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Letter to the Editor

The efficacy of ribavirin in Crimean-Congo hemorrhagic fever—randomized trials are urgently needed

The only antiviral drug used today in Crimean-Congo hemorrhagic fever (CCHF) is ribavirin; however, its efficacy is controversial due to the lack of randomized controlled trials.

The studies examining the efficacy of ribavirin in CCHF have generally been retrospective studies including insufficient numbers of patients, resulting in low power. We think that ribavirin should not be used in CCHF until randomized controlled studies have been conducted, and that only supportive treatment should be used.[1]

In response to the letter from Professor Onder Ergonul suggesting that our conclusions are wrong, we provide the scientific evidence outlined below.

First, Professor Ergonul suggests that a study published in 2013 showed ribavirin to decrease the mortality from CCHF.[2] However, in that retrospective study, the patients were grouped by severity as mild, moderate, and severe cases, and ribavirin decreased mortality only in moderate cases. It was reported that two of 134 cases receiving ribavirin and three of 18 cases not receiving ribavirin died, and that this difference was statistically significant. The mortality rates were low in the ribavirin group, but because the study was not randomized, the patient selection may have been biased; for example, severe cases may not have received ribavirin if this drug was not available at the hospital of admission and then died before it became available or after just a few doses. Therefore, we believe that the study result showing the decreased mortality in the ribavirin group is due to a type 1 error.

Second, Professor Ergonul suggests that some studies performed recently in Turkey have revealed as an outcome that ribavirin decreased mortality in CCHF.[2–5] One of these studies is related to healthcare employees coming into contact with the CCHF virus or being infected following CCHF exposure.[4] In that study, nine healthcare employees were administered ribavirin following injury with contaminated tools, two before any symptoms developed and seven after they had developed symptoms. It was suggested that the development of CCHF-related symptoms was prevented in two healthcare employees coming into contact with the CCHF virus. However, CCHF is a disease with a high probability of asymptomatic presentation, thus this invalidates that comment. Additionally, stating that ribavirin is effective in CCHF based on only two cases does not coincide with scientific study principles. Further, in that study, ribavirin was administered to seven healthcare employees developing CCHF, and it was reported that only one case died. When these seven study cases are examined in detail, it is observed that four cases were of moderate severity, two of mild severity, and one was of severe grade – the healthcare worker who died was the severe grade case. Therefore, it is more probable that survival is related to disease severity rather that the use of ribavirin.

In another study, mortality was found to be 0% in eight cases receiving ribavirin and 4.5% in 22 severe cases (one patient died) who did not receive ribavirin; it was claimed that mortality was much higher in the patients not receiving ribavirin.[5] However, the difference between the groups was not statistically significant and the patients were not randomized prospectively.

Professor Ergonul suggests that ribavirin use in CCHF is supported by two other studies included in our article.[6,7] However, these studies did not find that ribavirin reduced mortality, only that some laboratory parameters improved more rapidly in patients receiving ribavirin.

Professor Ergonul indicates that the study reported in a reference we cited was biased and that an editorial has been published in relation to this subject.[8,9] He further suggests that there was a bias in that study arising from ribavirin administration to more severe cases. However, it is known that clinicians in Turkey in 2004, the year in which the study was performed, administered ribavirin to all cases, without differentiating between mild and severe ones.

Third, in the only randomized controlled study examining the efficacy of ribavirin in CCHF, no statement about the recruitment of only late cases is available as suggested by the author.[10] In our opinion the only deficient aspect of this study was that the effect of ribavirin on mortality was not examined in the groups in which the cases were separated into early and late cases.

Professor Ergonul suggests that the conduct of a study examining the efficacy of ribavirin in CCHF is in contravention to the Declaration of Helsinki. This Declaration finds the administration of placebo to a group of patients to be inappropriate when a treatment method of proven benefit in a disease is available. However, it is our firm belief that the efficacy of ribavirin in CCHF is not proven, and on the contrary it has been demonstrated in many non-randomized, retrospective studies and case series that it has no effect on mortality. Therefore, we think that it is ethically acceptable to perform a randomized, placebo-controlled study in CCHF in relation to ribavirin use, stratifying for disease stage. Furthermore, ribavirin usage rates have decreased to 11.8% in Turkey according to the 2004–2007 data of the Turkish Ministry of Health, Department of Zoonotic Diseases, as reported by Ceylan et al.[1] and Turhan et al.[11] In other words, the drug is no longer used in the treatment of the disease.

Fourth, Professor Ergonul has suggested that in a study on the early administration of ribavirin in CCHF the mortality rate was 2.9% (10/342) and that this rate was lower than the rate of 5% (20/400) reported in another study in which the cases were not administered ribavirin.[3,12] In the study mentioned, the cases using ribavirin were not grouped as early and late cases, and early- and late-presenting cases were not compared in terms of mortality, in fact all cases were accepted as early applying cases; nevertheless it

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was claimed that mortality decreased in cases using ribavirin in the early phase.

Fifth, Professor Ergonul has attributed the demonstration of higher mortality in the first 8 days of patients receiving ribavirin compared to patients not receiving ribavirin to the clinicians' preference for the initiation of ribavirin administration only in severe cases.[8] However, as it is known that in 2004, the year in which the study was conducted in our country, ribavirin administration was initiated for every case regardless of disease severity, this comment is not valid.

It is clear that the studies in relation to ribavirin use in CCHF are insufficient and conflicting. We think that the persistent recommendation of a drug of unproven efficacy for a particular disease may mislead the physicians involved with this disease. Furthermore ribavirin has severe side effects, and the effects and side effects need to be balanced.

Therefore, we think that until ribavirin use in patients with CCHF has been clarified by a randomized controlled trial, it is appropriate to monitor patients using supportive treatment only. The use of ribavirin should be restricted to patients included in a study protocol.

We believe that performing a prospective, randomized, placebo-controlled study of ribavirin in CCHF is ethically acceptable and urgently needed.

Conflict of interest: No conflict of interest to declare.

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