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Case reports study of the first five patients COVID-19 treated with remdesivir in France.

Marie Dubert¹,* Benoit Visseaux²,4,* Valentina Isernia¹, Lila Bouadma³,4, Laurène Deconinck¹, Juliette Patrier³,4, Paul-Henri Wicky³,4, Diane Le Pluart¹, Laura Kramer⁵, Christophe Rioux¹, Quentin Le Hingrat²,4, Nadhira Houhou-Fidouh², Yazdan Yazdanpanah¹,4, Jade Ghosn¹,4,§, François-Xavier Lescure¹,4,ária.

Affiliations

1: AP-HP. Nord, Infectious and Tropical Diseases Department, Bichat-Claude Bernard University Hospital, Paris, France
2: AP-HP. Nord, Virology Department, Bichat-Claude Bernard University Hospital, Paris, France
3: AP-HP. Nord, Medical and Infectious Diseases Intensive Care Unit, Bichat-Claude Bernard University Hospital, Paris, France
4: University of Paris, French Institute for Health and Medical Research (INSERM), IAME, U1137, Team DesCID, Paris, France.
5: AP-HP. Nord, Pharmacy Unit, Bichat-Claude Bernard University Hospital, Paris, France

* and §: these authors contributed equally to this work as first authors (*) and last authors ($).

Corresponding author:
Dr Marie Dubert
SMIT, Hôpital Bichat-Claude Bernard, 46 rue Henri Huichard, 75018 Paris, France
e-mail: marie.dubert@aphp.fr

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Highlights

- Remdesivir has been found to be an *in-vitro* potent inhibitor of RNA viruses including SARS-CoV-2 but its *in-vivo* potency is still under active investigations.

- In this work, we depict the clinical features of 5 hospitalized COVID-19 patients under remdisivir compassionate use.

- Remdisivir infusion was associated with decreasing viral loads from nasopharyngeal samples despite active replication in the lower respiratory tract area evidenced for two patients.

- The treatment had to be interrupted for potential side effects for 4 out 5 patients including two alanine aminotransferase (ALT) elevation and two renal failure cases.
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as responsible for the COVID-19 outbreak worldwide. Data on treatment are scare and parallels are made between SARS-CoV-2 and other coronavirus. Remdesivir is a broad spectrum antiviral with efficient in vitro activity against SARS-CoV-2 and controversial evidence of clinical improvement in severe COVID-19 patients. We aimed to describe the clinical outcome and virological monitoring of the first five COVID-19 patients admitted in ICU for severe pneumonia related to SARS-CoV-2 and treated with remdesivir in the University hospital of Bichat, Paris, France.

SARS-CoV-2 RT-qPCR in blood plasma, lower and upper respiratory tract were monitored. Among the five treated patients, two needed mechanical ventilation and one high flow cannula oxygen. A significant decrease in SARS-CoV-2 viral load from upper respiratory tract was observed in most cases but two died with active SARS-CoV-2 replication in the lower respiratory tract. Plasma samples were positive for SARS-CoV-2 in only one patient. Remdesivir was interrupted for side effects among four patients, including 2 ALT elevations (3 to 5N) and 2 renal failures requiring renal replacement.

This case series of five COVID-19 patients requiring ICU for a respiratory distress and treated with remdesivir, highlights the complexity of remdesivir use in such critically ill patients.
Key words: SARS-CoV-2 viral load, remdesivir, antiviral therapy, viral pneumonia, case reports
**Background**

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified as responsible for the COVID-19 outbreak starting in China (Zhu et al. 2020). Treatment options investigated during SARS-CoV-1 and MERS-CoV epidemics, both other Betacoronavirus, have been proposed as possible therapeutics for SARS-CoV-2, such as ribavirin and IFNα-2b (Martinez 2020), lopinavir/ritonavir (Chu et al. 2004; Arabi et al. 2020), and hydroxychloroquine (Savarino et al. 2006; Chen et al. 2020; Gautret et al. 2020; Wang et al. 2020a), with controversial results. Remdesivir, a nucleotide analogue prodrug with a broad spectrum antiviral activity (Sheahan et al. 2017; Mulangu et al. 2019), seems promising for SARS-CoV-2 *in-vitro* (Wang et al. 2020a). Two case reports (Holshue et al. 2020; Kujawski et al. 2020) and a recent clinical study of 54 patients (Grein et al. 2020) showed encouraging results on COVID-19-patients. Conversely, a randomized study did not show significant clinical benefit but probably lacked power (Wang et al. 2020b). Five patients were treated with compassionate-use remdesivir in our center in Paris, France. Early findings have been previously described for two patients (Lescure et al. 2020). Here we describe for the first time the complete follow-up, tolerance and virological monitoring among those five patients.

