mislead the clinicians and policy makers, and could lead to devastating unexpected outcomes, such as not to start ribavirin at an early phase of the infection for a health care worker who had an needle-stick injury while dealing with CCHF patient.

In conclusion, in order not to mislead practitioners in the field, and not to cause more devastations in medical practise, this manuscript should be retracted from the scientific environment.

I declare that I do not have any conflict of interest related to either ribavirin or any epidemiologic studies.

References


Response to Ergonul: Scientific Evidence Versus Personal Beliefs In Crimean-Congo Haemorrhagic Fever Treatment

Dear editor,

We read Dr Ergonul’s detailed letter with great interest, however, it is impossible to agree with any of his comments due to the reasons below.

P-value and sample size are completely different things than the author thinks

We would like to refer Dr. Ergonul to some basic statistics textbooks because he has a misunderstanding of the logic of calculation of sample size and power.1–3 Using a statistical software does not replace theoretical knowledge, nowadays, any statistical software can easily crunch some numbers as a sample size or power whenever you provide the necessary information. However, a wrong interpretation can lead to misleading conclusions like in this letter. First, sample size is not the necessary number that would make a finding statistically significant as used in this letter.1,2 In our study, effect size that is the difference between the mortality rates of ribavirin users and non-users was 4.8% (7.1% among ribavirin users vs. 11.9% among non-users, p-value = 0.24). This p-value shows that the difference between the mortality rates is more likely to be due to chance rather than due to the effect of ribavirin.3 Of course, increasing the sample size can make this or any other result statistically significant! What if the results were 11.9% vs. 12.0%, then it is possible to calculate 32,350 patients as the necessary sample size to reach statistical significance and therefore the author can still claim that ribavirin was beneficial and sample size was insufficient. According to his logic, for each and every study in the literature with a non-significant p-value, a sample size that would lead to a significant p-value can be calculated and the study can be labeled as having “insufficient” sample size. Obviously, this is the wrong way of thinking and using sample size calculations, it is neither the p-value, nor the sample size but the effect size that matters most in clinical

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studies.\textsuperscript{1–3} For that reason, sample size is calculated by taking into consideration of the effect size the researchers would consider to be meaningful from the study they are conducting.\textsuperscript{1–3} Similarly, the author is falling into the same mistake when doing the power calculation, a post-hoc power calculation can not be done assuming that the result of the study should have been significant, instead a post-hoc power analysis can be carried out to detect an effect of some specified size or find out what effect size it would have been likely to detect.\textsuperscript{3,4} When calculated correctly, our study has 80\% power to detect a 10\% difference between the study arms (or 94\% power to detect a 20\% difference), this 10\% difference was deemed to be the minimum effect size by us to prove the efficacy of a drug in a non-randomized study like ours. It is well known that even a small amount of uncontrolled confounding (which is the case in most observational studies) can result in an effect size of 20\%–30\%.\textsuperscript{5}

In conclusion, we would like to point out that the correct version of Dr. Ergonul’s comment among epidemiologists is “P-value is not everything and effect size matters” and that is what we are concluding from this study; 4.8\% difference is not an effect size that matters and it is impossible even to speculate that ribavirin was beneficial from these results.

Confounders in the study

1. Number of days from the onset of illness: A careful reading of our manuscript would have shown the author that in contrast to his claims, we did collect data about the time from the start of symptoms as written in the first paragraph of “Data collection and statistical methods” section. What is more, we have done two separate analyses using the time from the start of symptoms, first we compared the average time from the start of symptoms between the patients who died and who survived. Second, we compared the survival rates between patients who were treated early vs late from the start of symptoms, both can be found on page 241 of the manuscript.

2. Severity of infection: Protopathic bias is not a new name for “confounding by indication” as stated by the author, it has been used in the literature since 1970s to define a type of specific bias that occurs when a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected.\textsuperscript{6,7} Obviously our study does not suffer from such a bias. In addition, the possibility of confounding by severity is very small in our study because in 2004, all the centers participating in this study, treated CCHF patients with ribavirin without any regard to the severity of disease. In contrast to the author’s claims, there is no indication that ribavirin treated patients were more severe in Table 1. On the contrary, untreated patients had higher LDH and ALT levels, higher rates of bleeding (37\% vs. 48\%), symptoms of altered sensorium such as confusion, drowsiness or coma (9.5\% vs. 14.1\%), hepatomegaly (13.5\% vs. 30.4\%) and splenomegaly (4\% vs. 14.1\%). All statistical tests in Table 1 were done according to the type and distribution of the variable and non-parametric tests were used when a continuous variable was non-normally distributed. In addition, we controlled for all the possible indicators of severity in the Cox multivariable model.

