The Efficacy of Oral Ribavirin in the Treatment of Crimean-Congo Hemorrhagic Fever in Iran

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We compared the mortality rate among patients suspected of having Crimean-Congo hemorrhagic fever (CCHF) who received treatment with oral ribavirin and those who did not. Ninety-seven (69.8%) of 139 treated patients suspected of having CCHF survived, and 61 (88.9%) of 69 treated patients with confirmed CCHF survived. The efficacy of oral ribavirin was 80% among patients with confirmed CCHF and 34% among patients suspected of having CCHF. Considering the limitations of observational studies, we conclude that oral ribavirin is an effective treatment for the hemorrhagic form of CCHF.

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal viral infection found in parts of Africa, Asia, Eastern Europe, and the Middle East [1]. For humans, infection with tickborne CCHF virus often results in a serious illness followed by death. It has been estimated that one-third of patients hospitalized with CCHF die, although many recover rapidly after a febrile illness [2]. There has been limited experience with alternative forms of CCHF therapy [2]. During a 1984 outbreak of CCHF at Tygerberg Hospital in South Africa, 2 different antiviral agents, ribavirin and human leukocyte interferon, were used to treat infected patients [3]. Another brief report from South Africa described the results of treating 12 patients infected with CCHF with ribavirin in an open-label trial [4]. Neither supportive therapy nor immunotherapy (employing convalescent-phase plasma obtained from other patients with CCHF) has been considered effective for the treatment of CCHF patients [5, 6, 7]. In a mouse model, ribavirin treatment significantly reduced mortality and extended the geometric mean time to death [2]. In vitro, ribavirin doses as low as 5 μg/mL caused transient reduction of virus loads [8].

In 1994, Fisher-Hoch et al. [9] reported a successful treatment of 3 nosocomial cases of CCHF in Pakistan with oral ribavirin. Since that time, ribavirin has been used for treatment of CCHF in different parts of the world [10]. But, to date, no randomized, controlled trial has been performed to confirm the efficacy of oral ribavirin in the treatment of patients infected with CCHF [11].

On the basis of this information, we evaluated the efficacy of oral ribavirin among Iranian patients with CCHF in a historical cohort study, incorporating information on the availability of the drug. It is worth mentioning that this study includes not only the largest series of patients with CCHF yet studied, but also the largest group of patients treated with ribavirin. The advantages of oral ribavirin over intravenous ribavirin, in terms of cost, convenience, and availability, are an important subject of this article.

Patients and methods. This study was conducted with a historical cohort, incorporating cases reported between June 1999 and the end of September 2001 on surveillance forms. The cohort consisted of 187 patients with suspected cases of CCHF, 81 of whom were confirmed serologically to have the disease.

Patients suspected of having CCHF were defined as those who had clinically observed signs and symptoms (e.g., fever, muscle pain, and bleeding), epidemiological risk factors (receipt of a tick bite, exposure to tick splashing [i.e., crushing a tick between 2 exposed body parts], travel to or residence in an area of endemicity for CCHF [we considered travel to or residence in the Iranian provinces of Sistan va Balouchestan, Esfahan, and Golestan to be an epidemiological risk factor, because, in 1999, when the first cases were reported, we noticed that most cases were from these 3 major provinces], contact with persons with suspected cases of CCHF, or contact with animals), and laboratory data consisting of a platelet count of <150,000 platelets/mm^3 and a WBC count of <3000 or >9000 cells/mm^3.

Patients with confirmed cases of CCHF were defined as those who met the criteria for having a suspected case of CCHF and also had serological test results that were positive for IgM and/or IgG by ELISA. Demographic data, including age, sex, oc-

