

# Ribavirin Aerosol in the Treatment of SARS-CoV-2

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## Case Report

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# Abstract

Ribavirin is an inosine monophosphate dehydrogenase inhibitor with demonstrated activity against coronaviruses, including SARS-CoV-2. Two hospitalized patients with COVID-19 (confirmed by positive tests for SARS-CoV-2) received treatment with ribavirin for inhalation solution (ribavirin aerosol) as part of a compassionate use program. Patient 1 was a 33-year-old male with an unremarkable medical history. Patient 2 was a 29-year-old male who was an active smoker. Both patients were managed according to international and Italian treatment guidelines for COVID-19. In addition, therapy with ribavirin aerosol 100 mg/mL was administered for 30 minutes twice daily for 6 days (ie, 12 doses) in both patients. In order to address concerns about a possible increase in viral dispersal with the use of a nebulizer, healthcare providers remained outside the patient room during ribavirin aerosol administration. Pretreatment chest computed tomography scans showed pseudonodular areas in the upper right lobe with associated ground glass opacities (Patient 1) and multiple areas of parenchymal consolidation in both lower lobes with associated ground glass opacities (Patient 2) that were almost completely resolved on imaging at the end of ribavirin treatment. No adverse reactions to ribavirin treatment were observed in either patient. Both patients recovered fully, and 2 sequential nasopharyngeal swabs obtained after hospital discharge tested negative for SARS-CoV-2. Ribavirin aerosol appears to be efficacious in the treatment of patients with COVID-19. The compassionate use study of ribavirin aerosol is ongoing and will provide additional data across a broader patient population.

## Introduction

The virus responsible for the COVID-19 pandemic, SARS-CoV-2, is a betacoronavirus similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV).<sup>1</sup> SARS-CoV-2 is known, in some instances, to induce an excessive pro-inflammatory host response, including aberrant induction of inflammatory cytokines, which is associated with severe lung pathology and can result in patient mortality.<sup>2,3</sup> As in patients with SARS-CoV or MERS-CoV, some patients with SARS-CoV-2 infection develop acute respiratory distress syndrome, and pulmonary ground glass opacities are commonly observed on imaging.<sup>2,4</sup> A 2020 report illustrated similarities between the pathological features observed in a patient with confirmed SARS-CoV-2 and those typically seen in SARS and MERS coronavirus infections.<sup>5</sup>

Ribavirin is an inhibitor of inosine monophosphate dehydrogenase, a key enzyme in the de novo synthesis of guanine nucleotides, and has demonstrated in vitro activity against a number of emerging viruses.<sup>6,7</sup> Ribavirin inhibits RNA synthesis by disrupting the activity of viral RNA-dependent RNA polymerases (RdRp), crucial enzymes in the life cycle of coronaviruses, and also inhibits mRNA capping.<sup>6-8</sup> Ribavirin has been used against RdRp of the hepatitis C virus,<sup>8</sup> and oral ribavirin (in combination with other medications) is approved by the US Food and Drug Administration (FDA) and European Medicines Agency for the treatment of chronic hepatitis C infection.<sup>9,10</sup>

Ribavirin for inhalation solution (ribavirin aerosol) is approved by the FDA and Health Canada for the treatment of infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus,<sup>11,12</sup> and has been made available in Italy for patients with COVID-19 as part of a compassionate use program. Aerosol administration of ribavirin has been shown to be effective against multiple variants of influenza.<sup>13-15</sup> In order to evaluate the activity of ribavirin and other anti-polymerase drugs against SARS-CoV-2, a 2020 study used homology modeling to build the Wuhan SARS-CoV-2 RdRp and then assessed the binding properties of different antiviral compounds using molecular docking.<sup>8</sup> Authors concluded that ribavirin demonstrated tight binding to the SARS-CoV-2 RdRp and could potentially interfere with protein synthesis, leading to viral eradication.<sup>8</sup>

An open-label, compassionate use study was initiated to evaluate the safety and efficacy of ribavirin aerosol (10 mL of 100 mg/mL in nebulizer reservoir administered for 30 minutes twice daily [bid] for  $\leq 6$  days) in the treatment of hospitalized adults who tested positive for SARS-CoV-2 and were experiencing respiratory distress. Here, data are presented for the first 2 patients treated for SARS-CoV-2 infection in this compassionate use study.