**Cases presentations**

**Participants and source of data**

We enrolled all patients admitted in the University Hospital Bichat-Claude Bernard, Paris, France, between January 24 and March 1, 2020, diagnosed with COVID-19 and treated with remdesivir (Gilead Sciences). Indication criteria for compassionate-use remdesivir were defined with the French national regulatory authorities and French ministry of health: signs of severe illness at diagnosis or subsequent clinical aggravation (respiratory symptoms or general signs). Since March 22, all patients requiring an antiviral treatment are enrolled in the Discovery study (2020-000936-23). The Institutional Review Board of Bichat Hospital approved this report and waived the need for informed consent from individual patients, due to the nature of retrospective chart review and the absence of identifying images or personal/clinical details that compromise anonymity.

**Procedures**

All patients received remdesivir via intravenous infusion with a loading dose of 200 mg and a maintenance daily dose of 100 mg for a maximum duration of 14 days. All nasopharyngeal and broncho-alveolar samples were collected on universal transport media (Virocult, Sigma)
and transported in the laboratory within 24h. All RT-qPCR were performed according to the WHO recommended procedure (Corman et al. 2020) after an extraction on MagnaPure (Total NA large volume kit, Roche Diagnostic) from 200 µL of transport media and amplification on an ABI 7500 (Life technologies). Quantification was done using a standardized RNA transcript control obtained from the European Virus Archive Program. Bacterial and mycological investigations were conducted on a separate sample without virological transport media using the usual procedures for bacterial growth. Broncho-alveolar lavages were also tested with a mPCR assay (FilmArray Pneumonia assay, BioFire, BioMérieux) for virus and bacteria detection, and fungal culture with mass spectrometry identification for Aspergillus detection. All samples were processed in a BSL3.

Results (Figure 1)

Case #1
A 31-year Chinese male originating from Wuhan and reporting flu-like symptoms for 6 days was diagnosed with COVID-19 on January 24, 5 days after his arrival in Paris. He was immediately hospitalized with mild lymphopenia (1000 G/L), thrombopenia (146 G/L), and no abnormalities on chest X-ray. The RT-qPCR on nasopharyngeal samples was positive with a SARS-CoV-2 viral load (VL) at \(10.5 \log_{10}\) copies/mL. On illness day 10, he was referred to intensive care unit (ICU) due to oxygen saturation worsening (PO\(_2\)=58mmHg; flow nasal cannula 4 L/min), and bilateral lung ground glass and alveolar opacities on chest CT-scan with no increase in VL. Remdesivir was started on January 29, 2020 (illness day 11) and was stopped at day 15, because of alamine aminotransferase (ALT) elevation (195UI/L versus 46UI/L before remdesivir administration) and a maculopapular rash. A rapid decline of viral load, from 27.6 Ct to undetectability at day 2 of remdisivir infusion was observed. Skin and liver abnormalities improved within three days after discontinuing treatment. The patient was discharged on February 12.

Case #2
An 80-year-old tourist originating from Hubei Province, with past medical history of thyroid cancer, presented on January 25 with fever and diarrhea for 4 days. The chest X-ray showed bilateral alveolar opacities but he did not fulfill the COVID-19 case definition at the time. Airborne and contact precautions were observed and the COVID-19 diagnosis was eventually retained 3 days later. On January 26, an acute respiratory failure with multiple organ failures triggered his admission to ICU. A broad spectrum antibiotherapy was started and adapted for coinfection with a susceptible \textit{Acinetobacter baumannii} (diagnosed on multiplex PCR and...
confirmed by tracheal aspirates culture) and an *Aspergillus flavus* (tracheal aspirates culture). Remdesivir was started on January 29 but was discontinued on January 31 as the patient needed renal replacement therapy. The nasopharyngeal viral load decreased from 21.0 Ct before infusion to 28.9 on day 2 of infusion. CT-scan on January 31 showed bilateral alveolar condensations, ground glass and pulmonary cysts. On February 5, because of the disease severity and the persistence of viral detection, remdesivir was re-initiated. Multiple organ failures persisted without any other coinfection identified. He died on February 14.

**Case #3**

A 39-year old male airport worker, obese (BMI=33kg/m²) and with obstructive sleep apnea syndrome was diagnosed with severe COVID-19 and admitted to ICU on February 26. He had cough and fever since February 21. He presented an acute respiratory failure (PaO₂=74mmHg; high debit nasal cannula 40 L/min, 40%) and basal interstitial syndrome on chest X-ray. Remdesivir was started on February 27. Virus RNA levels slightly increased, from 32.5 to 28.8 Ct, during the first 4 days of infusion and started to decline at day 5 later until undetectability On March 1, he was referred to Infectious Diseases ward and was weaned off oxygen on illness day 13. VL was reduced below the RT-qPCR detection limit on day 14. Remdesivir was discontinued after 8 administrations, because of ALT elevation (116 UI/L versus 43UI/L before remdesivir administration) and a maculopapular rash. These symptoms resolved five days after remdesivir discontinuation and the patient was discharged on illness day 20.