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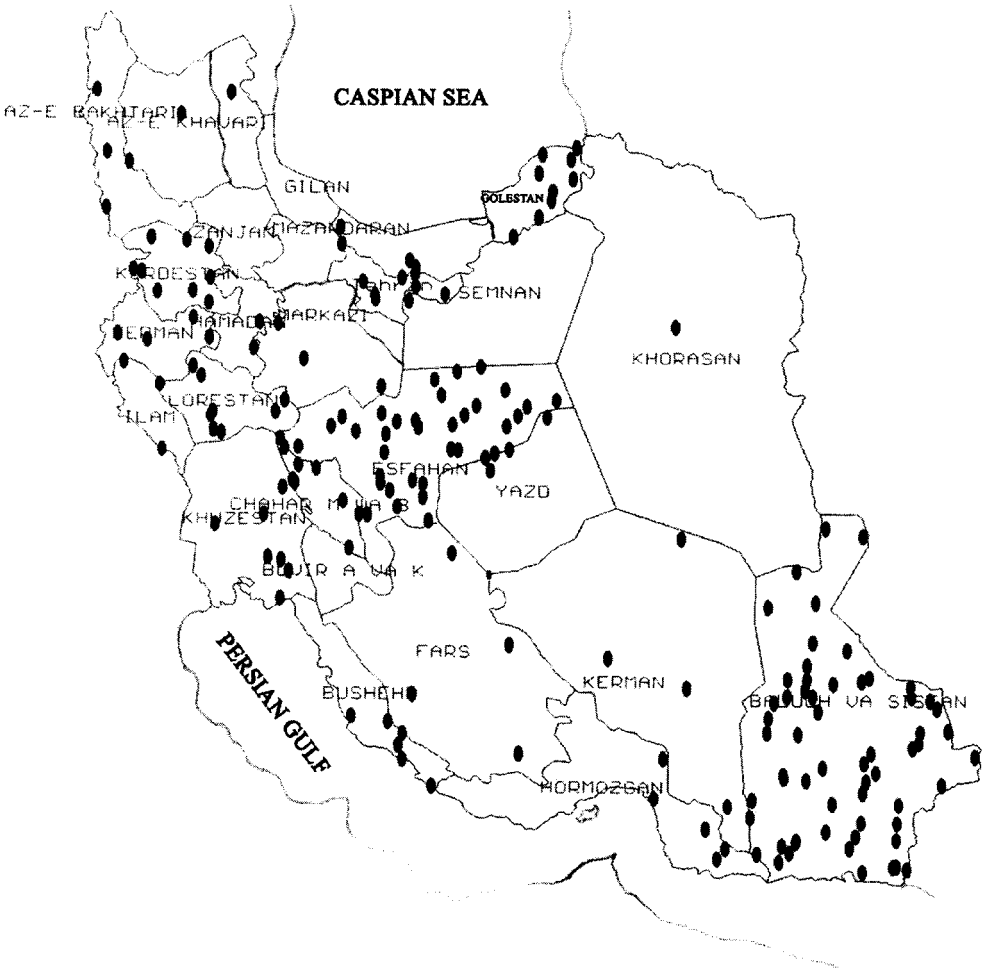

Figure 1. The places of residence of patients with suspected cases of Crimean-Congo hemorrhagic fever in Iran, 1999–2000

cupation, and place of residence, were recorded for all patients suspected of having CCHF. Occupation was recorded in 2 major groups: group 1 consisted of those whose occupation placed them at risk (e.g., physician, butcher, or nurse), and group 2 consisted of those whose occupation was considered safe (e.g., teacher or household worker). Questions concerning epidemiologic factors, as mentioned above, were also asked. The date of the first clinical signs and the date of laboratory findings were recorded. The patients with suspected cases of CCHF were treated with oral ribavirin at the time they were first suspected to have the disease. Their serum samples (1, 2, or 3 samples) were sent to the reference laboratory. The first serum sample was collected when patients were identified as having a case of suspected CCHF, and ribavirin was administered after the first sample was collected. The second and third samples (if the patient was alive and accessible) were collected 5 and 10 days later, respectively. Unfortunately, no data was recorded concerning the interval between the start of ribavirin therapy and the death for the patients who died despite receiving ribavirin.

Samples collected early in the study were sent to the reference laboratory in South Africa (National Institute for Virology, Sandringham), and all samples were evaluated for the presence of dengue fever virus, Rift Valley fever virus, yellow fever virus, Lassa fever virus, Marburg virus, Ebola virus, and hantavirus. None of the samples tested positive for the agents of any viral hemorrhagic fevers other than CCHF. Samples collected later in the study were sent to the Pasteur Institute of Senegal in Dakar (Arboviruses and Viral Hemorrhagic Fever Department), and these latter samples were tested only for CCHF virus, yellow fever virus, and Rift Valley fever virus. The results of serologic tests were unavailable for up to 3 weeks after the date the serum samples were sent to the Pasteur Institute; therefore, we initiated ribavirin therapy before receiving the results.