## Methods And Results

Ethics committee approval of the compassionate use program (IRCCS Lazzaro Spallanzani, Rome, Italy; and San Raffaele Scientific Institute, Milan, Italy) was obtained before treatment was initiated. Both patients provided written informed consent for participation in the compassionate use program and for their information and images to be included in this article.

Ribavirin was administered using the PARI BOY® SX inhalation system (PARI GmbH, Starnberg, Germany); the nebulizer was driven by wall air at a standard flow rate. Ribavirin was provided in 6-g vials that were diluted with 60 mL of distilled water. For each ribavirin treatment, 10 mL of solution was placed in the nebulizer reservoir.

## Patient 1

A 33-year-old man presented at a hospital emergency department in Milan on July 5, 2020 with a high fever (39°C) and chills. His medical history was considered unremarkable, with the exception of *Helicobacter pylori* gastritis occurring 2 months before. Clinical laboratory test results showed a normal white blood cell (WBC) count (5200/ $\mu$ L; lymphocytes, 1100/ $\mu$ L) and a markedly elevated C-reactive protein level (81.7 mg/L). Chest x-ray was negative for pneumonia and a nasopharyngeal swab for SARS-CoV-2 was also performed. The patient refused hospitalization.

On July 8, the patient presented to the emergency department of San Raffaele Hospital, after the nasopharyngeal swab test conducted 3 days earlier was positive for SARS-CoV-2. On physical examination, cardiac activity was normal, and no bronchospasm findings or rales were observed. Blood gas analysis, with the patient on room air, showed a pH of 7.45, pCO<sub>2</sub> of 32 mmHg, pO<sub>2</sub> of 90 mmHg,

and SpO<sub>2</sub> of 97%. The patient was admitted to the hospital. A second nasopharyngeal swab and a test for SARS-CoV-2 antibodies were both negative. Blood tests on July 9 showed mild leucopenia (WBC, 3400/ $\mu$ L). Laboratory testing ruled out other bacterial and viral etiologies, including legionella, pneumococcus, chlamydia trachomatis, mycoplasma pneumoniae, tuberculosis, human immunodeficiency virus, and aspergillosis. A chest computed tomography (CT) scan without contrast showed pseudonodular areas of parenchymal thickening in the right upper lobe, with associated ground glass areas, and some reactive mediastinal lymph nodes (Fig. 1A). On July 10, bronchoscopy and bronchial washing (with an antibiotic solution) were performed to aid in diagnosis. Analysis of the bronchial washing fluids included microbiological and cytological examinations and a polymerase chain reaction assay, which were positive for SARS-CoV-2.

Immediately after bronchoscopy, antimicrobial empiric treatment with oral azithromycin (500 mg qd) and parenteral ceftriaxone (2 g/d) was started on July 10 and continued for 6 days. Low-molecular-weight heparin (4000 IU bid) was administered until hospital discharge. The patient did not require supplemental oxygen during the hospitalization, with SpO<sub>2</sub> maintained at > 97% on room air. On July 13, it was confirmed that the patient met the inclusion/exclusion criteria for the ribavirin compassionate use study. Antibiotics were discontinued on July 16. Nebulized ribavirin (100 mg/mL for 30 minutes bid) was administered for 6 days (ie, 12 doses total) beginning in the afternoon of July 13. Healthcare providers remained outside the patient room during ribavirin aerosol administration. The patient was remotely monitored through a window during drug administration and vital signs were remotely measured every 10 minutes. No bronchospasm was reported during treatment, no changes in heart rhythm were recorded, and no clinically meaningful negative changes in laboratory parameters were identified. On the third day of ribavirin therapy, a repeat nasopharyngeal swab, a conjunctival sample, and a SARS-CoV-2 antibody test were performed, all of which were negative. The patient completed 6 days of treatment and ribavirin aerosol was well tolerated, including no adverse effects on the skin or eyes observed.

