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ARTICLE

Ribavirin aerosol in hospitalized adults with respiratory distress and COVID-19: An open-label trial

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Abstract

There is an unmet medical need for effective treatments for hospitalized patients with coronavirus disease 2019 (COVID-19). Ribavirin is a broad-spectrum antiviral with demonstrated in vitro activity against multiple viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This trial evaluated the potential of ribavirin inhalation solution (ribavirin aerosol) to reduce COVID-19 disease severity in adults with confirmed SARS-CoV-2 infection and a diagnosis of respiratory distress. This phase I, multicenter, open-label, nonrandomized trial was conducted from February 2021 through August 2021. Patients received ribavirin aerosol (100 mg/ml for 30 min or 50 mg/ml for 60 min) twice daily for up to 6 days. The primary end point was change from baseline in clinical status severity, rated on a 7-point scale (1 [death]; 7 [not hospitalized; no limitations on activities]), at day 7 (or end-of-treatment/early termination) and day 30 (follow-up). Fifty-one patients were treated with ribavirin aerosol (mean age, 51.5 years; 78.4% men); mean number of doses was 9.7 (range, 1–12). Improvement of ≥1 level in clinical status severity was observed in 31.4% (16/51) and 78.4% (40/51) of patients at end-of-treatment and day 30, respectively. Of 21 patients who required a ventilator, 16 (76.2%) were able to discontinue ventilator use. Five patients (9.8%) died between end-of-treatment and day 30. Three patients (5.9%) discontinued study treatment due to adverse events. No deaths were considered related to study treatment. These data provide preliminary evidence that ribavirin aerosol may be an efficacious treatment for respiratory distress in adults with COVID-19.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

In a subset of patients, coronavirus disease 2019 (COVID-19) disease progresses to involve the lower respiratory tract potentially leading to acute respiratory distress syndrome. Ribavirin is a broad-spectrum antiviral medication with demonstrated in vitro activity against multiple viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

WHAT QUESTION DID THIS STUDY ADDRESS?
The aim of this open-label, nonrandomized trial was to provide a preliminary assessment of the potential utility of ribavirin inhalation solution (ribavirin aerosol) in the treatment of hospitalized adults with COVID-19 and respiratory distress.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Administration of ribavirin aerosol was associated with improvement in the clinical status of many treated patients, with corresponding improvements in several indicators of pulmonary function. Ribavirin aerosol was generally well-tolerated in this patient population.
HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
The findings of this preliminary study suggest that treatment with ribavirin aerosol may have clinical utility in the treatment of hospitalized patients with COVID-19, and further evaluation in a controlled clinical trial is warranted.

INTRODUCTION

The 2019 coronavirus disease (COVID-19) outbreak that started in Wuhan, China quickly spread to become a global pandemic, challenging healthcare systems and society.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, is a β-coronavirus similar to SARS-CoV and Middle East respiratory syndrome (MERS)-CoV.[2,3] In comparison with SARS-CoV and MERS, SARS-CoV-2 has higher transmissibility but a lower mortality rate.[4] Respiratory system involvement is the most common complication of SARS-CoV-2 infection, and some patients develop acute respiratory distress syndrome (ARDS).[4] Both direct viral effects and host immune responses contribute to the development of ARDS,[4] with pathologic changes that include diffuse alveolar damage and pulmonary ground-glass opacities.[5–8] A survey of the global literature estimated that up to one-third of hospitalized patients with COVID-19 develop ARDS, which is often fatal.[9,10] Although the availability of COVID-19 vaccines and adoption of preventive behaviors can reduce the rate and severity of infection,[11] there remains an urgent need for effective therapeutics.[12] One strategy for efficient development of COVID-19 treatments is the evaluation of existing medications,[13,14] and a number of antiviral and immunomodulatory drugs have been used to treat COVID-19 respiratory distress.[4]