Our patients were from different provinces of Iran (figure 1 and figure 2) and were clinically identified by infectious diseases specialists and internists on the basis of the definition for a patient suspected of having CCHF. They were then treated with oral ribavirin, and the summary surveillance forms (which included information on outcome; i.e., death or survival) were sent to the Ministry of Health and Medical Education. All the

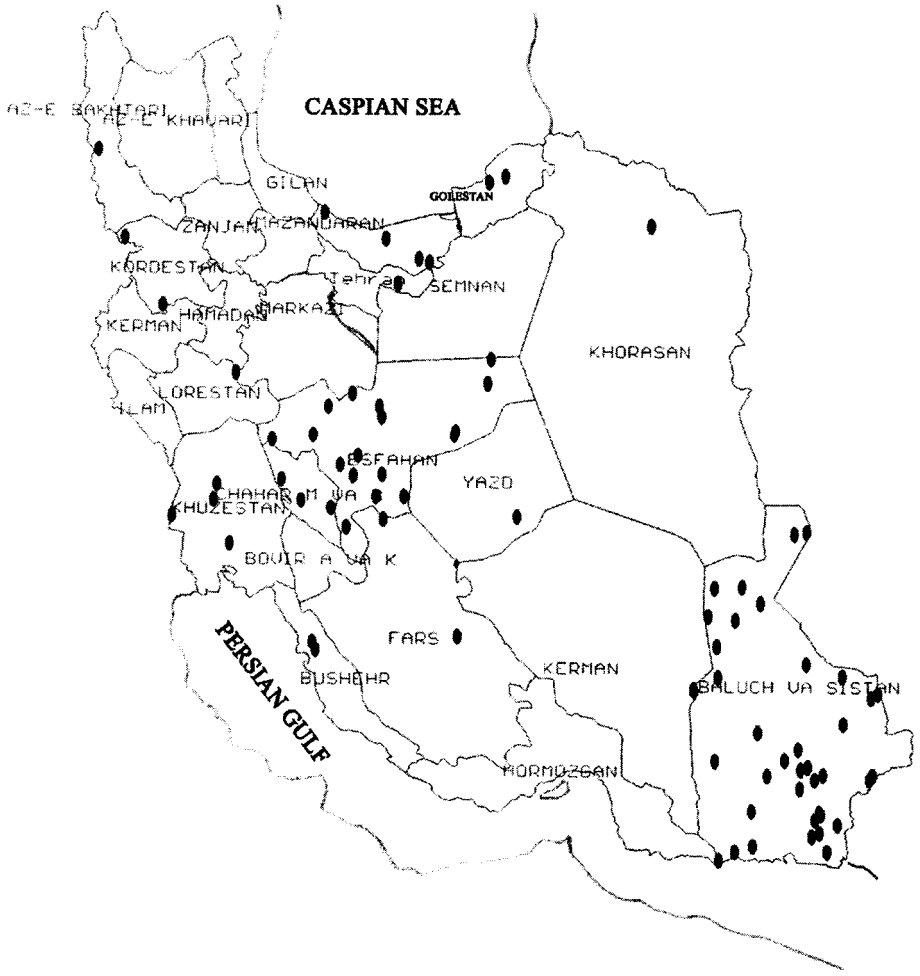

Figure 2. The places of residence of patients with serologically confirmed cases of Crimean-Congo hemorrhagic fever in Iran, 1999–2000

patients were treated in the local hospitals where they had presented with clinical manifestations.

Oral ribavirin was administered within a mean of 4 days after onset of symptoms at the dosage recommended by the World Health Organization (WHO) (30 mg/kg as an initial loading dose, then 15 mg/kg every 6h for 4 days, and then 7.5 mg/kg every 8h for 6 days). The total duration of treatment was 10 days. Those patients who had nausea and vomiting received ribavirin by nasogastric tube. Ribavirin was administered in the form of tablets (200 mg) made in the United Kingdom for Durbin PLC. It is worth mentioning that the first study patients reported in 1999 did not receive ribavirin because it was not available in our country. Since 2000, on the basis of limited reports on the efficacy of ribavirin in the treatment of CCHF, all study patients suspected of having CCHF were treated with oral ribavirin, administered at the dosage mentioned above.

