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Perspective

Ribavirin is not effective against Crimean–Congo hemorrhagic fever: observations from the Turkish experience[☆]



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SUMMARY

Crimean–Congo hemorrhagic fever (CCHF) is a viral infection associated with a high mortality rate. Ribavirin is the only drug used in the treatment of this disease. Studies investigating the effectiveness of ribavirin in CCHF have been retrospective and to date have included only a small number of cases. In recent years, due to climate changes, the number of cases of CCHF in Turkey has increased, and experience in the treatment of CCHF has improved. Several studies have evaluated the efficacy of ribavirin in Turkey, including one randomized controlled trial and two studies with a large number of cases. In these studies, ribavirin therapy was not shown to decrease mortality rates; the mortality rate was 2–9% in patients treated with ribavirin and 5.6–11% in those who were not treated with this drug. These findings suggest that patients with CCHF should be followed with supportive care only until randomized controlled trials with larger groups have been conducted.

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1. Introduction

Crimean–Congo hemorrhagic fever (CCHF) is a viral infection seen in Asia, Europe, and the Middle East, and has a high mortality rate.^{1,2} CCHF is caused by a virus of the genus *Nairovirus*, family *Bunyaviridae*.^{1,2} The mortality rate is 3–30% and varies according to geographic area.^{1,2} The virus is usually transmitted to humans through tick bites or direct contact with the blood of an infected person during the acute phase of the disease.^{1,2} According to the World Health Organization, CCHF has been seen in 34 countries, and more than 50 cases are reported annually in four countries, including Turkey.³ The tropical climate zone is gradually expanding with the impact of global warming and this has enlarged the geographic area covered by the ticks that spread the disease.¹

The pathogenesis of this disease can be divided into three phases: pre-hemorrhagic phase, hemorrhagic phase, and convalescent phase.^{1,2} After transmission of the virus, it replicates and spreads through the bloodstream and causes flu-like symptoms lasting for 1 week (pre-hemorrhagic phase).^{1,2} After this stage, viral replication decreases, and macrophage-derived cytokines cause macrophage activation syndrome (hemorrhagic phase). During this second phase, death may occur due to hemophagocytosis and

disseminated intravascular coagulation (DIC).^{1,2} Disorders of hemostasis are the most important features of CCHF. DIC is thought to occur via three mechanisms: increased release of tissue factor, direct injury, and the release of proinflammatory mediators.^{3–5} Increased synthesis of cell surface tissue factor activates the extrinsic coagulation pathway. A direct injurious effect on the endothelium and platelets occurs.^{3,4} Proinflammatory mediators released from virus-infected monocytes lead to destruction of endothelial cells and platelets.⁵ DIC presents as a decrease in clotting factors and platelets.¹ In addition, the liver dysfunction that occurs in the course of the disease contributes to a decrease in coagulation factors.¹ As a result of these events, massive bleeding can occur in CCHF.¹

2. Ribavirin treatment

Although the main treatment option for CCHF is supportive therapy, ribavirin inhibits viral replication *in vivo* and has been shown to reduce death in murine models.⁶ Ribavirin is a guanosine analog with broad-spectrum antiviral activity.⁶ Until recently, studies supporting the use of ribavirin in CCHF have been retrospective, with a small number of cases.^{7–12} Important clinical questions are emerging due to the increasing number of patients in our country; also, ribavirin therapy is being evaluated for the treatment of CCHF. Ribavirin is the only antiviral drug used in CCHF and its effectiveness remains controversial.^{7–13} Although some studies have suggested that the use of ribavirin is effective in CCHF, others suggest the opposite.^{7–13} The most well-known study on ribavirin treatment was conducted in Iran by Mardani et al.⁷ In that

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study, eight of 69 patients treated with ribavirin died (11.6%), while seven of 12 patients who were not treated with ribavirin died (58.3%); this difference was statistically significant. However, the small number of cases in the control group and the retrospective design of the study may have decreased the reliability of the results. Mortality rates reported by Mardani et al. were higher than those in Turkey. This is because the CCHF strains in Turkey are different from those in Iran.¹⁴ In vivo studies have shown that different CCHF virus strains respond differently to ribavirin;¹⁵ this may explain why patients did not respond well to ribavirin therapy in Iran.