Ribavirin is a broad-spectrum antiviral agent with demonstrated in vitro activity against a number of potentially lethal viruses, including SARS-CoV-2.[15,16] Ribavirin, a nucleotide inhibitor, was shown to decrease expression of transmembrane serine protease 2 (TMPRSS2) at both mRNA and protein levels in vitro and also to inhibit activity of the TMPRSS2 enzyme.[16] As TMPRSS2 has an extracellular protease domain that promotes fusion of viral and host cell membranes, inhibition of TMPRSS2 protease activity may contribute to the antiviral effects of ribavirin.[16] In addition, ribavirin inhibits RNA-dependent RNA polymerase (RdRp), a complex of nonstructural proteins crucial for the replication of RNA viruses, including SARS-CoV-2.[17,18] In a study that created a validated model for the SARS-CoV-2 RdRp, molecular docking analyses demonstrated tight binding of ribavirin to the coronavirus RdRp, indicating that ribavirin could disrupt polymerase function and inhibit viral replication.[19] Other proposed mechanisms of action for ribavirin include competitive inhibition of inosine monophosphate dehydrogenase, which alters the balance of intracellular nucleotide concentrations; inhibition of mRNA capping; enhanced viral mutagenesis; and attenuation of host immune responses.[20]

A retrospective study of patients with severe COVID-19 compared those who received intravenous ribavirin (500 mg every 12 h, $n = 44$) with a control group that received appropriate antimicrobial therapy and supportive care only ($n = 71$).[21] Median time to negative conversion for SARS-CoV test was shorter in the ribavirin group (12.8 days) compared with the control group (14.1 days) and the mortality rate was lower (17.1% vs. 24.6%); however, these differences were not statistically significant.[21] Results of a small retrospective study of critically ill patients ($n = 19$) suggested that oral ribavirin therapy (0.15 g every 8 h) could benefit patients with COVID-19 by increasing viral clearance.[22] Clinically, ribavirin (in formulations for intravenous or oral administration) has also been used off-label in combination with other agents (e.g., corticosteroids, interferon, and other antivirals) in the treatment of hospitalized patients with mild COVID-19.[23,24]

Ribavirin for inhalation solution (ribavirin aerosol) is an aerosolized formulation of ribavirin approved in the United States and Canada for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus.[25,26]

Ribavirin aerosol was made available to hospitalized patients with SARS-CoV-2 infection via a compassionate use program. In a case series comprising the first five patients treated in the compassionate use study (twice daily for 6 days), rapid improvement in respiratory symptoms occurred after initiation of ribavirin aerosol therapy, followed by effective viral clearance, whereas pretreatment pulmonary abnormalities observed on imaging (i.e., parenchymal thickening and ground glass opacities) improved or resolved in four of the five patients.[27] The current trial was designed to provide a preliminary evaluation of ribavirin aerosol for reducing the severity of COVID-19 disease in patients with confirmed SARS-CoV-2 infection and a diagnosis of respiratory distress.

METHODS

Trial design

This phase I, prospective, open-label, nonrandomized, two-arm trial (ClinicalTrials.gov: NCT04551768; EudraCT: 2020–003353-29) was conducted from February 2021 through August 2021 at seven sites in three countries (Greece, Brazil, and Mexico). The trial was conducted in accordance with the Guidelines for Good Clinical Practice, ethical principles that have their origin in the Declaration of Helsinki, and applicable local regulations. The protocol was approved by an institutional review board or independent ethics committee at each study site. All patients provided written informed consent prior to the initiation of any study procedures.

Patients

This trial enrolled patients aged ≥18 years currently hospitalized with laboratory-confirmed SARS-CoV-2 infection and a diagnosis of respiratory distress, defined as a ratio of partial arterial oxygen pressure and fraction of inspired oxygen (PaO_2/FiO_2) of <300 mmHg. In addition, patients were required to have ≥1 of the following: (1) radiographic infiltrates observed by imaging (e.g., chest x-ray and computed tomography [CT] scan), (2) evidence of rales/crackles on clinical examination and peripheral capillary oxygen saturation (SpO_2) of ≤94% on room air, or (3) mechanical ventilation and/or supplemental oxygen requirement. Reasons for exclusion included: pregnancy or breast feeding, respiratory distress unrelated to SARS-CoV-2 infection, clinically significant pulmonary fibrosis, secondary bacterial pneumonia, a history of chronic obstructive pulmonary disease or bronchospasm prior to SARS-CoV-2 infection, anemia, hypotension, or mechanical ventilation for >7 days.

