Placebo-Controlled, Double-Blind Trial of Intravenous Ribavirin for the Treatment of Hantavirus Cardiopulmonary Syndrome in North America

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Background. Ribavirin is active in vitro against hantaviruses, but the findings of an open trial of the use of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome (HCPS) were inconclusive.

Methods. Subjects with suspected HCPS in the prodrome or cardiopulmonary phase but without shock were eligible for randomization to receive either intravenous ribavirin (33 mg/kg [≤2 g], followed by 16 mg/kg [≤1 g] given every 6 h for 4 days and by 8 mg/kg [≤.5 g] given every 8 h for 3 days) or placebo (administered for 7 days or until the initial Sin Nombre virus antibody test result was confirmed to be negative). The primary outcome was survival at day 28 of the study without the need for extracorporeal membrane oxygenation (ECMO).

Results. Thirty-six subjects were enrolled in the trial from March 1996 through July 2001, at which point the study was terminated prematurely because of both the slow rate of accrual of subjects and the findings of a futility analysis. Of the 36 subjects enrolled, 23 (all of whom were enrolled during the cardiopulmonary stage of HCPS) had HCPS confirmed by serologic testing. The severity of illness at entry into the study was similar among the 10 subjects with HCPS who received ribavirin and the 13 subjects with HCPS who received placebo. The proportion of subjects who survived and who did not require ECMO was similar among ribavirin recipients and placebo recipients (70% vs. 62%, respectively); 2 ribavirin recipients and 2 placebo recipients died, including 3 of 7 subjects treated with ECMO. The frequency of adverse events, including anemia, was similar between treatment groups.

Conclusions. The rate of accrual of subjects in the present study was inadequate to clearly assess the safety or efficacy of ribavirin in the treatment of HCPS. However, ribavirin was well tolerated, and the lack of trends supporting the use of intravenous ribavirin suggests that it is probably ineffective in the treatment of HCPS in the cardiopulmonary stage.

Since the recognition of hantavirus cardiopulmonary syndrome (HCPS) in 1993, HCPS has been identified throughout most of North and South America and in Panama. Known also as “hantavirus pulmonary syndrome” (HPS), we prefer the term “hantavirus cardiopulmonary syndrome” because almost all fatalities associated with this syndrome are caused by cardiogenic shock [1, 2]. In the United States, 379 cases of HCPS have been reported through 1 September 2004, for a case-fatality rate of 36% (http://www.cdc.gov/ncidod/diseases/hanta/hspsnoframes/episides/epis14.htm). In Canada, 47 cases of HCPS were reported through 31 December 2003, for a case-fatality rate of 36% (H. Art-soh, unpublished data). Sin Nombre virus (SNV) is the etiologic agent of all cases of HCPS in Canada and of all but a handful of cases of HCPS in the United States, including all of the cases that occurred among subjects enrolled in the present study.

Ribavirin is active in vitro against all hantaviruses.
tested [3, 4]. Intravenous ribavirin has been reported to be effective in the treatment of hemorrhagic fever with renal syndrome (HFRS), which is caused by the prototype hantavirus Hantaan virus [3]. In an open-label trial of intravenous ribavirin for the treatment of HCPS, which was conducted in the United States in 1993–1994, nonrandomized, untreated patients were used as control subjects [5]. Treatment was often delayed by the need to ship the study drug from regional distribution centers, and treatment was not allowed during the prodrome phase of HCPS, in part because rapid serologic testing was not available. Rapid serologic testing subsequently became available and was shown to be highly sensitive during both the prodromal and cardiopulmonary phases of HCPS [6]. The current trial was designed to evaluate the efficacy and safety of ribavirin in the treatment of HCPS and to allow enrollment of subjects with cases of HCPS that were in either the prodromal phase or the cardiopulmonary phase.

SUBJECTS AND METHODS

Study population. Males and nonpregnant females who were ≥12 years of age and who had suspected or serologically confirmed acute hantavirus disease that was in the prodromal or cardiopulmonary phase were eligible for enrollment in the study. A presumptive diagnosis of HCPS required the presence of a compatible prodromal illness with fever of <12 days’ duration; myalgia, with or without nausea and vomiting, abdominal pain, or diarrhea; absence of upper respiratory tract symptoms at the onset of symptoms; a platelet count of <150,000 cells/mm²; and, for patients with HCPS in the cardiopulmonary phase, immunoblasts comprising at least 10% of peripheral blood lymphocytes. The study drug was not administered to premenopausal women until the result of a serum or urine pregnancy test was confirmed to be negative.