In contrast to studies in Iran, ribavirin therapy has not been shown to decrease the mortality rate in Turkey.^{9–13} In these studies, the mortality rate was 2–9% in patients treated with ribavirin and 5.6–11% in patients who were not treated with ribavirin. There was no difference in terms of mortality, length of hospital stay, and transfusion of blood products among the patients treated and not treated with ribavirin.^{9–11,13} Studies of the effectiveness of ribavirin in CCHF were retrospective and included few cases.^{7–12} Therefore, determining the effectiveness of ribavirin in CCHF is problematic. Only one randomized controlled trial evaluating the efficacy of ribavirin has been performed in Turkey.¹³ This study compared 64 patients given ribavirin and 72 without treatment. There was no significant difference in mortality rate, proportion of patients requiring platelet transfusion, length of hospital stay, recovery time, or laboratory parameters. Since 2002, when the first cases were reported in Turkey, the number of cases of CCHF has increased steadily. Two studies with a large number of cases showed no change in the course of disease with ribavirin treatment.^{16,17} Four hundred patients with CCHF confirmed by PCR were treated with supportive therapy.¹⁶ Twenty (5%) of these patients died. This mortality rate is similar to that of other studies of ribavirin for the treatment of CCHF in Turkey.^{9–11,13} In another study, the mortality rate of 336 patients taking ribavirin was 7.1% compared with 7% in 514 patients without treatment ($p > 0.05$).¹⁷

Other studies have suggested that ribavirin is not effective for the treatment of CCHF.^{9–13} However, some researchers have considered ribavirin to be effective, especially when administered during the early period of the disease.⁸ Giving ribavirin to patients during the early and late periods of the disease produces different results. In one study that included a large number of cases, the mortality rate in patients who started ribavirin within the first 4 days after the onset of symptoms was no different to that of patients who started treatment later.¹⁰ In another study from Turkey, one of 21 patients treated during the first 4 days after the onset of symptoms died compared to two of 20 patients treated 4 days after the onset of symptoms; this difference was not significant.¹² In another study, the initiation of ribavirin in the first 4 days after the onset of symptoms was compared with starting treatment later and was shown to reduce mortality rates from 40% to 15.7% ($p = 0.031$).⁸ Again in this study, the mortality rate of patients receiving ribavirin before bleeding was lower than that of patients receiving ribavirin later (8% and 35.8%, respectively, $p = 0.018$). Reports that ribavirin is more effective during the first period of disease have also concluded that it decreases viral replication during the first week and so reduces the mortality rate. This hypothesis is supported by the fact that viral load is the most important factor contributing to mortality in CCHF.¹⁸ However, a study from Turkey contradicts this hypothesis.¹¹ In that study, 10 patients were given ribavirin and 40 were treated with supportive therapy. In the first 6 days of treatment, both viral load decline and mortality rates were similar in the two groups. In CCHF, viral load is important for determining the mortality rate, but ribavirin has not been shown to decrease viral load.

An analysis of studies in Turkey between 2004 and 2007 has shown a gradual decrease in the use of ribavirin (67.9%, 21.8%,

Table 1
CCHF-related mortality rate and ribavirin use in Turkey, 2004–2007

Year	Total number of CCHF patients	Number of patients using ribavirin	Mortality rate
2004	249	169 (67.9%)	5.2%
2005	266	58 (21.8%)	4.9%
2006	438	71 (16.2%)	6.2%
2007	717	85 (11.8%)	4.6%

16.2%, and 11.8%); despite this, mortality rates have not changed significantly (5.2%, 4.9%, 6.2%, and 4.6%, respectively) (Table 1).¹⁹ This finding indicates the ineffectiveness of ribavirin.

Although the efficacy of ribavirin in CCHF is highly controversial, its use is justified based on its being the only drug available. However, serious side effects are the major obstacle to this becoming a recommendation. In one study, 126 patients given ribavirin and 92 patients without treatment were followed; mortality rates did not differ. However, if only the first 8 days were considered, the mortality rate was 10.3 times higher in those receiving ribavirin.¹⁰ The increased mortality in that study was related to the toxic effects of ribavirin. In patients with a poor clinical course, ribavirin can increase the mortality rate due to severe organ damage. Similarly, in severe acute respiratory syndrome (SARS), patients with severe hypoxemia treated with ribavirin had a higher mortality rate due to the effects of the drug.²⁰ Another obstacle to the use of ribavirin is its genotoxic effect.^{21–23} Ribavirin has been shown to have a mutagenic effect on lymphocytes and sperm.^{22,23}

3. Conclusion

All of these findings suggest that patients with CCHF should be followed with supportive care only until randomized controlled trials including larger populations have been conducted.

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