Treatment and assessments

Patients were treated with open-label ribavirin aerosol using one of two delivery regimens, both administering 2000 mg/day of ribavirin (Table 1). Regimen was determined by the investigator (i.e., nonrandomized) based on clinical judgment. Aerosolization was carried out using a high efficiency jet nebulizer (Pari LC [PARI Respiratory Equipment, Inc.] or comparable) flowing at a rate of ~8 to 10 L of air or O_2 per minute. Ribavirin aerosol was administered twice daily for 6 days but was stopped earlier if the patient was discharged from the hospital. All patients continued standard of care treatment according to local guidelines throughout hospitalization; all concomitant medications deemed necessary for patient care were permitted, except those assessed by the investigator as having a potential chemical or pharmacologic interaction with ribavirin aerosol.

Clinical status severity (CSS) was rated on a 7-point scale that was modified from a previous COVID study[28]: 1 (death); 2 (hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation); 3 (hospitalized, on noninvasive ventilation or high-flow oxygen devices); 4 (hospitalized, requiring supplemental oxygen); 5 (hospitalized, not requiring supplemental oxygen); 6 (not hospitalized, limitation on activities); and 7 (not hospitalized, no limitations of activities). CSS ratings, SpO_2 levels, vital signs, and arterial blood gases (at a minimum) were assessed twice daily during the 6 days of treatment (prior to each ribavirin aerosol administration), on day 7 (or end of treatment/early termination), and at the follow-up visit on day 30 (±5 days). Arterial blood gas was not collected on day 30. Adverse events (AEs) were monitored throughout the study and clinical laboratory testing and urinalysis was conducted on days 1, 7 (or end of treatment), and 30 (±5 days). Patients who discontinued study participation during treatment or follow-up were requested to complete end-of-treatment or end-of-study assessments.

TABLE 1 Drug delivery regimens for ribavirin aerosol

Treatment	Solution volume in nebulizer, ml	Administration schedule	Total daily dose, mg
Ribavirin aerosol 100 mg/ml	10	30 min, twice daily, for up to 6 days	2000
Ribavirin aerosol 50 mg/ml	20	60 min, twice daily, for up to 6 days	2000

Statistical analysis

The primary end point was change from baseline in CSS rating. Secondary end points were time to recovery of gas exchange to a PaO_2/FiO_2 ratio of ≥300 mmHg for ≥24 h and time to reach SpO_2 of >94% for ≥24 h. The primary safety end point was the percentage of patients with AEs leading to study drug discontinuation. There was no formal sample size estimation; the planned enrollment population was ~50 patients. Data were analyzed using descriptive statistics unless otherwise indicated. Change from baseline in the CSS rating, PaO_2/FiO_2 ratio, and SpO_2 level were determined using a mixed-model repeated measures analysis. The analysis models included treatment and visit as main effects, baseline value as a covariate, interaction between treatment and timepoint, interaction between baseline value and timepoint, and subject as a random effect; covariance was modeled with an unstructured covariance matrix. There was no imputation of missing data. Similar analyses were conducted by time since diagnosis (<7 days vs. ≥7 days). Analyses were conducted using SAS version 9.4 or higher (SAS Institute).

RESULTS

Patients

Fifty-one patients received ≥1 treatment dose with ribavirin aerosol (100 mg/ml, $n = 41$; 50 mg/ml, $n = 10$; Table 2). All patients had a baseline CSS rating of 2 to 4. One patient had received COVID-19 vaccine (2 doses) prior to study enrollment, and three patients received ≥1 dose of COVID-19 vaccine during the study. The mean number of ribavirin aerosol doses received during the study was 9.7 (range, 1–12), with a mean (SD) of 10.1 (3.2) doses in the 100 mg/ml group and 7.8 (4.7) doses in the 50 mg/ml group. Overall, 54.9% (28/51) of patients received all 12 doses: 58.5% (24/41) in the 100 mg/ml group and 40.0% (4/10) in the 50 mg/ml group. Concomitant treatments included glucocorticoids (92.2% [47/51]), primarily dexamethasone (64.7% [33/51]); anticoagulants (92.2% [47/51]); and remdesivir (25.5% [13/51]). Overall, 36 patients (70.6%) completed treatment and 28 patients (54.9%) completed the trial (i.e., day 30 assessment; Figure 1).

