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Ribavirin therapy for severe COVID-19: a retrospective cohort study

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ABSTRACT

The aim of this study was to compare ribavirin therapy versus supportive therapy only for patients with severe coronavirus disease 2019 (COVID-19). A total of 115 patients with laboratory-confirmed COVID-19 were retrospectively analysed. All patients received supportive care as well as regular laboratory and clinical monitoring. The 115 patients comprised 44 patients who received intravenous ribavirin (treatment group) and 71 who did not (control group). Baseline laboratory and clinical characteristics were similar between the two groups. The negative conversion time for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR in the ribavirin group was 12.8 ± 4.1 days compared with 14.1 ± 3.5 days in the control group ($P = 0.314$). Moreover, 7/41 patients (17.1%) in the ribavirin group died compared with 17/69 (24.6%) in the control group ($P = 0.475$). Adverse effects were similar between the two groups. In conclusion, in patients with severe COVID-19, ribavirin therapy is not associated with improved negative conversion time for SARS-CoV-2 test and is not associated with an improved mortality rate. Further assessment in designed randomised controlled trials is recommended.

1. Introduction

The 2019 novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease that is causes, named coronavirus disease 2019 (COVID-19), which was first discovered in Wuhan, China, in December 2019, is a serious concern worldwide. Patients with COVID-19 show respiratory diseases and severe pneumonia. Since the detection of the outbreak, the number of cases has been increasing worldwide; as of early April 2020, more than 9000 cases and more than 3000 deaths have been reported in China alone, and more than 950 000 cases in other countries. Treatment of patients with COVID-19 consists of supplemental oxygen, admit to an isolation ward, supportive care, antimicrobial therapy and respiratory support [1,2]. To date, no antiviral therapy has been approved for the treatment of COVID-19.

Several therapeutic interventions for coronavirus infection were studied during the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks in 2003 and 2012, respectively [3,4]. Reviews of the literature suggest that ribavirin might be of benefit in patients with coronavirus infection [4]. However, other studies have shown that ribavirin may not improve outcomes [5,6]. In addition, ribavirin has potential adverse effects [7], therefore its clinical use should be carefully assessed.

The aim of this study was to evaluate and compare the efficacy of ribavirin in the treatment of patients with severe COVID-19 pneumonia.

2. Study population and methods

2.1. Setting

This single-centre, retrospective cohort study included patients diagnosed with laboratory-confirmed SARS-CoV-2 infection in Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) from January–February 2020.

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2.2. Informed consent

This study was approved by the Ethics Commission of Union Hospital. Owing to the rapid emergence of this infectious disease, the need for written informed consent was waived.

2.3. PCR assay

SARS-CoV-2 infection was confirmed by positive reverse transcription PCR (RT-PCR) of respiratory tract samples. Two RT-PCR tests were used for SARS-CoV-2 diagnostic confirmation. Nucleocapsid protein (N) and open reading frame 1ab (ORF1ab) were amplified during RT-PCR [8].

2.4. Patients

Patients were excluded if they met the following exclusion criteria: (i) age <18 years or >80 years; and (ii) transferred to another hospital (after the first consultation, some patients with special medical insurance types were transferred to the corresponding hospitals for treatment). Patients were considered severe COVID-19 patients if they met any of the following condition: (i) oxygen saturation ≤93% at resting state; (ii) respiratory rate ≥30 breaths/min; and (iii) arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) ≤300 mmHg [9].

2.5. Procedure

The experimental group comprised patients who received intravenous ribavirin 500 mg every 12 h (Zhengzhou Cheuk-fung pharmaceutical Co., Ltd., Xinzheng City, Zhengzhou, China), whereas those who did not receive ribavirin therapy formed the control group. The control group received no other potential antiviral treatments. All patients received appropriate antimicrobial therapy and supportive care. In addition to routine clinical monitoring, liver enzymes, renal function, electrolytes and blood cell counts were assessed regularly throughout the course of treatment.

2.6. Outcomes

The outcomes for the study were (i) the negative conversion time for SARS-CoV-2 RT-PCR test and (ii) mortality rate in the two groups.

2.7. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (S.D.) and categorical variables were expressed as number (%). The χ^2 test and *t*-test were used to determine any statistical difference between the proportions and means of the two groups. Single-factor analysis was used for comparison of clinical and laboratory features in the different groups. Univariate and multiple logistic regression models were used to evaluate the associations between patients receiving ribavirin or not and the risk of death. All analyses were performed with EmpowerStats (http://www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and the statistical software package R (http://www.R-project.org; The R Foundation). A *P*-value of <0.05 (two-sided) was considered statistically significant.