3. Severity of gastrointestinal symptoms: This study was not conducted to investigate the pharmacological efficacy of oral ribavirin but to show its efficacy in real life as it is used and highly recommended by Dr. Ergonul in this letter and in other publications. This is a haemorrhagic fever, most of the severe cases have gastrointestinal bleeding, of course, using an oral drug is questionable, and that is what we are showing in this study.

4. Duration of use: Some patients use the drug shorter than the others, this happens in every study evaluating the efficacy of a treatment especially with severe diseases. This is one of the reasons for our use of survival analysis, in this type of analysis these patients “contribute” to the analysis as long as they stay in the dataset that is until they die, dropout or are discharged from the hospital.

Our results are consistent and reliable

The aim of our study was to evaluate the efficacy of ribavirin, not to describe the course of illness. In all the studies evaluating the efficacy of a treatment, baseline laboratory characteristics are given because these are the baseline confounders that should be adjusted in the analysis. It is unnecessary and impossible to adjust for the ever-changing laboratory values during the course of a disease, in the statistical analyses this would result in unresolvable matrices therefore it is not done. Last but not least, in drug studies these laboratory values may be affected from treatment and they become “intermediate variables” in the statistical sense and therefore they can not be used the statistical models.\textsuperscript{1}

Again, a more careful reading of our manuscript could have shown the author that the central tendency measures were actually given right in the table itself, for platelet counts it is indicated just one line above, as the “median”! It is impossible to understand why the author thinks of non-parametric tests are some kind of magical statistical tests that could make non-significant p-values significant and keeps repeating this incorrect idea, but for all the laboratory values we did actually use non-parametric tests (such as Mann–Whitney U test) due to the non-normal distribution of these variables and the results were still non-significant as can be seen in Table 1.

Correlations of our laboratory values many not be as the author expects, but we wonder how can one be so sure that “this much” platelet count should go together with “that much” AST, ALT or LDH levels? There is limited data on the baseline laboratory values of CCHF patients and our study describes a much bigger population than the other studies, therefore we will suggest that, may be the author should adjust his “expectations” about CCHF patients’ laboratory values according to our paper instead of suspecting our data quality.

How many patients had the adverse events?

We suspected adverse events from the results of our statistical analysis; this was not a primary finding of our study. That is why it was not a major focus of our paper and it was mentioned in the discussion section, only as one of the possible explanations of statistically significant time-interaction in the survival model. In any type of study, even clinical trials, it is very
difficult to ascribe an adverse event to a drug; this usually requires more than one study and a very large sample size. Some of our patients had already compromised liver function and multiorgan failure, in such a situation it is almost impossible to detangle the adverse effect of a drug from the natural course of the disease. In addition, there are reports of severe adverse events related to ribavirin during short term use, such as hepatic failure, pancreatitis and severe anemia which resulted in transfusions and withdrawal from studies.8,9 We believe these reports support our suspicion that when severely ill patients were given ribavirin, even just anemia on top of a bleeding tendency may be sufficient enough to compromise the condition of a patient.

Name of the study

Quasi-experimental study design is very different from a historical control study and it is a much better design for drug studies since it alleviates some factors which may lead to selection bias and confounding by severity.10,11 We would like to assert once more that our study qualifies as a quasi-experimental design and reiterate how it was conducted. When it was planned in 2003 the aetiology of the haemorrhagic fever cases were still unknown and data was collected from those patients who were admitted to the study centers with an unspecified haemorrhagic fever; during this time none of them received ribavirin. When the epidemic season ended in the winter of 2003–2004, the aetiology of the disease was confirmed and the study group decided to treat all patients with ribavirin when the cases started to resurface in the spring of 2004. So, there was a clear time point during the course of our study, which defined a complete change in the treatment of patients without selection of the patients according to severity.11

Is ribavirin a choice for CCHF at all?

Ribavirin has been recommended for various viral infections, from influenza to Lassa fever.8 A single clinical trial has shown some efficacy of ribavirin in haemorrhagic fever with renal syndrome which is caused by a bunyavirus, however it was not effective in Rift Valley fever and hantavirus pulmonary syndrome which are also caused by bunyviruses.8 Animal studies give just a glimpse of how a drug might act in human beings, in fact they are quite controversial and some recent studies have shown that animal studies mostly fail to predict human outcomes.12 Hence the standard approach in testing the drug efficacy is to start with Phase 1 after animal studies and continue until Phase 3/4. None of these Phase studies has been conducted with ribavirin to establish its efficacy and safety in humans therefore, it has not been approved for this indication by any leading regulatory agency including the Turkish Ministry of Health.