TABLE 2 Demographics and baseline clinical characteristics

Parameter	All ($N = 51$)	Ribavirin aerosol 100 mg/ml ($n = 41$)	Ribavirin aerosol 50 mg/ml ($n = 10$)
Age, years			
Mean (SD)	51.5 (11.0)	51.8 (11.4)	50.4 (9.8)
Median (range)	49.0 (27–78)	50.0 (27–78)	49.0 (37–72)
Male, *n* (%)	40 (78.4)	32 (78.0)	8 (80.0)
Race, *n* (%)			
White	49 (96.1)	41 (100)	8 (80.0)
Black	1 (2.0)	0	1 (10.0)
Not reported	1 (2.0)	0	1 (10.0)
Time since COVID-19 diagnosis			
Median (range), days	6.0 (1–24)	6.0 (1–24)	3.5 (2–15)
<7 days, *n* (%)	30 (58.8)	24 (58.5)	6 (60.0)
≥7 days, *n* (%)	21 (41.2)	17 (41.5)	4 (40.0)
Baseline PaO_2/FiO_2 ratio, mmHg, mean (SD)	156.8 (70.4)	148.8 (64.6)	193.4 (87.7)
Baseline SpO_2 level, mean (SD)	93.4 (4.2)	93.0 (4.5)	94.8 (2.5)
Baseline Clinical Status Severity, *n* (%)			
2	1 (2.0)	1 (2.4)	0 (0)
3	14 (27.5)	11 (26.8)	3 (30.0)
4	36 (70.6)	29 (70.7)	7 (70.0)

Abbreviations: COVID-19, coronavirus disease 2019; PaO_2/FiO_2, partial arterial oxygen pressure/fraction of inspired oxygen; SpO_2, peripheral capillary oxygen saturation.

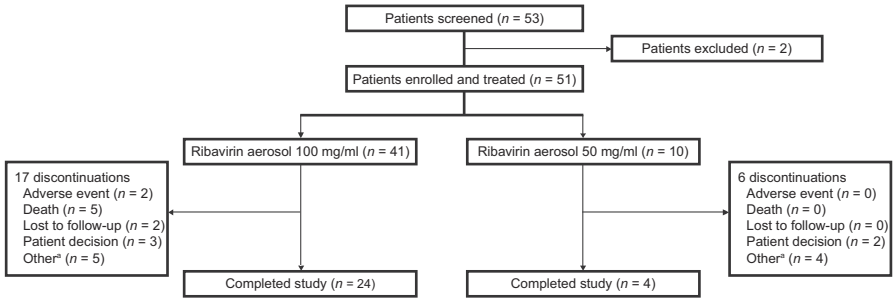

FIGURE 1 Patient disposition. [a]Other reasons for study discontinuation included hospital discharge before the end of treatment ($n = 5$) and unable/inconvenient to return for day 30 assessment ($n = 4$).

Efficacy

Given the total dose per day was equivalent and there were few patients in the ribavirin aerosol 50 mg/ml treatment arm, results were analyzed for the overall population ($N = 51$). Improvement of ≥1 level in CSS rating (primary efficacy end point) was observed in 31.4% (16/51) of patients at the end of treatment and 78.4% (40/51) of patients on day 30 (Figure 2). In a subgroup analysis by ventilator status at baseline, improvement of ≥1 level in CSS rating was observed at end of treatment in four of 15 (26.7%) patients with ventilator use and 12 of 36 (33.3%) patients without ventilator use at baseline; improvement of ≥1 CSS level was observed at day 30 in 66.7% and 83.3% of patients, respectively. Of 21 patients who required the use of a ventilator (CSS rating 2 or 3) at any point during the trial, 16 patients (76.2%) were able to discontinue ventilator use with a median time to ventilator discontinuation of 626.8 h (i.e., 26.1 days; 95% confidence interval [CI], 93.0–722.0 h [3.9–30.1 days]). No patients died during ribavirin aerosol treatment (through day 7) and five patients (9.8%) died prior to the day 30 safety follow-up assessment. Four of these deaths occurred in patients on mechanical ventilation at baseline (4/15; 26.7%). The five deaths were not considered related to study medication.