One day after completion of ribavirin aerosol treatment regimen, a chest CT scan showed resolution of pseudonodular areas previously described, with only minimal residual subpleural areas of parenchymal thickening (Fig. 1B). On the same day, a nasopharyngeal swab tested negative for SARS-CoV-2. The patient was discharged on July 22 (~ 3 days after completing ribavirin treatment) and returned to quarantine. At the end of quarantine, 2 sequential nasopharyngeal swabs for SARS-CoV-2 yielded negative results.

## **Patient 2**

A 29-year-old man experienced symptoms of high fever (39°C), sore throat, dry cough, and dysgeusia beginning on July 17, 2020. On July 21, he presented at a hospital emergency department. He was an active smoker, but his medical history was otherwise considered unremarkable. Laboratory workup showed normal WBC, d-dimer, and fibrinogen levels, and markedly elevated levels of C-reactive protein (75 mg/L) and lactic dehydrogenase (560 U/L). A blood gas analysis on room air showed a pH of 7.5, pO<sub>2</sub> of 128 mmHg, and SpO<sub>2</sub> of 98%. Chest x-ray showed only minimal accentuation of the interstitial texture. A

nasopharyngeal swab detected the presence of SARS-CoV-2, and the patient was sent home with prescriptions for hydroxychloroquine and azithromycin.

On July 29, the patient presented San Raffaele Hospital emergency department with persistent fever, malaise, and dry cough. On physical examination, cardiac activity was normal, and no bronchospasm findings or rales were observed. Blood gas analysis on room air showed a pH of 7.45, pCO<sub>2</sub> of 27 mmHg, pO<sub>2</sub> of 128 mmHg, and SpO<sub>2</sub> of 98%. Blood tests were remarkable for lymphocytopenia (940/ $\mu$ L) and elevated C-reactive protein (75 mg/L) and lactic dehydrogenase (560 U/L). A chest CT scan without contrast showed multiple areas of parenchymal consolidation affecting the lower lobes of both lungs with associated ground glass areas (Fig. 2A). The patient was admitted to the hospital on July 30. Laboratory testing ruled out other bacterial and viral etiologies for pneumonia.

Due the critical condition of this patient and the fact that secondary infections had not yet been excluded, he was treated with levofloxacin 750 mg qd, parental dexamethasone 6 mg/d, oral lopinavir/ritonavir (200 mg/50 mg tablet bid), and low-molecular-weight heparin (4000 IU bid) beginning on July 30. On August 5, levofloxacin and lopinavir/ritonavir were discontinued, and dexamethasone was switched to oral prednisone 25 mg qd, which was reduced to 12.5 mg qd for 2 days and then discontinued. Low-molecular-weight heparin was administered until hospital discharge. Serologic testing for SARS-CoV-2 antibodies performed on July 31 was negative. On July 31, the patient was enrolled in the ribavirin aerosol compassionate use study.

Nebulized ribavirin (100 mg/mL for 30 minutes bid) was administered for 6 days (ie, 12 doses total) beginning in the afternoon of July 31. Healthcare providers remained outside the patient room during ribavirin aerosol administration, with the patient remotely visually monitored. On the basis of blood gas analysis parameters, supplemental low flow oxygen was provided on Days 2 and 3 of ribavirin therapy. On the third day of ribavirin aerosol therapy, a repeat nasopharyngeal swab tested positive for SARS-CoV-2, whereas a conjunctival sample was negative. The patient completed 6 days of treatment and ribavirin aerosol was well tolerated, including no adverse effects on the skin or eyes. No bronchospasm was reported during treatment, no changes in heart rhythm were recorded, and no clinically meaningful negative changes in laboratory parameters were observed.