Criteria for exclusion from the study included pregnancy or breast-feeding, a likely diagnosis other than HCPS, immune-compromised status, receipt of systemic corticosteroids within 30 days before enrollment in the study, a mean arterial pressure (MAP) of <60 mm Hg for 2 h despite optimal medical management, a cardiac index of <2.1 L/min/m², arterial oxygen pressure of <65 mm Hg in intubated subjects receiving 100% oxygen, or the presence of unilateral pulmonary infiltrates that did not become bilateral within 24 h. Subjects provided written, informed consent, which included an agreement to practice birth control for 6 months. The clinical trial was approved by the institutional review boards of all participating institutions.

Study medication. Subjects received either intravenous ribavirin (33 mg/kg [≤2 g] as a loading dose, followed by 16 mg/kg [≤1 g] given q6h for 4 days and by 8 mg/kg [≤500 mg] given q8h for 3 days) or placebo for 7 days. This regimen was found to be effective in the treatment of HFRS [3]. Randomization to treatment was done in groups of 4, with 2 subjects randomized to receive ribavirin and the other 2 subjects randomized to receive placebo. The study drug was kept in the research pharmacy at each site, and identification numbers (in sequence) were assigned to subjects at the time of their enrollment in the trial. All staff at each study site were blinded as to treatment assignment. The study drug was discontinued if the result of testing for SNV antibody was negative or when extracorporeal membrane oxygenation (ECMO) was initiated. Ribavirin and matching placebo were provided by ICN Pharmaceutical (Costa Mesa, CA).

Serologic testing for hantavirus. Serum samples were tested for IgG and IgM antibodies to SNV nucleocapsid and G1 antigens by use of a strip immunoblot assay. Testing was performed at the University of New Mexico in Albuquerque [6].

Primary and secondary end points. The primary end point of the study was survival at day 28 after study entry. When centers participating in the study began using ECMO as salvage therapy for patients for whom death appeared to be imminent, the primary end point was revised to survival at day 28 after study entry without the use of ECMO. Secondary efficacy evaluations included determination of the Murray lung score (a lung-injury score based on hypoxemia, compliance, positive end-expiratory pressure, and the number of quadrants showing alveolar consolidation on chest radiographs); development, duration, and severity of shock; duration of hospitalization and duration of stay in the intensive care unit; and the peak level of lactic acid and the duration of this peak level. The safety parameters that were evaluated encompassed the development, duration, and severity of anemia; elevation of transaminase and creatinine levels; and the development of pancreatitis and elevations in the serum level of amylase.

Serial clinical and laboratory evaluations. Patients were followed daily on days 1–7 of the study, on days 14, 28, and 84, and at 6 months, by physical examination and assessment of vital signs. On each of the aforementioned days, except for day 6, a complete blood cell count with differential was determined; electrolyte, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, amylase, and uric acid levels, and serum levels of lactate were measured; and a chest radiograph was obtained. A pregnancy test was performed on day 84 and again at 6 months. Spirometry was performed and diffusion capacity of the lung for carbon monoxide was measured on day 7, as well as at subsequent visits, if the patient did not require mechanical ventilation. Urinalysis and a coagulation screening test were performed at study entry and on days 3, 5, 7, 28, and 84 of the study.

Data safety and monitoring board (DSMB). A DSMB was established at the National Institutes of Health (Bethesda, MD). After the enrollment of 15 patients with confirmed infection, a review of the safety and efficacy data was performed in which members of the DSMB were blinded to the study treatment.
Table 1. Demographic characteristics, at baseline, of patients with confirmed hantaviral infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ribavirin recipients</th>
<th>Placebo recipients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>44.0 (23–58)</td>
<td>39 (23–56)</td>
<td>.40</td>
</tr>
<tr>
<td>Male</td>
<td>4 (40)</td>
<td>5 (38)</td>
<td>1.00</td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4 (40)</td>
<td>6 (46)</td>
<td>.73</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>1 (8)</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>5 (50)</td>
<td>3 (23)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (10)</td>
<td>3 (23)</td>
<td></td>
</tr>
<tr>
<td>Days from onset of symptoms,a</td>
<td>3.5 (2–11)</td>
<td>6 (1–11)</td>
<td>.41</td>
</tr>
<tr>
<td>Received intubationb</td>
<td>4 (40)</td>
<td>4 (31)</td>
<td>.69</td>
</tr>
<tr>
<td>$F_{io_2}$, median range</td>
<td>0.43 (0.21–1.0)</td>
<td>0.28 (0.21–0.6)</td>
<td>.90</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless indicated otherwise. $F_{io_2}$, inspired oxygen fraction, where room air is 0.21 and 100% oxygen is 1.0.

a At randomization to treatment.
b Data are for 8 patients. The 2 remaining patients were breathing room air at randomization.
c Data are for 6 patients. The 7 remaining patients were breathing room air at randomization.

assigned; this review did not result in an alteration of the study design or in premature termination of the trial because of drug toxicity.