3. Results

A total of 134 individuals were diagnosed with severe COVID-19 between January–February 2020. Baseline characteristics were similar between patients who received ribavirin and those who did not. After excluding ineligible patients, 115 patients were included in the current study, comprising 71 in the control group and 44 in the treatment group (Fig. 1). The mean ± S.D. age of all 115 patients was 54.9 ± 15.1 years and 62 (53.9%) were male (Table 1). Mean ± S.D. laboratory values on the day of SARS-CoV-2 diagnosis were haemoglobin 125.5 ± 18.2 g/L, peripheral white blood cell count 9.55 × 10^9/L ± 6.03 × 10^9/L, absolute neutrophil count 5.7 × 10^9/L ± 3.5 × 10^9/L, lymphocyte count 0.9 × 10^9/L ± 0.5 × 10^9/L, platelet count 194.1 × 10^9/L ± 83.8 × 10^9/L, alanine aminotransferase (ALT) 38.3 ± 32.6 U/L, aspartate aminotransferase (AST) 40.1 ± 20.3 IU/L, blood urea nitrogen (BUN) 4.8 ± 3 mmol/L and serum creatinine 73.1 ± 25.1 μmol/L. Of the 115 patients overall, 28 (24.3%) required non-invasive ventilation support and 9 patients (7.8%) required invasive ventilation support. All patients received broad-spectrum antibiotic therapy. In the treatment group, ribavirin was initiated within a median of 4 days (range 1–12 days) of the SARS-CoV-2 diagnosis and within a median of 8 days (range 1–18 days) from symptom onset. There were no statistically significant differences in clinical characteristics (Table 1) or support measures (Table 2) between the two groups. The negative conversion time for SARS-CoV-2 test in patients who received ribavirin was 12.8 ± 4.1 days compared with 14.1 ± 3.5 days in the control group ($P = 0.314$). The overall mortality rate was 20.9% (24/115). The mortality rate was 17.1% (7/41) in the ribavirin group and 24.6% (17/69) in the control group; there was no significant difference in mortality between the two groups ($P = 0.475$).

Ribavirin treatment was well tolerated and there were no early discontinuations due to adverse effects. There were no significant differences in laboratory parameters (haemoglobin, leukocyte count, lymphocyte count, C-reactive protein, platelet count, serum creatinine, BUN, ALT and AST) between the two groups after the treatment course (Table 3).

4. Discussion

With the global pandemic of COVID-19, there is an urgent need for effective therapeutic interventions in patients with severe SARS-CoV-2 infection. This study shows that ribavirin is not associated with reduced time to negative conversion time for SARS-CoV-2 test and does not provide a survival benefit compared with control treatment (supportive therapy only).

In this study, treatment with ribavirin was well tolerated. Anaemia is a common complication of ribavirin therapy and has been observed in previous studies investigating the treatment of MERS-CoV and SARS-CoV infection [4,10]. In the current study, the degree of change in haemoglobin values during admission was 5.3 g/L in the treatment group and 10.4 g/L in the control group. There was no statistical difference between the two groups ($P = 0.051$). In addition, there were no interruptions in treatment due to anaemia.

Whether to use ribavirin treatment was based on the doctor's clinical experience. Moreover, during a particular period at the peak of the outbreak, ribavirin was sometimes out of stock, which may also have led to treatment without ribavirin. Although use of ribavirin or not was not completely random, there were no statistically significant differences in clinical characteristics (included medical history, demographic data, physical examination, and haematological, biochemical and radiological results) or support measures (immunoglobulin therapy, ventilation support and corticosteroid therapy) between the ribavirin and control groups, making the two groups comparable.

It was thought that ribavirin might be useful for treating coronavirus infection because of its broad-spectrum inhibition of RNA viruses. Several studies have shown that ribavirin has useful activity against SARS-CoV in vitro [11,12]. However, other studies have found that ribavirin did not inhibit the virus in vivo and did not

Table 1
Baseline characteristics on the day of diagnosis of SARS-CoV-2 infection and outcome of severe COVID-19 patients [a]