Least-squares mean change in CSS rating was 0.3 (95% CI, 0.0–0.6) at the end of treatment and 2.3 (95% CI, 1.8–2.8) at day 30. Recovery of gas exchange (defined as PaO_2/FiO_2 ratio of ≥300 mgHg for ≥24 h, assessed during the treatment period) was observed in nine patients (17.6%). Additional improvements were observed in other respiratory assessments (Table 3). Of 39 patients with available data at the end of treatment, 11 patients (28.2%) had a PaO_2/FiO_2 ratio of ≥300 mgHg; recovery of oxygen saturation was observed in 51.0% of the 51 patients, with median time to saturation recovery of 124.8 h (i.e., 5.2 days; Table 3). SpO_2 levels were >94% in 50% and 76.7% of patients at the end of treatment and day 30, respectively (Table 3). In 28 patients who completed the day 30 assessment, SARS-CoV-2 test results were negative in 24 patients (85.7%), positive in two patients (7.1%), and indeterminate in two patients (7.1%).

Outcomes were also evaluated based on time since COVID-19 diagnosis (<7 days vs. ≥7 days) at baseline. Improvement of ≥1 level in CSS rating was observed at end of treatment in nine of 30 patients (30%) enrolled <7 days since diagnosis and seven of 21 patients (33.3%) with ≥7 days since diagnosis; improvement of ≥1 CSS level was observed at day 30 in 76.7% and 81% of patients, respectively. Recovery of gas exchange (PaO_2/FiO_2 ratio of ≥300 mgHg for ≥24 h) was observed in 16.7% of patients with <7 days since COVID-19 diagnosis at baseline and 19% of patients with ≥7 days since diagnosis; percentage of patients with recovery of oxygen saturation was 46.7% and 57.1%, respectively.

Adverse events

The most common AEs reported during the trial were primarily respiratory related, and the majority of AEs were mild or moderate in intensity (Table 4). An AE of anemia was reported in one patient (2.0%). AEs led to discontinuation of study medication in three patients (5.9%); all were considered serious AEs (COVID-19 exacerbation [$n = 2$] and bronchospasm [$n = 1$]). AEs considered by the investigator to be treatment related were reported in four patients (7.8%): a serious AE of bronchospasm in one patient (who died of COVID-19) and non-serious AEs in three patients (dizziness [$n = 1$], dizziness and headache [$n = 1$], and cough [$n = 1$]). There were no additional post-baseline abnormal laboratory test results or changes from baseline in laboratory test results considered clinically significant by investigators.

DISCUSSION

This phase I, open-label trial was conducted to provide a preliminary evaluation of ribavirin aerosol as a treatment for hospitalized patients with respiratory distress due to SARS-CoV-2 infection. Patient demographics and baseline characteristics were consistent with those expected for a hospitalized population receiving treatment for COVID-19. When ribavirin aerosol was initiated, all