This study was performed to evaluate survival rates among 2 groups of patients (those treated with ribavirin and those not treated). Because the patients were suspected of having CCHF only on the basis of clinical findings and laboratory results, we also studied the 81 patients with serologically-confirmed cases to increase the power of our study. One hundred and thirty-nine of 187 patients with suspected cases of CCHF (69 of 81 patients with serologically-confirmed cases of CCHF) were treated with oral ribavirin, and survival rates in the 2 groups were compared. Statistical analysis of the data was performed using the statistical package of Stata (Stata Corporation) and Epi-Info (Centers for Disease Control and Prevention). Variables were analyzed with the χ^2 test and Fisher's exact test to verify the differences between the 2 groups.

Results. Eighty-one of 187 patients with suspected cases of CCHF were confirmed to have CCHF by serologic test results. One patient was confirmed to have CCHF by means of virus isolation in addition to positive serologic test results (the first samples were evaluated for virus with use of mice and cell cultures at the South African National Institute for Virology [Sandringham, South Africa] by R. Swanepoel; however, after the outbreak was confirmed, virus isolation was not performed for the later cases). In all patients with confirmed cases of

Table 1. Demographic, epidemiological, and clinical data for 187 patients with suspected and 81 patients with confirmed cases of Crimean-Congo hemorrhagic fever in Iran, 1999–2001

Variable	Suspected cases		Confirmed cases	
	Proportion (%) of patients treated with ribavirin[a]	*P*	Proportion (%) of patients treated with ribavirin[a]	*P*
Demographic characteristics				
Sex				
Male	102/128 (79.7)	.022	52/59 (88.1)	NS
Female	37/59 (62.7)		17/22 (77.3)	
Age in years				
<33	71/103 (68.9)	NS	31/39 (79.5)	NS
⩾33	68/84 (80.9)		38/42 (90.5)	
Epidemiological factors				
Occupation class				
At risk	42/50 (84.0)	NS	24/29 (82.7)	NS
Low risk	97/134 (72.4)		45/49 (91.8)	
Place of resisdence				
Sistan va Balouchestan	56/60 (93.3)	—	36/39 (92.3)	—
Esfahan	25/32 (78.1)		16/16 (100.0)	
Golestan	11/12 (91.7)		6/7 (85.7)	
Other	47/83 (56.6)		11/19 (57.9)	
Animal contact				
Yes	96/121 (79.3)	.037	58/64 (90.6)	.011
No	41/64 (64.1)	.037	10/16 (62.5)	
Human contact				
Yes	11/17 (64.7)	NS	9/13 (69.2)	NS
No	128/170 (75.3)		60/68 (88.2)	
Clinical findings				
Fever				
Yes	138/185 (97.8)	NS	68/80 (85.0)	—
No	0/1 (0.0)		—	
Hemorrhage				
Yes	138/186 (74.2)	—	68/80 (85.0)	—
No	—		—	
Thrombocy topenia				
Yes	137/182 (75.3)	NS	68/80 (85.0)	—
No	1/4 (0.25)		—	
Total	139/187 (74.3)		69/81 (85.2)	

NOTE. NS, not significant ($P > .05$).

[a] No. of patients with variable who were in the ribavirin-treated group/no. of patients with variable (%).

CCHF, IgM was detected by ELISA. The demographic and epidemiological data for both groups, along with some clinical and laboratory findings, are displayed in table 1, and includes data from 187 patients with suspected cases of CCHF and 81 patients with confirmed cases of CCHF. Figure 1 and figure 2 show the place of residence for each patient and demonstrate that most patients were reported to be from the 3 major provinces of Sistan va Balouchestan, Esfahan, and Golestan. As shown in table 1, the treated group of patients with suspected cases of CCHF had a higher prevalence of animal contact than did the untreated group (χ^2 test, $P = .037$). The sex difference was only significant for suspected cases (χ^2 test, $P = .022$). For all other variables, there were no such differences ($P > .05$). Table 1 also demonstrates that the treated group of patients

Table 2. Absolute and relative frequency of outcome for 187 Iranian patients with suspected Crimean-Congo hemorrhagic fever, 1999–2001.

	No. (%) of patients		
Patient group	Who died	Who recovered	Total
Treated with ribavirin	42 (30.2)	97 (69.8)	139 (74.7)
Historical control	22 (45.8)	26 (54.2)	48 (25.7)
Total	64 (34.2)	123 (65.8)	187 (100)

NOTE. Relative risk, 0.66; 95% CI, 0.45–0.98; χ^2, 3.87 ($P < .05$).

with confirmed cases of CCHF had a higher prevalence of animal contact than did the untreated group (Fisher exact test, $P = .011$). For all other variables, there were no such differences ($P > .05$).