**Statistical analysis.** When the study was designed, we assumed that the mortality rate among subjects with hantavirus infection who were given placebo would be $\geq 50\%$. Sample-size calculations were performed with 80% power and a significance level of 5% (by a 2-sided test), to detect an overall reduction of 50% in the mortality rate among subjects treated with ribavirin, compared with subjects given placebo. A total of 130 subjects (65 in each group) was required.

Characteristics at baseline were recorded for all subjects. For the primary and secondary efficacy end points, descriptive statistics were collected only for those patients with confirmed SNV infection. For safety end points, descriptive statistics were collected for all subjects. For continuous variables, the Wilcoxon rank sum test was applied, and, for categorical data, Fisher’s exact test was applied to test the difference between the 2 treatment groups. The time-to-event distribution was estimated using the product-limit method of Kaplan and Meier and was compared using the log-rank test [7].

**RESULTS**

From March 1996 through July 2001, 36 subjects were enrolled in the present study, including 26 subjects at the University of New Mexico, 7 subjects at the University of Alberta (Edmonton, Alberta, Canada), 2 subjects at the University of Utah (Salt Lake City), and 1 subject at the University of Colorado (Denver). Ten of the 23 subjects with confirmed SNV infection received intravenous ribavirin, and 13 received placebo. The demographic characteristics of the ribavirin recipients and the placebo recipients were similar at baseline (table 1). Thirteen subjects had negative results of serologic tests for SNV, and administration of the study drug was discontinued after a median of 3 doses (range, 1–11 doses) had been given, when the results of serologic testing became available. Because accrual of subjects occurred at a slow rate, the study was terminated before the target number of enrolled subjects was reached.

**Survival for 28 days without ECMO.** The proportion of
Table 2. Outcomes for subjects with confirmed hantaviral infection.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ribavirin recipients (n = 10)</th>
<th>Placebo recipients (n = 13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival at day 28 of the study, no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>8 (80)</td>
<td>11 (85)</td>
<td>1.00^a</td>
</tr>
<tr>
<td>Without ECMO</td>
<td>7 (70)</td>
<td>8 (62)</td>
<td>1.00^a</td>
</tr>
<tr>
<td>Time to either death or ECMO initiation, median h (range)</td>
<td>4 (3–15)</td>
<td>24 (4–64)</td>
<td>.85^b</td>
</tr>
</tbody>
</table>

NOTE. ECMO, extracorporeal membrane oxygenation.

^a By Fisher’s exact test.

^b By log-rank test.

patients who survived without the need for ECMO was similar among ribavirin recipients (7 [70%] of 10 subjects) and placebo recipients (8 [62%] of 13 subjects) (figure 1). The median duration from the time of administration of the first dose of the study drug to either death or initiation of ECMO was 4 h (range, 3–15 h) for ribavirin recipients versus 24 h (range, 4–64 h) for placebo recipients (P = .85; log-rank test). Two ribavirin recipients and 2 placebo recipients died, including 3 of 7 subjects who were treated with ECMO (table 2). Overall, 8 (80%) of 10 ribavirin recipients and 11 (85%) of 13 placebo recipients survived at day 28 of the study. No deaths occurred after day 28 of the study.

Secondary efficacy outcomes. There were no significant differences or trends in any of the secondary outcome measurements. The MAPs (figure 2) and the Murray lung scores (figure 3) were similar in the 2 treatment groups. Lactic acidosis (lactic acid level, >2 mmol/L) developed in 6 (60%) of 10 ribavirin recipients and in 9 (69%) of 13 placebo recipients (P = .69). There were no significant differences in either the median duration of lactic acidosis (median duration in each treatment group, 2 days; P = .81) or the median peak level of lactic acid among ribavirin recipients versus placebo recipients (4.4 vs. 2.8 mmol/L, respectively; P = .60).

Treatment with ECMO. Seven subjects, including 3 ribavirin recipients and 4 placebo recipients, were treated with ECMO. Six of these 7 subjects received care at the University of New Mexico, and 1 subject received care at the University of Alberta. Table 3 shows the hemodynamic parameters and laboratory values that documented the need for salvage therapy and that were obtained just before initiation of ECMO.

