25.4	26.1	24.2	26.8
Previous comorbidities	Hypertension	None	None	Asthma
Parameters on admission				
Pa/FiO_2 (mmHg)	101	90	130	120
Heart rate (bpm)	95	95	90	115
Systolic/Diastolic Blood pressure (mmHg)	130/65	130/75	140/70	150/80
ECG/Echo pattern	Normal	Normal	Normal	Normal
Therapies				
Hydroxychloroquine	Yes	Yes	Yes	Yes
Previous antiviral therapy	LPV/r, DRV/c	LPV/r, DRV/c	LPV/ r,DRV/c	LPV/r, DRV/c
Monoclonal antibody	TCZ	TCZ	TCZ	TCZ
Second Dose TCZ	Yes	No	Yes	Yes
Glucocorticoid	No	No	No	No
ICU LOS (days)	18	15	11	9
Survival	Yes	Yes	No	Yes

Table 1: The table reports the clinical characteristics, parameters on admission, therapies, length of stay and survival in patients receiving remdesivir. LPV/r = Lopinavir/ritonavir; DRV/c = Darunavir/cobicistat; TCZ = Tocilizumab; LOS = Length of stay.

Before RDV treatment, all patients received HCQ and antiretroviral therapy (LPV/r or DRV/c). The antiviral drug (LPV/r) was stopped during the ICU stay in case of significant increase in bilirubinemia (> 3 mg/dl). The days immediately preceding RDV administration, all four patients received monoclonal antibody (TCZ). A second dose of TCZ was given after 24 hours except patient 2 due to the presence of superinfection. When RDV treatment started, antiretrovirals were stopped in all patients while HCQ was administered in combination.

RDV was prematurely stopped in two patients: a) in patient 1 RDV was discontinued at day 5 of therapy, together with HCQ, because of a torsade de pointes, caused by QT prolongation, requiring cardiac resuscitation; b) in patient 3 RDV was discontinued at day 5 of therapy because of unexpected death due to acute pulmonary embolism.

Nasal swab SARS-CoV-2 RNA became negative in three of four RDV-treated patients (patient 1, 2 and 4). However, in patient 1 SARS-CoV-2 RNA test reverted to positive after RDV discontinuation, while patient 3 did not repeat nasal swab before dying. We also noted an increase in lymphocyte count in all patients after RDV treatment, and three patients (patients 1, 2 and 3) experienced both ALT and AST increase, ranging from 5 to 8 times the upper normal limit. No patient had either a previous history of liver disease, or visceral obesity, viral hepatitis B and C and/or a history of prior hepatotoxic medication intake or alcohol abuse. Ultrasound scan performed during hospitalisation did not show signs of advanced liver disease. Liver toxicity occurred in all patients after LPV/r but manifested mostly as bilirubin increase. In contrast, the switch to RDV translated into a fast reduction of bilirubin and a significant increase in ALT/AST by day 3 of therapy in three of four patients. The patient 4 did not show any increase of ALT/AST. In no cases RDV was stopped prematurely because of liver injury because this hepatocellular injury did not progress to severe liver damage or induce liver failure in three patients.

Currently, the three surviving patients are at home and have resumed their normal lives and undergo periodic checks (follow-up).

Discussion

With our case series of four critically ill patients, we provided relevant data about in-vivo viral suppression of RDV. In fact, despite treatment with antiretroviral therapies (LPV/r or DRV/c) combined with HCQ, the nasopharyngeal viral load was persistently positive in these patients. After the administration of RDV, in three patients we noted the negativity of nasopharyngeal swab SARS-CoV-2 RNA. Furthermore, we observed that a shorter course of RDV correlated to a transient viral suppression, while a longer course translated into a seemingly more stable viral clearance. Lymphocyte count increased in all patients after RDV treatment. Since the beginning, it was observed that the patient with severe disease had a significantly low lymphocyte count, suggesting that lymphopenia may correlate with disease severity. Lymphocytes in patients with COVID-19 might gradually decrease with the disease progression. But the mechanism of significant reduction in lymphocytes remains unclear [13].

However, it is unclear if the observed effects on viral clearance and lymphocyte count can translate into a real clinical benefit, like reduction in LOS or mortality rate. On this aspect, data in the literature are discordant. In a preliminary report of a multinational trial of >1000 patients with confirmed COVID-19 and pulmonary involvement, RDV resulted in faster time to recovery (median 11 versus 15 days with placebo) but the trend towards lower mortality was not statistically significant (7 versus 12%) [14]. The most evident benefit was in patients who had severe illness (hypoxia or need for supplemental oxygen) but were not yet intubated. While in a randomised trial from China of 237 patients with severe COVID-19 RDV and placebo had similar times to clinical improvement (median 21 versus 23 days) and mortality rates (14 versus 13%) [15]. It seems that RDV, reducing the viral load, can prevent rather than treat the severe form of COVID-19. This hypothesis needs further scientific evidence.

In our study, one patient developed severe cardiac arrhythmia during RDV protocol. However the patient also received HCQ, a drug associated with the prolonged QT interval on ECG, torsades de pointes, ventricular arrhythmia [16,17]. As a consequence, it was hard to distinguish if the cardiac event was related or not to RDV. The risk of cardiovascular outcomes with RDV remains largely unknown [18], and hypotension and arrhythmias have been documented following the use of RDV [19-21]. Mulangu et al. [19] reported cardiac arrest in one patient in the phase III study investigating RDV in the context of Ebola virus disease. However, the authors stated that this death could not readily be distinguishable from underlying fulminant Ebola virus disease itself. Also, Wang et al. [15] reported cardiac arrest in a COVID-19 patient treated with RDV.

In three patients, previously treated with TCZ, we noted raising in AST and ALT levels after RDV administration. Increasing in liver transaminases by hepatocellular injury and gastrointestinal events, including diarrhoea and haemorrhage of the lower gastrointestinal tract, have also been reported with the use of RDV [15, 19,22,23]. However, in our cases, the simultaneous administration of TCZ could represent a bias. Also TCZ can cause liver injury with raising in AST and ALT levels [24].

In the literature, multiple organ dysfunction, septic shock, acute kidney injury were reported as adverse events among patients treated with RDV either on a compassionate-use basis or in a clinical trial [15,20]. Respiratory failure and acute respiratory distress syndrome have been cited as adverse events in patients taking RDV [15], although this may be related to underlying disease (COVID-19) rather than to RDV.

Conclusion

According to our results and despite the observational nature of the study, it seems that a long course of RDV can reduce the viral load persistently in critically COVID-19 patients. However, it is unclear if this effect can translate in reduction of LOS and death rate. We believe that RDV can prevent rather than treat the development of a severe form of the disease. The clinicians should be alerted about the development of serious adverse events related to RDV administration. In particular, strict monitoring of cardiac rhythm and liver function is crucial, especially in patients receiving drugs such as HCQ and TCZ. Further well-designed clinical trials, evaluating RDV benefit-risk ratio for COVID-19 patients, are needed.

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None

Author Contributions

Conception and Design, RC De Rosa; Data Collection, RC De Rosa; Statistical analysis and interpretation, RC De Rosa, A. Romanelli; Writing-Original draft preparation, RC De Rosa, A. Romanelli, S. Mascolo; Writing-Review & editing, RC De Rosa; Supervision RC De Rosa; Project Administration, RC De Rosa.

Conflict of Interest

The authors declare no conflict of interest.

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