Characteristic	Control group (n = 71)	Ribavirin group (n = 44)	P-value
Age (years)	55.1 ± 16.2	54.6 ± 13.3	0.862
Sex			0.069
Male	43 (60.6)	19 (43.2)	
Female	28 (39.4)	25 (56.8)	
Temperature (°C)	38.7 ± 0.6	38.8 ± 0.6	0.302
Cough			0.583
No	44 (62.0)	25 (56.8)	
Yes	27 (38.0)	19 (43.2)	
Pharyngalgia			0.935
No	68 (95.8)	42 (95.5)	
Yes	3 (4.2)	2 (4.5)	
Dyspnoea [b]			0.961
No	60 (85.7)	37 (86.0)	
Yes	10 (14.3)	6 (14.0)	
Fever [b]			0.231
No	2 (3.3)	0 (0.0)	
Yes	59 (96.7)	43 (100.0)	
Lymphocyte count ($\times 10^9$/L)	0.9 ± 0.5	1.0 ± 0.6	0.592
Leukocyte count ($\times 10^9$/L)	4.9 ± 3.8	3.8 ± 2.6	0.113
Haemoglobin (g/L)	127.6 ± 18.7	122.0 ± 17.2	0.119
Platelet count ($\times 10^9$/L)	197.3 ± 88.8	188.9 ± 75.9	0.611
Prothrombin time (s)	13.5 ± 1.3	14.0 ± 2.1	0.140
aPTT (s)	41.1 ± 11.5	39.8 ± 6.5	0.503
Procalcitonin (μg/L)	0.2 ± 0.3	0.3 ± 0.5	0.324
C-reactive protein (mg/L)	67.4 ± 49.1	65.4 ± 61.6	0.853
ESR (mm/h)	47.8 ± 32.7	48.3 ± 25.6	0.934
Serum creatinine (μmol/L)	75.5 ± 27.9	69.3 ± 19.4	0.213
BUN (mmol/L)	5.2 ± 3.1	4.3 ± 2.8	0.132
Glomerular filtration rate ()	93.1 ± 25.9	94.6 ± 18.1	0.733
ALT (U/L)	41.6 ± 38.5	32.6 ± 18.3	0.159
AST (U/L)	41.7 ± 21.1	37.4 ± 18.9	0.289
Lactate dehydrogenase (U/L)	377.4 ± 166.6	381.9 ± 160.2	0.901
CT imaging findings [b]			0.804
No lesion	2 (2.9)	1 (2.4)	
Ground-glass opacity	53 (77.9)	30 (73.2)	
Consolidative pulmonary opacities	13 (19.1)	10 (24.4)	
No. of infected lung lobes [b]			0.509
0	2 (3.3)	1 (3.2)	
1	6 (9.8)	1 (3.2)	
2	8 (13.1)	3 (9.7)	
3	4 (6.6)	0 (0.0)	
4	4 (6.6)	2 (6.5)	
5	37 (60.7)	24 (77.4)	
Smoking history			0.906
Never smoked	65 (91.5)	40 (90.9)	
Smokes or previously smoked	6 (8.5)	4 (9.1)	
Drinking history			0.892
Never drinks	64 (90.1)	40 (90.9)	
Drinks or previously drank	7 (9.9)	4 (9.1)	
Hypertension			0.238
No	55 (77.5)	38 (86.4)	
Yes	16 (22.5)	6 (13.6)	
Cardiovascular disease			0.072
No	66 (93.0)	44 (100.0)	
Yes	5 (7.0)	0 (0.0)	
Diabetes mellitus			0.946
No	61 (85.9)	38 (86.4)	
Yes	10 (14.1)	6 (13.6)	
Cancer			0.424
No	65 (91.5)	42 (95.5)	
Yes	6 (8.5)	2 (4.5)	
Cerebrovascular disease			0.730
No	70 (98.6)	43 (97.7)	
Yes	1 (1.4)	1 (2.3)	
Negative conversion time for SARS-CoV-2 test (days)	14.1 ± 3.5	12.8 ± 4.1	0.314
Death[c]			0.475
No	52 (75.4)	34 (82.9)	
Yes	17 (24.6)	7 (17.1)	

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; aPTT, activated partial thromboplastin time; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography.

[a] Data are presented as the n (%) or mean ± standard deviation.

[b] There were missing data for dyspnoea, fever, CT imaging findings and number of infected lung lobes.

[c] Two participants in the control group and three participants in the treatment group were still receiving treatment in hospital at the end of the study.