Forty-two (30.2%) of 139 patients with suspected cases of CCHF who were treated with ribavirin died (table 2). The efficacy of oral ribavirin in the group of patients with suspected cases CCHF was determined to be 34% (RR, 0.66; 95% CI, 0.45–0.98). Eight (11.6%) of 69 patients with confirmed cases of CCHF who were treated with ribavirin died (table 3). The efficacy of oral ribavirin in the group of patients with confirmed cases of CCHF was determined to be 80% (RR, 0.20; 95% CI, 0.09–0.45).

Discussion. In this study, the efficacy of oral ribavirin was determined to be 34% among patients suspected of having CCHF and 80% among patients with confirmed cases of CCHF. Fisher-Hoch et al. [9] reported the survival of 3 patients with CCHF treated with ribavirin in Pakistan in 1994, and, if it had been possible for them to treat more patients, their findings could have been comparable to ours.

Until 3 decades ago, there was no effective treatment for CCHF. Lazarev [12] reported that serum obtained from those patients who survived CCHF was effective in treatment of CCHF in new patients when administered via intramuscular injection. He demonstrated that the serum was effective only when administered within 3 days after the onset of the disease and that it led to a decrease in fever and hemorrhagic manifestations. Later, he recommended that, as this primary information was not enough, further evaluation was needed. A brief report from South Africa described the result of treating 12 patients with CCHF with intravenous ribavirin in an open-label trial [4]. Ribavirin therapy was started early (within 4 days after the onset of the disease) for 7 patients, and none died. Ribavirin therapy was initiated late (at least 5 days after the onset of the disease) for 5 patients, and 3 died [4]. In another report, oral ribavirin was used in the treatment of 3 patients in Pakistan with nosocomial CCHF, administered at a dosage of 4 g daily for 4 days and then 2.4 g daily for the following 6 days [9]. The 3 patients were not expected to respond to therapy, but this treatment saved their lives. In an animal model, ribavirin reduced the mortality rate among infant mice experimentally infected with CCHF virus [2].

Table 3. Absolute and relative frequency of outcome for 81 Iranian patients with confirmed Crimean-Congo hemorrhagic fever, 1999–2001.

	No. (%) of patients		
Patient group	Who died	Who recovered	Total
Treated with ribavirin	8 (11.6)	61 (88.4)	69 (85.2)
Historical control	7 (58.3)	5 (41.7)	12 (14.8)
Total	15 (18.5)	66 (81.5)	8 (100)

NOTE. Relative risk, 0.20; 95% CI, 0.09–0.45; χ^2, 14.80 ($P < .001$).

Ribavirin has been shown to have activity in vitro against CCHF virus in concentrations as low as 5 mg/mL [8]. The intravenous preparation of ribavirin is recommended for treatment of viral hemorrhagic fevers, and the oral form for postexposure prophylaxis [13]. Oral ribavirin has been used for postexposure prophylaxis for patients with CCHF, but its efficacy has not been formally assessed [3].

Ribavirin is well-absorbed from the gastrointestinal tract [3], and the oral formulation would be expected to attain levels in the blood comparable to those attained by the intravenous formulation [8]. Most cases of CCHF are reported in African and Middle Eastern countries, where oral ribavirin is more readily available, more easily licensed, and cheaper than the intravenous formulation. Therefore, we performed a historical cohort study based on surveillance data to evaluate the efficacy of oral ribavirin in our patients. Treatment choice was based on the availability of the drug. It is worth mentioning that the mortality rate among our group of patients with confirmed CCHF who were not treated with ribavirin (58.3%) is comparable with some published rates (10% to >50%) [5, 6, 8]. Because of the fact that there is no randomized, controlled trial in the literature and the fact that none can be performed, because it would violate medical ethics, the results of this study provide valuable information for deciding how to treat patients with CCHF. The WHO has recommended intravenous ribavirin for treatment of patients with CCHF; the results of our study show that oral ribavirin is also an effective treatment for patients with the hemorrhagic form of CCHF. Further investigations comparing the intravenous and oral ribavirin formulations are recommended.

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