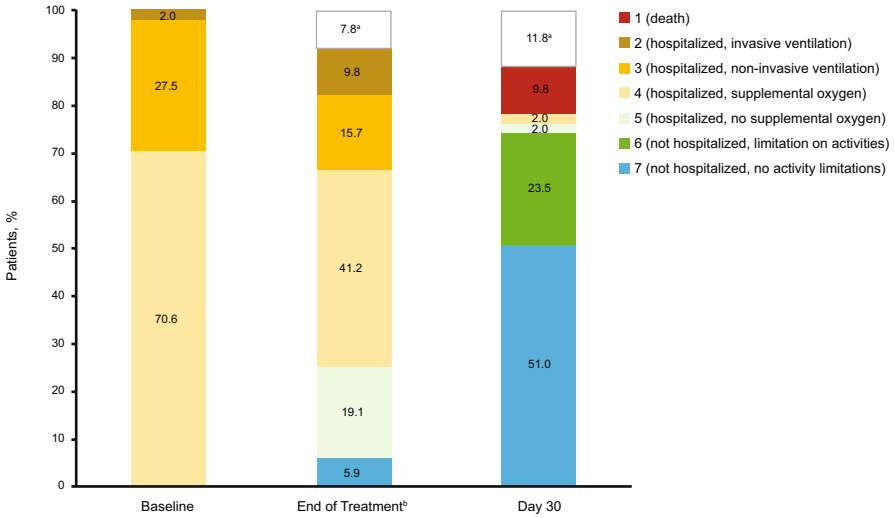

FIGURE 2 Patient clinical status severity rating ($N = 51$). [a]No assessment for four patients at end of treatment and six patients at day 30/end of study. [b]Day 7 or end of treatment/early termination.

TABLE 3 Respiratory outcomes

Parameter	Ribavirin aerosol ($N = 51$)
PaO_2/FiO_2 ratio	
LSM change from baseline (95% CI), mmHg	109.4 (59.1, 159.7)
≥300 mgHg at end of treatment, n/n (%)	11/39 (28.2)
SpO_2	
LSM change from baseline at end of treatment[a] (95% CI), %	0.4 (−0.6, 1.3)
LSM change from baseline at day 30 (95% CI), %	2.6 (1.5, 3.6)
SpO_2 > 94%, n/n (%)	
End of treatment[a]	23/46 (50.0)
Day 30	23/30 (76.7)
Recovery of oxygen saturation[b], n/n (%)	26/51 (51.0)
Median time to recovery of saturation (95% CI), h	124.8 (51.8, NE)

Abbreviations: CI, confidence interval; LSM, least squares mean; NE, not estimable; PaO_2/FiO_2, partial arterial oxygen pressure/fraction of inspired oxygen; SpO_2, peripheral capillary oxygen saturation.

[a]Day 7 or end of treatment/early termination.

[b]SpO_2 level of >94% for ≥24 h.

patients were receiving respiratory support (i.e., mechanical ventilation, non-invasive ventilation, or supplemental oxygen). Improvements were seen in CSS rating and other measures of efficacy (i.e., PaO_2/FiO_2 ratio and SpO_2) at the end of treatment and a subsequent follow-up visit on day 30, and ribavirin aerosol treatment was generally well-tolerated.

Although this trial was not powered for statistical comparisons between patient subgroups, it appeared that outcomes were somewhat less favorable in patients who required mechanical ventilation at baseline (CSS rating of 2 or 3) compared with those receiving supplemental oxygen (CSS rating of 4). Surprisingly, rates of improved clinical status, recovery of gas exchange, and recovery of oxygen saturation were generally similar for patients who had shorter (<7 days) versus longer (≥7 days) time since COVID-19 diagnosis. Other research has suggested that antiviral therapies are more effective against SARS-CoV-2 when initiated early in the disease course.[29]

An experimental dosing regimen of ribavirin aerosol of 2000 mg per day (administered as either 10 ml of 100 mg/ml for 30 min twice daily or 20 ml of 50 mg/ml for 60 min twice daily) was used in this trial. The long duration of administration recommended by the US Food and Drug Administration (FDA) for patients with respiratory syncytial virus (20 mg/ml administered continuously for 12–18 h/day)[25] was an obstacle to the use of ribavirin aerosol in the treatment of patients with COVID-19. Preclinical studies have shown that increasing the concentration of the ribavirin solution in the nebulizer reservoir could substantially reduce treatment time.[30–32] Ribavirin was effective for preventing mortality in a lethal influenza A infection model: mice were treated with a solution of 100 mg/ml in the nebulizer reservoir at a flow rate of 10 L

TABLE 4 Summary of AEs

Patients with an AE, *n* (%)	Ribavirin aerosol (*N* = 51)
Any AE	21 (41.2)
AE leading to study treatment discontinuation	3 (5.9)
AE leading to study discontinuation	2 (3.9)
Treatment-related AE	4 (7.8)
Serious AE	9 (17.6)[a]
Death	5 (9.8)
Maximum intensity of AE	
Mild	7 (13.7)
Moderate	6 (11.8)
Severe	8 (15.7)
AE reported in ≥2 patients	
COVID-19	6 (11.8)
Bronchospasm	2 (3.9)
Dizziness	2 (3.9)
Increased fibrin D dimer	2 (3.9)
Respiratory failure	2 (3.9)

Abbreviation: AE, adverse event.