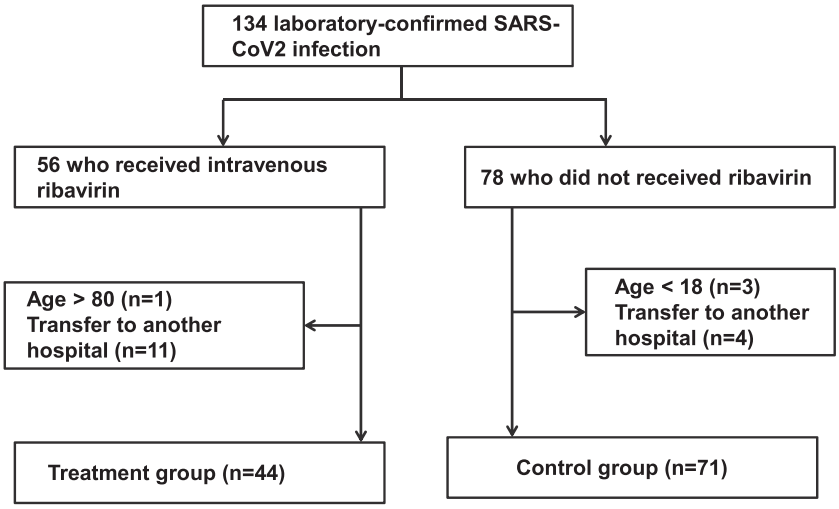

Fig. 1. Flow diagram for study inclusion. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2
Support measures offered during the course of SARS-CoV-2 infection [a]

Support measure	Control group (n = 71)	Ribavirin group (n = 44)	P-value
Immunoglobulin therapy			0.143
No	46 (64.8)	33 (75.0)	
Yes	25 (35.2)	11 (25.0)	
Non-invasive ventilation support			0.750
No	53 (74.6)	34 (77.3)	
Yes	18 (25.4)	10 (22.7)	
Invasive ventilation support			0.302
No	64 (90.1)	42 (95.5)	
Yes	7 (9.9)	2 (4.5)	
Corticosteroid therapy [b]			0.288
No	45 (65.2)	30 (75.0)	
Yes	24 (34.8)	10 (25.0)	

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Data are presented as n (%).
[b] There were missing data for immunoglobulin therapy and corticosteroid therapy.

Table 3
Laboratory parameters following therapy for severe COVID-19 [a]

Parameter	Control group (n = 71)	Ribavirin group (n = 44)	P-value
Haemoglobin (g/L)	115.8 ± 19.8	116.0 ± 16.7	0.952
Haemoglobin change (g/L)	−10.4 ± 12.6	−5.3 ± 13.5	0.051
Leukocyte count ($\times 10^9$/L)	6.4 ± 3.6	5.7 ± 3.0	0.283
Lymphocyte count ($\times 10^9$/L)	1.1 ± 0.6	1.1 ± 0.5	0.720
C-reactive protein (mg/L)	39.1 ± 48.1	28.2 ± 37.9	0.233
Platelet count ($\times 10^9$/L)	243.3 ± 103.8	263.4 ± 128.2	0.367
Serum creatinine (μmol/L)	69.7 ± 26.8	63.3 ± 21.4	0.195
BUN (mmol/L)	5.8 ± 4.3	4.4 ± 2.7	0.068
ALT (U/L)	62.1 ± 187.3	35.8 ± 17.7	0.372
AST (U/L)	56.9 ± 145.9	34.3 ± 21.7	0.327

COVID-19, coronavirus disease 2019; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Data are presented as the mean ± standard deviation.

promote the recovery of patients infected with SARS-CoV [13,14]. A retrospective cohort study showed that ribavirin and interferon alfa-2a therapy improved survival at 14 days but not at 28 days in patients with severe MERS-CoV infection [4]. It should also be pointed out that a large, retrospective, multicentre study on different types of interferon with ribavirin to treat critically ill MERS cases did not improve survival [6]. Therefore, we should consider to remove the suggestion that patients with COVID-19 be treated with ribavirin.

This study is limited by its single-centre, retrospective and non-randomised nature. Inevitably, selection bias cannot be completely ruled out. Incontrovertibly, new interventions should be evaluated in randomised controlled clinical trials. However, such an approach is generally accepted in emerging diseases such as SARS-CoV-2 infection. In addition, the sample size required to achieve 90% power of test is approximately 1048 patients. Thus, the sample size in the current study is limited and it is possible that small effects were missed. Nevertheless, the results can provide a reference for further studies based on a larger sample size randomised clinical trial or other populations.

In conclusion, severe COVID-19 is associated with a relatively high mortality rate. Intravenous ribavirin therapy is not associated

with improved negative conversion time for SARS-CoV2 test or a reduced mortality rate. Ribavirin therapy was well tolerated and there were no significant adverse effects. These results should be verified in randomised controlled clinical trials. The role of ribavirin in patients with mild SARS-CoV-2 infection also requires further study.

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Ethical approval: This study was approved by Ethics Commission of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) [2020-0039]. Owing to the rapid emergence of this infectious disease, the need for written informed consent was waived.

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