**Case #4**

A 76-year French male, known for chronic kidney injury (creatinine=115µmol/L, normal range=50-70µmol/L), was admitted on February 22 for cough and fever for 24 hours and transferred in our center on February 26 after diagnosis of COVID-19. He presented a SpO₂=92% on air and pulmonary posterior ground glass on chest CT scan. On illness day 11, he was transferred in ICU due to oxygen saturation worsening (PO₂=69mmHg; flow low nasal cannula=3 L/min). The nasopharyngeal viral load was already very low at 38.5 Ct but remdesivir was initiated on March 3 and discontinued on March 12, without any side effect, as SARS-CoV-2 VL was constantly negative. He was weaned off oxygen on illness day 19 and discharged on illness day 23.

**Case #5**
A 70-year old male with a past medical history of chronic obstructive bronchopneumopathy was diagnosed with COVID-19 on March 1 with cough and fever since February 23 while taking non-steroid anti-inflammatory drugs for renal lithiasis. He was admitted to ICU on March 2 with an acute respiratory distress syndrome. Remdesivir was started on March 4 (illness day 11) and discontinued on March 6 because of acute kidney injury (creatinine level up to 396µmol/L) needing renal replacement therapy. Nasopharyngeal samples viral load strongly decreased from 26 Ct to undetectability on day 2 of remdesivir infusion. However, SARS-CoV-2 viral load was detectable in broncho-alveolar lavage on March 10. Cefotaxime was initiated because of a *Haemophilus influenzae* respiratory coinfection. Nevertheless, he developed multiple organ failures and a refractory acute respiratory distress syndrome despite prone position and adapted mechanic ventilation. Dexamethasone and LPV/r were started on March 12. He died on March 24 (illness day 31).

**Discussion and conclusions**

This case series of five COVID-19 patients requiring ICU for a respiratory distress treated with remdesivir, three (#1, #3, #4) had a favorable outcome despite the initial respiratory severity. They were weaned off oxygen between illness day 14 to 19 and discharged between illness day 20 and 26. Patients #2 and #5 died in ICU on illness day 25 and 31 with multiorgan failure. Remdesivir initiation yielded a decrease in nasopharyngeal VL in all but patient #2, for whom the treatment was re-introduced after an early interruption without additional decrease neither in upper nor lower respiratory tract. For patient #5, a viral replication was still ongoing in the lower respiratory tract despite a concomitant undetectable VL in the nasopharyngeal area, thus highlighting the discrepancies between viral replication in upper and lower respiratory tract among the most severe patients. Plasma samples were only positive for SARS-CoV-2 for patient #2.

As described in previous case reports (Grein et al. 2020; Kujawski et al. 2020), four out of five patients experienced major side effect under remdesivir (two acute renal injuries and two maculo-papular rash with a cytolytic hepatitis). Both kidney failure events could be either related to remdesivir or SARS-CoV-2 infection. None of our patients received immunomodulatory drugs. Grein *et al.* (Grein et al. 2020) described 53 COVID-19-patients treated with remdesivir, among which 30 on mechanical ventilation. After a median follow-up of 18 days after remdesivir initiation, a total of 25 (47%) were discharged, 7 (13%) died and 10 were still under invasive mechanical ventilation. No virological data were available in this report. A recent randomized controlled study (Wang et al. 2020b) did not show clinical
benefit but probably lacked power. Noteworthy, 12% of patients in the remdesivir group discontinued remdesivir due to adverse events (vs 5% in the placebo group).

To conclude, the five patients presented herein highlight some difficulties with remdesivir infusion when administered in most advanced patients. A particular attention should be given to hepatic and kidney function when administrating this treatment.
**Abbreviations:**

- HIV-1, Human immunodeficiency virus 1; ICU, intensive care unit; UNL, upper normal limit.
- SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VL, viral load.
Declarations

Ethics approval and consent to participate

The present report has been approved by the French Ethics Committee (NCT04262921).

Consent for publication: The Institutional Review Board of Bichat Hospital approved this report and waived the need for informed consent from individual patients, due to the nature of retrospective chart review and the absence of identifying images or personal/clinical details that compromise anonymity.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors’ contributions:

All authors have read and approved the manuscript.

MD, VI, YY, JG, XL wrote the manuscript, took care of the patients in the infectious and tropical diseases department.

LD, DLP and CR took care of the patients in the infectious and tropical diseases department.

BV participated to the virological tests and wrote the manuscript.

QLH and NHF participated to the virological tests.

LB, JP and PHW took care of the patients in the medical and infectious intensive care unit.

LK assisted in obtaining and dispensing the drug.

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References


Figure Legends: Clinical and viral evolution of included patients.

For each patient, type of hospital ward is indicated by the color rectangles, supplemental O2 requirement by the dashed blue line and remdesivir infusion by the red line. Viral load is given with black diamonds and black line for nasopharyngeal swabs, with green squares for lower respiratory tract samples when available and red circles for plasma samples. The viral load is estimated by the Ct (cycle threshold) values. The lower the Ct value, the higher is the viral load. A sample is negative above 40 Ct.
Hospitalisation
I.C.U. admission
Time after patient death

Supplemental O2
Remdisivir infusion
Potential side effect
1st day symptom-free
Nasopharyngeal viral loads
Lower respiratory tract viral loads
Plasma viral loads

SARS-CoV-2 RT-qPCR – Log_{10} copies/mL

Day of illness