[a]Twelve serious AEs were reported in nine patients: COVID-19 ($n = 5$), bronchospasm ($n = 2$), COVID-19 pneumonia ($n = 1$), pneumonia ($n = 1$), pulmonary sepsis ($n = 1$), and acute respiratory failure ($n = 1$), and respiratory failure ($n = 1$).

of air per minute, which produced aerosol droplets that contained 2.3 mg of ribavirin per liter with a mass median aerodynamic diameter of 1.8 μm.[30] Ribavirin aerosol 100 mg/ml (10 ml in the reservoir) administered for 30 min would deliver an estimated 1760 μg/ml to the alveolar lining fluid, which is ~64 times the half-maximal response against a clinical isolate of COVID-19 in vitro (26.7 μg/ml; data on file). Administration of ribavirin aerosol 100 mg/ml for 30 min results in a calculated dose of 5.1 mg/kg, which is approximately half the systemic exposure (10.9 mg/kg) of the FDA-approved dose of 20 mg/ml administered for 12 h.[30] The dose of ribavirin aerosol used in this study—1000 mg per treatment (administered as 10 ml of 100 mg/ml or 20 ml of 50 mg/ml)—was based on the findings from preclinical research and is consistent with the dosing in the COVID-19 compassionate use study (10 ml of 100 mg/ml).[27] Because blood samples for pharmacokinetic analysis were not collected in the current study, the systemic exposure to ribavirin in these patients was unknown.

The pharmacokinetics and safety of aerosolized ribavirin has been evaluated in a single-dose study (500 mg, 1000 mg, or 2000 mg of ribavirin administered at varying solution concentrations and treatment durations) in healthy volunteers.[33] The pharmacokinetic profile of plasma ribavirin was linear across the dose range; for ribavirin doses of 10 ml of 50 mg/ml (500 mg), 20 ml of 50 mg/ml (1000 mg), 10 ml of 100 mg/ml (1000 mg), and 20 ml of 100 mg/ml (2000 mg), area under the curve to the last measurable concentration of total ribavirin in plasma was 1.25, 2.54, 2.15, and 5.96 μg/ml*h, respectively. AEs were reported in three of 24 (12.5%) participants who received ribavirin aerosol and two of eight (25.0%) participants who received placebo; no severe or serious AEs were reported.

In the current trial, investigators had the option of using ribavirin aerosol 100 mg/ml administered for 30 min twice daily, the dosing regimen in a European compassionate use trial,[27] or an alternate delivery regimen of 50 mg/ml administered for 60 min twice daily. Treatment selection was based primarily on investigators' considerations regarding duration of administration and was not related to any potential safety concerns; in the trial, >80% of patients received the higher concentration (i.e., shorter) treatment. Both delivery regimens of ribavirin aerosol were generally well-tolerated. Commonly reported AEs were respiratory in nature, consistent with manifestations of the disease under study, and few AEs were considered treatment-related. The occurrence of anemia, which has been reported during postmarketing surveillance in patients treated with ribavirin aerosol, was reported in only one patient during the current trial.

At the time this trial was conducted, only one patient had been vaccinated against COVID-19 prior to enrollment. Although it is important to consider potential interactions between COVID-19 vaccines and concomitant medications,[34] antiviral medications, including ribavirin, would not be expected to alter the response to vaccines that do not utilize a live virus. During the study period, there was limited availability of authorized medications in the countries where patients were enrolled (i.e., Greece, Brazil, and Mexico). Since that time, certain antiviral medications have been authorized for emergency use in these countries (e.g., nirmatrelvir/ritonavir in Mexico, and molnupiravir in Brazil). The SARS-CoV-2 delta variant was the most common variant identified globally during the study period; the omicron variant had not yet been identified. The mortality rate in this trial was 9.8%. Although cross-study comparisons should be made with caution, this appears to be lower than the COVID-19 mortality rate reported during a generally similar time frame in comparable patient populations.[35,36] The development of effective therapeutics, in addition to vaccines, is vital to the global management of COVID-19. A number of existing medications have potential utility in the treatment of COVID-19.[14] Although further research failed to confirm benefits initially attributed to hydroxychloroquine,[14] other antiviral medications have been authorized by regulatory authorities (e.g., remdesivir) or are under investigation.