Safety. There were no significant differences in the frequency of adverse events between treatment groups. There was a trend toward a higher incidence of anemia among ribavirin recipients, but this trend was limited to cases of mild to moderate anemia (hemoglobin level, 7.0–9.4 g/dL). Mild to severe anemia (hemoglobin level, 6.5–9.4 g/dL) was recorded for 4 (40%) of 10 ribavirin recipients and for 4 (31%) of 13 placebo recipients; the single case of severe anemia (hemoglobin level, 6.5–6.9 g/dL) occurred in a placebo recipient. There was no evidence of hepatotoxicity, nephrotoxicity, or development of pancreatitis as a result of treatment with ribavirin. With regard to increases in serum levels of amylase, severe toxicity (2.1–5 times the upper...
we would have needed power to determine efficacy, a futility analysis predicted that the present trial. Although the study did not have adequate efficacy because of the small number of subjects enrolled in and B.H., unpublished data).

similar for Sin Nombre and Hantaan viruses [3, 4] (R. Medina

susceptibility of SNV , compared with that of Hantaan virus

think that it was because of any difference in the ribavirin

were not even able to demonstrate trends toward the efficacy

from administration of the first dose of the study drug to either
definition of the prodrome phase of HCPS. First, we do not

designing the present trial, we envisioned enrolling most subjects during the prodrome phase of HCPS, to allow

When we designed the present trial, we envisioned enrolling

most subjects during the prodrome phase of HCPS, to allow

the highest sensitivity of serologic testing during the prodrome phase [1, 6, 8], we were unable to enroll any subjects during the prodrome phase of HCPS. Although many of the study subjects sought medical care during the prodrome phase, HCPS generally was not considered as a diagnosis at this time, and patients were not referred until after the onset of the cardiopulmonary phase of the syndrome. Once the cardiopulmonary phase of HCPS begins, we believe

Table 3. Hemodynamic parameters and laboratory values documenting the need for salvage therapy before initiation of extracorporeal membrane oxygenation (ECMO).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart rate, a beats/min</th>
<th>Cardiac index, b L/min/m²</th>
<th>MAP, c mm Hg</th>
<th>Lactate level, d mmol/L</th>
<th>PaO₂/FIO₂ e</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>170</td>
<td>2.1</td>
<td>55</td>
<td>19.5</td>
<td>80</td>
</tr>
<tr>
<td>B</td>
<td>122</td>
<td>2.1</td>
<td>79</td>
<td>3.9</td>
<td>42</td>
</tr>
<tr>
<td>C</td>
<td>172</td>
<td>1.7</td>
<td>79</td>
<td>2.1</td>
<td>77</td>
</tr>
<tr>
<td>D</td>
<td>159</td>
<td>3.9</td>
<td>68</td>
<td>4.0</td>
<td>56</td>
</tr>
<tr>
<td>E</td>
<td>166</td>
<td>2.0</td>
<td>41</td>
<td>6.6</td>
<td>132</td>
</tr>
<tr>
<td>F</td>
<td>158</td>
<td>2.4</td>
<td>80</td>
<td>5.2</td>
<td>93</td>
</tr>
<tr>
<td>G</td>
<td>141</td>
<td>4.2</td>
<td>53</td>
<td>13.5</td>
<td>51</td>
</tr>
</tbody>
</table>

NOTE. Values in bold are life-threatening values mandating institution of ECMO. MAP, mean arterial pressure.

a Median value, 159 beats/min.

b Median value, 2.1 L/min/m².

c Median value, 68 mm Hg.

d Median value, 5.2 mmol/L.

e Median value for the ratio of PaO₂ to FIO₂. 77. PaO₂ is the arterial oxygen pressure in millimeters of mercury. FIO₂ is the inspired oxygen fraction, where room air is 0.21 and 100% oxygen is 1.0.
that the rate of disease progression and the time to death are too rapid for ribavirin to be of benefit.

Ribavirin treatment is associated with potentially serious adverse effects, including anemia and the potential for teratogenicity if used in pregnant women. Although the number of subjects enrolled was too small to conclude that ribavirin is safe, we were reassured by the low rate of adverse effects noted in the present study. There were no significant differences in the frequency of adverse events, including anemia, between the 2 treatment groups. We were able to obtain the results of serologic testing within 24 h after testing at the University of New Mexico and within 48–72 h after testing at the other sites, so exposure to ribavirin was limited to a median of 3 doses (range, 1–11 doses) for persons without HCPS. As such, among seronegative subjects, the risk of adverse effects was probably minimized by our ability to discontinue the study drug after a few doses.