A chest CT scan performed on the last day of ribavirin aerosol treatment showed almost complete resolution of the previously described parenchymal consolidation and ground glass areas (Fig. 2B). On the same day, a nasopharyngeal swab tested negative for SARS-CoV-2. Serologic testing performed at the end of ribavirin aerosol therapy was positive for SARS-CoV-2 antibodies. The patient was discharged from the hospital on August 7 and returned to quarantine. At the end of quarantine, 2 sequential nasopharyngeal swabs for SARS-CoV-2 yielded negative results.

## Discussion

Identification of pharmacologic treatments that induce viral containment and clearance of SARS-CoV-2 is important for addressing the global COVID-19 pandemic.<sup>6</sup> The details reported here illustrate the potential benefit of ribavirin aerosol administration in hospitalized patients with COVID-19. These 2 young adult males with confirmed SARS-CoV-2 infection were initially treated empirically with antibiotics. Patient 2 also received corticosteroids and other antiviral medications. Ribavirin aerosol treatments (12 doses administered over 6 days) were provided as part of a compassionate use program. Pretreatment CT scans showed pseudonodular areas of parenchymal thickening in the upper right lobe with associated ground glass opacities (Patient 1) and multiple areas of parenchymal consolidation in both lower lobes with associated ground glass opacities (Patient 2) that were almost completely resolved on post-treatment imaging. Both patients recovered fully, and 2 sequential nasopharyngeal swabs obtained after hospital discharge were negative for SARS-CoV-2.

An experimental dosing regimen of aerosolized ribavirin was developed for the treatment of SARS-CoV-2 infection in order to deliver medication in a shorter treatment period. The FDA-recommended dosing for patients with respiratory syncytial virus is a solution of 20 mg/mL with continuous aerosol administration for 12–18 hours per day for 3–7 days.<sup>11</sup> Research using animal models demonstrated that the use of a higher concentration ribavirin solution (60 mg/mL) could significantly reduce treatment time.<sup>16,17</sup> Ribavirin 100 mg/mL administered using a more efficient nebulizer was effective in reducing mortality in a lethal influenza A virus mouse model.<sup>18</sup> Administration of ribavirin aerosol 100 mg/mL for 30 minutes is estimated to deliver 1760 µg/mL to the alveolar lining fluid, which is 64 times the half maximal response ( $EC_{50}$ ) of 26.7 µg/mL observed against a clinical isolate of SARS-CoV-2 in vitro (data on file). Administration of ribavirin aerosol as recommended in the treatment of respiratory syncytial virus (20 mg/mL over 12 hours)<sup>11</sup> results in an estimated dose of 10.9 mg/kg, whereas compassionate use study administration (ribavirin aerosol 100 mg/mL for 30 minutes) results in an estimated dose of 5.1 mg/kg, which represents approximately half the systemic exposure (data on file).

In vitro and clinical data suggest that ribavirin may be an effective therapeutic in the medical management strategy of patients with COVID-19. In vitro research has demonstrated antiviral efficacy for lopinavir and ribavirin against SARS-associated coronavirus, and a clinical study showed that patients with probable SARS-CoV treated with a combination of lopinavir/ritonavir, ribavirin (oral or intravenous), and corticosteroids (n = 41) had a significantly lower rate of adverse clinical outcomes (ie, acute respiratory distress syndrome or patient mortality) than a historical control group treated with ribavirin and corticosteroids (n = 111;  $P < 0.001$ ).<sup>19</sup> Other in vitro studies have shown that MERS-CoV is sensitive to a combination of ribavirin and interferon  $\alpha$ -2b.<sup>20</sup> A publication of a 38-year-old man diagnosed with COVID-19 reported the successful use of intravenous ribavirin as one component of medical therapy that also included antibiotics, antitussives, bronchodilators, and interferon  $\alpha$ -1b.<sup>21</sup> A 2020 open-label, randomized, phase 2 trial in hospitalized patients with COVID-19 evaluated 14-day combination therapy (n = 86) with oral lopinavir/ritonavir, oral ribavirin, and subcutaneous interferon  $\beta$ -1b (in the subset of 52 patients admitted < 7 days from symptom onset) compared with a control group that received only oral

lopinavir/ritonavir (n = 41).<sup>22</sup> That study found that the combination treatment was significantly better for alleviating symptoms, reducing viral load, and shortening the duration of hospitalization.