Because ribavirin is an antiviral agent that inhibits RNA synthesis by disrupting the activity of viral RdRp,[19,20] its therapeutic activity against SARS-CoV-2 does not involve targeting spike proteins. This represents a therapeutic advantage, given the multiple variants of SARS-CoV-2 with numerous mutations in spike proteins being identified globally,[37] as these mutations would not be expected to impact the antiviral efficacy of ribavirin.

Treatment of COVID-19 in hospitalized patients typically includes multiple medical therapies. Because additional medications (e.g., corticosteroids and remdesivir) were permitted in this study of ribavirin aerosol, it is not possible to identify the relative contributions of each agent to the overall therapeutic effect. The potential utility of a combination of at least ribavirin with interferon-α2b is supported by findings from in vitro[38] and primate[39] studies of MERS disease and an open-label study of hospitalized adults with COVID-19.[23] Other combinations that may optimize efficacy include use of ribavirin with an immunomodulatory drug, in order to target both the direct viral effects and host immune responses that contribute to respiratory distress in patients with COVID-19.[4]

The course of COVID-19 typically begins with binding of inhaled SARS-CoV-2 to cells in the nasal epithelium and progresses, in a subset of patients, to involvement of the upper respiratory tract and migration into the lower respiratory tract.[40] For patients with lower respiratory tract involvement, the viral infection spreads horizontally through the alveolar epithelial cells potentially leading to ARDS.[40] Inhaled treatments, such as ribavirin aerosol, offer a therapeutic advantage in the treatment of COVID-19–related respiratory distress because the drug is delivered directly to the site of infection, which may potentiate efficacy while reducing the incidence of systemic AEs. Local delivery can also bypass other pharmacokinetic obstacles to reaching the lung parenchyma, such as the alveolar damage and changes in the lung microvasculature caused by SARS-CoV-2 and accompanying inflammation.[41]

However, there are concerns regarding the use of aerosolized therapies in patients with acute respiratory infections, notably the potential for viral exposure to healthcare providers.[42] One US state health department has issued recommendations regarding the use of nebulizers in the treatment of patients with COVID-19: personal protective equipment for healthcare workers should include N95 or higher-level respirator, gown, gloves, and eye protection; the door to the patient's room should be closed during treatment; and healthcare workers should remain at a safe distance (≥6 feet) or possibly outside the room (if this can be done safely).[43]

The primary limitations of this trial are the lack of a control group, the lack of clarity regarding the contributions of concomitant medications (e.g., corticosteroids and remdesivir), and the absence of data regarding systemic exposure levels to ribavirin. In addition, the timing of assessments may have impacted interpretation of the efficacy results. The CSS rating was not necessarily captured at relevant milestones of patients' clinical progress. For example, a number of patients had post-treatment clinical status rated as "hospitalized" in the morning, even though they were discharged from the hospital on that study day. In those situations, the CSS rating underestimated the level of improvement at the end of treatment. In addition, because there were no scheduled assessments between days 7 and 30, the precise timing of improvement was unknown in many patients with improvement first documented on day 30.

Findings of this open-label trial suggest that ribavirin aerosol may be a safe and effective treatment for adults with respiratory distress due to SARS-Cov-2 infection. Further research is warranted comparing ribavirin aerosol with an appropriate control treatment (e.g., standard care) in a larger population of hospitalized patients with COVID-19.

AUTHOR CONTRIBUTIONS

M.B. and R.J.I. designed the research. G.P. and M.R.B. performed the research. All authors analyzed the data and all authors wrote the manuscript.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

For information on data sharing considerations, please visit https://www.bauschhealth.com/responsibility/access-to-clinical-study-data.

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