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Effect of oral ribavirin treatment on the viral load and disease progression in Crimean-Congo hemorrhagic fever

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SUMMARY

Objectives: Crimean-Congo hemorrhagic fever (CCHF) is a lethal hemorrhagic disease. There is currently no specific antiviral therapy for CCHF approved for use in humans. In this study we aimed to investigate the effect of oral ribavirin treatment on the viral load and disease progression in CCHF.
Methods: The study population was composed of patients who had a definitive diagnosis of CCHF by means of clinical presentation plus detection of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR). Ten patients who received oral ribavirin for 10 days and 40 control patients who received supportive treatment only were included in the study. Ribavirin treatment consisted of oral ribavirin 4 g/day for 4 days and then 2.4 g/day for 6 days. Viral load and hematological and biochemical laboratory parameters, which were measured daily, were analyzed.
Results: Mean age (37.4 vs. 45.5, $p = 0.285$), gender (male 50% vs. 62.5%, $p = 0.470$), days from the appearance of symptoms to admission (4.3 vs.4.4 days, $p = 0.922$), and initial complaints were similar between the ribavirin group and the control group. Upon hospital admission, mean viral load was 8.2×10^8 copies/ml in the ribavirin group and 8.3×10^8 copies/ml in the control group ($p = 0.994$). During follow-up, no statistically significant differences were found between the groups with regard to the decrease in viral load, the reduction in alanine aminotransferase and aspartate aminotransferase levels, and the increase in platelet count. The case-fatality rate was 20% (2/10 patients) in the ribavirin group and 15% (6/40 patients) in the control group ($p = 0.509$).
Conclusion: In this study, oral ribavirin treatment in CCHF patients did not affect viral load or disease progression.

1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal infection caused by the CCHF virus belonging to the genus *Nairovirus* of the family *Bunyaviridae*. The CCHF virus is transmitted to humans by Hyalomma ticks or by direct contact with the blood of infected humans or domestic animals.[1] Presently, CCHF is a public health problem in more than 30 countries in Africa, Asia, Southeast Europe, and the Middle East.[2,3] Since 2002, a rapid emergence of CCHF has occurred in the central, northern, and eastern regions of Turkey.[4,5] By the end of 2007, there had been 1820 confirmed cases and 92 deaths (a case-fatality rate of 5%) in Turkey.[6]

Treatment options for CCHF are limited. There is currently no specific antiviral therapy for CCHF approved for use in humans.[1] The World Health Organization (WHO) currently recommends ribavirin as a potential therapeutic drug for CCHF.[3,7] Ribavirin has been found to be effective against CCHF virus in vitro,[8,9] but the efficacy of ribavirin remains controversial.[10,11]

For many viral diseases, including CCHF, viral load measurement has become an important part of disease management. Furthermore, increased severity of the CCHF disease has been shown to correlate with high viremia titers.[12,13]

In this study, we aimed to investigate the effect of oral ribavirin treatment on the viral load and disease progression in CCHF patients in Turkey.

2. Materials and methods

2.1. Patient population

This case–control study was conducted at the Ankara Numune Education and Research Hospital between 2006 and 2008. The

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Table 1
Comparison of baseline characteristics and laboratory findings between the ribavirin group and the control group