Potential advantages with ribavirin aerosol treatment for patients with COVID-19 versus oral or intravenous formulations include direct targeting of medication to the site of infection and a lower risk for adverse events associated with systemic administration. However, there are concerns about using an aerosol treatment in patients infected with SARS-CoV-2 due to the potential for increased risk of viral exposure to healthcare providers. It is known that the drug can disperse into the bedside area during treatment with ribavirin aerosol,<sup>11</sup> and the extent to which treatment may also impact virus dispersal is unclear. In addition to the standard precautions taken when treating patients with COVID-19, it is recommended that healthcare providers wear a facemask (as well as eye protection, gloves, and gown), close the door to the patient room, and remain at a safe distance (possibly outside the door) during nebulizer treatments.<sup>23</sup> In the current report, healthcare providers wore FFP3 masks and remained outside the patient room during ribavirin aerosol treatment. The short duration of therapy (30 minutes bid) means that this additional limitation in patient contact would not be expected to compromise patient care.

## Conclusion

Ribavirin is an inosine monophosphate dehydrogenase inhibitor with demonstrated activity against coronaviruses, including SARS-CoV-2, in preclinical research. The positive preliminary findings obtained and reported here, both in terms of efficacy and safety, support the continuation of the ongoing compassionate use study and the execution of further clinical studies (eg, ClinicalTrials.gov identifiers: NCT04356677 and NCT04551768) to evaluate whether ribavirin for inhalation (ribavirin aerosol) may be a useful option in the treatment of patients with COVID-19.

## Declarations

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Emanuela Messina reports nothing to disclose.

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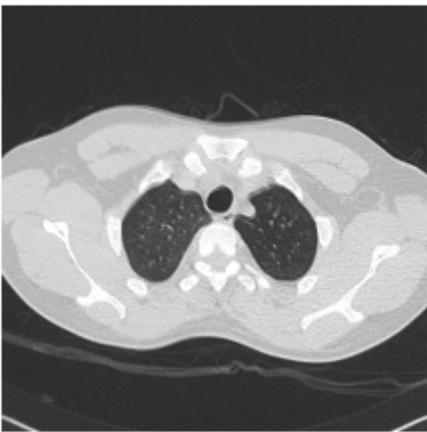
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## Figures

**A.**



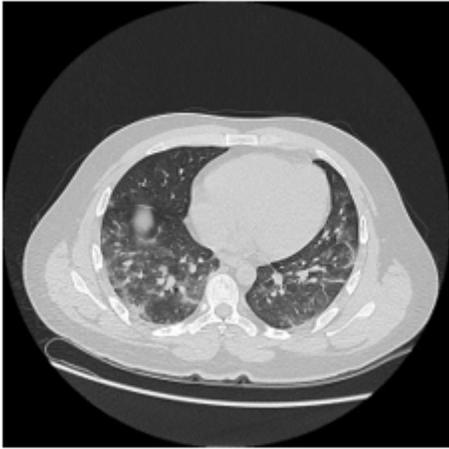
**B.**



**Figure 1**

Chest computed tomography scans without contrast for Patient 1 at (A) pretreatment, showing pseudonodular areas in the upper right lobe with associated ground glass areas and some reactive mediastinal lymph nodes, and (B) after 6 days of therapy with ribavirin solution for inhalation, showing resolution of the pseudonodular areas and minimal residual subpleural areas.

**A.**



**B.**



**Figure 2**

Chest computed tomography scans without contrast for Patient 2 at (A) pretreatment, showing multiple areas of parenchymal consolidation affecting the lower lobes of both lungs with associated ground glass areas, and (B) after 6 days of therapy with ribavirin solution for inhalation, showing almost complete resolution of the parenchymal consolidation and ground glass areas.