When it comes to the clinical studies; there are only 7 studies with a comparison group in the literature investigating the efficacy of ribavirin on mortality in CCHF patients.13–19 Five of these studies are from Turkey, none of them showed a significant effect of ribavirin. Other 2 studies are both from Iran and they reported a statistically significant effect.13,15 However, ribavirin related results of these studies are extremely questionable. Mardani et al.13 reported that 69 patients were treated with ribavirin and 12 were not treated and in Alavi Naini et al.15 236 patients were treated in contrast to 19 who did not receive ribavirin. Why are the numbers of controls so small in these studies? Who were those control patients? Why did they not receive ribavirin? In historical control studies, the major problem is the choice of controls, they must be selected in a way that would make them comparable (similar) to the treatment group.1,2,5 Who were those few controls in Iran studies, so that they did not receive ribavirin in a country where every suspected case of CCHF receives ribavirin? It is possible that these patients were from the year 1999 when the cases first started to appear or they were the patients who were living in very rural areas or they were diagnosed very late that they actually could not receive ribavirin. So were they able to receive enough supportive treatment, which is the mainstay of treatment in CCHF? In Mardani et al.13 it is openly reported that the treatment choice was based on availability, doesn’t this statement make one wonder who were those patients deprived of treatment when all the others received it? There is not a single sentence or table in these papers reporting even the demographics of controls, let alone comparison of characteristics of control and treatment groups which may entirely be responsible for their findings. Recently, surveillance data collected by the Turkish Ministry of Health was published, showing that ribavirin use in CCHF in Turkey, decreased from 68% to 11.8% between the years 2004 and 2007, but the mortality stayed the same, around 5% during the same period. We believe nothing but only inefficacy of ribavirin can account for a six times decrease in use while the mortality staying the same.20

Self-citation of reviews and book chapters of one’s own which rely on poor quality primary research does not increase the available evidence or convince anyone about the efficacy of ribavirin.

Primum non nocere

The author’s statement that our paper will result in devastating situations by causing clinicians withhold treatment in post-exposure situations is a groundless allegation, because there is nothing in our paper about prophylaxis; it is exclusively related to treatment. We believe that the major ethical problem in this situation is strongly recommending a drug, which has neither been shown to be effective nor approved for CCHF and depriving patients of their rights for further research in this area for a better treatment.

As we have replied in detail above, our study does not suffer from serious design problems as alleged by the author; our statistical results are consistent and our power is sufficient. Actually, we are adamant that our results should be a warning to clinicians that the author’s claims of ribavirin’s efficacy does not depend on any sound scientific evidence but biased personal views of the author which could result in harm to the patients.

References


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Ethical concern

SIR

I read the article by Elaldi N et al. appeared on Journal of Infection 2009 Mar;58(3):238–44 which is titled “Efficacy of oral ribavirin treatment in Crimean-Congo haemorrhagic fever: a quasi-experimental study from Turkey” with a great concern. First of all, ethically, I assume there should be a declaration of “conflict of interest” at the end of the article according to the Committee on Publishing Ethics (COPE) and World Association of Medical Editors (WAME) agreements. I was not able to see that acknowledgement and I am specifically asking the distinguishing authors if any of them have a relation to any organization which is a scientific paper producing organization in Turkey. If so, what reason made them not to declare this conflict of interest? My second concern, if there is any conflict of interest relating to the pharmaceutical companies (such as promotional support to some international medical congress) which they are the main producers of ribavirin for the western countries. Ribavirin is clearly approved by World Health Organization (WHO) and Center for Disease Control and Prevention (CDC), the only anti-viral agent officially recommended for the treatment of CCHF. As far as to my best knowledge, there is an unofficial ban on using the ribavirin for CCHF due to marketing policy of the western drug cartel because of possibility of drug resistance in HCV. So far, they are afraid of losing the efficacy of ribavirin for chronic hepatitis C virus infection if the drug prescribes widespread for other viral indications such as CCHF.

There are many studies coming from different countries that strongly support the use of ribavirin in the treatment of CCHF. Further more, it is unethical to do a controlled study for the efficacy of ribavirin in CCHF treatment. So far, WHO and CDC also recommended this use; and especially they strongly advocated the use for the health care workers who might have an unfortunate exposure to blood and other bodily fluids contaminated with the CCHF virus. Since there