Characteristic	Ribavirin group ($n=10$)	Control group ($n=40$)	p-Value
Age, years	37.4 ± 17.9	45.5 ± 19.3	0.285[a]
Male sex	5 (50%)	25 (62.5%)	0.470[b]
Duration of complaints until hospitalization, days	4.3 ± 1.4	4.4 ± 1.4	0.922[a]
Most common complaints			
Myalgia	10 (100%)	37 (92.5%)	0.504[c]
Fever	10 (100%)	38 (95%)	0.637[c]
Lack of appetite	10 (100%)	38 (95%)	0.637[c]
Headache	9 (90%)	31 (77.5%)	0.349[c]
Nausea and/or vomiting	8 (80%)	25 (62.5%)	0.257[c]
Bleeding (any kind)	3 (30%)	14 (35%)	0.539[c]
Physical findings			
Fever, temperature >38 °C	4 (40%)	19 (47.5%)	0.670[c]
Hepatomegaly	0 (0%)	3 (7.5%)	0.504[c]
Splenomegaly	1 (10%)	1 (2.5%)	0.363[c]
Rash			
Maculopapular	1 (10%)	7 (17.5%)	0.491[c]
Petechiae	3 (30%)	7 (17.5%)	0.314[c]
Bleeding			
Ecchymosis	2 (20%)	7 (17.5%)	0.584[c]
Epistaxis	2 (20%)	9 (22.5%)	0.618[c]
Hematemesis	2 (20%)	3 (7.5%)	0.258[c]
Melena	0 (0%)	5 (12.5%)	0.311[c]
Somnolence	2 (20%)	5 (12.5%)	0.429[c]
Laboratory findings			
Platelet count ($\times 10^9$/l)	52.8 ± 47.5	58.1 ± 41.3	0.544[d]
WBC count ($\times 10^9$/l)	2.320 ± 1.203	2.707 ± 1.210	0.444[d]
AST level, U/l (normal range 5–34 U/l)	305 ± 280	336 ± 331	0.780[d]
ALT level, U/l (normal range 0–55 U/l)	133 ± 92	166 ± 214	0.560[d]
LDH level, U/l (normal range 123–243 U/l)	737 ± 439	649 ± 416	0.559[d]
CPK, U/l (normal range 25–200 U/l)	512 ± 401	918 ± 1044	0.525[d]
PT, s (normal range 11.5–15.5 s)	12.4 ± 2	12.7 ± 2	0.653[a]
aPTT, s (normal range 20–34 s)	42.8 ± 19.5	40.9 ± 15	0.971[d]
INR (normal range 0.8–1.2)	0.98 ± 0.16	1.02 ± 0.16	0.551[a]
Fibrinogen, mg/dl (normal range 180–350 mg/dl)	251 ± 74	264 ± 73	0.734[d]

Data are n (%) of patients or mean value ± standard deviation.
WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio.
[a] Student's t-test.
[b] Chi-square test.
[c] Fisher's exact test.
[d] Wilcoxon–Mann–Whitney test.

study population was composed of patients with a definitive diagnosis of CCHF by means of clinical presentation plus detection of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR). Patients with suspected cases of CCHF were offered oral ribavirin therapy upon hospital admission. Ribavirin treatment was initiated before laboratory confirmation of the CCHF diagnosis, as the results were only available a few days after obtaining the samples. If a patient agreed to use ribavirin treatment, they were treated with oral ribavirin 4 g/day for 4 days and then 2.4 g/day for 6 days. Only ribavirin-treated patients with a confirmed CCHF diagnosis by RT-PCR were included in the study. Control patients received supportive treatment only. All patients also received preparations of erythrocytes, platelets, and fresh frozen plasma, depending on their homeostatic state.

In total, this study included 10 case patients (patients who received oral ribavirin) and 40 control patients (patients who received supportive treatment only). For each ribavirin case, four control cases were randomly selected to match one ribavirin case with respect to similar initial viral loads and duration of symptoms. Matching ribavirin and control cases in a 1:4 ratio maximized the power of the analysis.

Written informed consent was obtained from the patient and/or their family members for all patients enrolled in this study. Also, for each patient, permission was obtained from the Turkish Ministry of Health to use ribavirin for an unlicensed indication. This study also followed procedures in accordance with the ethical standards of the Helsinki Declaration.

2.2. Laboratory assessments

Quantitative measurements of CCHF virus were performed daily. A TaqMan-based one-step RT-PCR assay was used for detection and quantification of CCHF virus RNA.[14] The assay was performed in a Perkin-Elmer 7700 Sequence Detection System by using the combination of reverse-transcriptase (MBI Fermentas) and Hot Start Taq DNA Polymerase (Birion GmBH) enzymes. Biochemical and hematological laboratory parameters were measured on a daily basis after hospital admission.

2.3. Statistical analysis

Viral loads and hematological and biochemical laboratory parameters, measured on a daily basis, were analyzed. Patient outcomes were also analyzed. The Chi-square test or Fisher's exact test was used when appropriate to compare proportions. Continuous variables were compared using an independent-groups t-test if normality assumptions were met; otherwise groups were compared using the Wilcoxon–Mann–Whitney test.