In the present open-label trial, among the 128 subjects treated with ribavirin, pancreatitis developed in 5 subjects and possible pancreatitis developed in 2 subjects for whom safety data were available [5]. It was reassuring that there was no difference in the incidence of elevated serum levels of amylase between ribavirin recipients and placebo recipients in the present trial. Although the number of subjects enrolled in our study was small, the data from the present study do not support a significant role for ribavirin in the development of pancreatitis.

The present trial was designed in 1994, at a time when we had only slightly more than 1 year of clinical experience with HCPS, before ECMO was used as rescue therapy, and before anyone had experience in conducting a controlled trial of treatment for HCPS. One of the primary benefits of the present trial is what it has taught us about the design and conduct of controlled trials of treatment for HCPS.

First, our efforts to enroll subjects during the prodrome phase—on the basis of clinical criteria and the presence of thrombocytopenia, but without waiting for the results of IgG and IgM antibody testing—were not successful. All 12 subjects who met the study-entry criteria for suspected hantavirus in the prodrome phase subsequently were found to be seronegative for hantavirus. This rate of enrollment of subjects without HCPS is unacceptably high, particularly for a drug with an adverse event profile such as that for ribavirin. Therefore, future studies should exclude subjects with suspected HCPS in the prodrome phase who lack confirmation of serologic test results, unless the study drug is considered to have minimal associated risk and/or we can improve the specificity of the clinical diagnosis.

Second, we learned that we could identify subjects with HCPS in the cardiopulmonary phase on the basis of clinical and laboratory criteria but, of importance, before serologic confirmation. This was a matter of concern at the start of the study, because, in the open-label study of persons with presumed HCPS in the cardiopulmonary phase, infection was serologically confirmed for only 30 (21%) of 140 subjects who were treated with ribavirin [5]. Of the remaining 110 subjects, 105 were seronegative and 5 did not have serologic testing performed. In the present study, 23 (96%) of 24 subjects who were enrolled in the trial during the cardiopulmonary phase were found to be seropositive.

Third, the rate of subject accrual in the present study was slow, even in epidemic years. The main reasons for the slow accrual of subjects were (1) that patients who presented with shock were almost always excluded from the study on the basis of our exclusion criteria and a belief that the need for salvage therapy was imminent, and (2) that the treating physician thought that ribavirin was unlikely to work quickly enough to benefit a patient with HCPS who was already in shock. Future trials involving subjects with HCPS in the cardiopulmonary phase should allow study enrollment of subjects who are in shock and should evaluate agents with a rapid onset of action.

On the basis of current knowledge, there are several promising treatments that could be evaluated in controlled trials. First, patients with serious or fatal HCPS in the United States and Chile have significantly lower titers of serum neutralizing antibody on the day of admission to the hospital, compared with patients who have diseases of mild severity [8] (P. Vial, unpublished data), and neutralizing antibody is protective in an animal model of lethal Andes virus infection [9]. Therefore, there is a rationale for evaluation of administration of neutralizing antibody for the treatment of HCPS. There is also strong evidence that suggests an immunologic basis for the cardiopulmonary phase [10], and there is an ongoing controlled trial in Chile that is evaluating the use of corticosteroids for patients who present in the cardiopulmonary phase.

In summary, we did not meet our goal for enrollment of subjects, and the present study lacked adequate power to determine whether ribavirin was safe and effective in the treatment of HCPS. However, the lack of trends favoring use of ribavirin and the rapid progression to death or initiation of ECMO after initiation of the study drug suggest that, although intravenous ribavirin was well tolerated, it probably is not effective for the treatment of HCPS after the onset of the cardiopulmonary phase. We were unable to enroll subjects during the prodrome phase, and efforts to do so that were based solely on clinical presentation and presence of thrombocytopenia led to enrollment of subjects without SNV infection. With only a small associated risk of enrollment of subjects without hantavirus infection in the study, we were able to identify subjects with disease in the cardiopulmonary phase; however, accrual was slowed by the exclusion of subjects with shock.
MEMBERS OF THE COLLABORATIVE ANTIVIRAL STUDY GROUP RIBAVIRIN CONTROLLED TRIAL FOR HCPS

Participating centers (locations) and members of the Collaborative Antiviral Study Group are as follows: University of New Mexico (Albuquerque, NM): G.J.M., D.G., B.H., C.O.H., H.L., F.T.K., Suzanne Popejoy, Joseph Hubbard, and Karl Johnson; University of Alberta (Edmonton, Alberta, Canada): L.M. and A.L.; University of Utah (Salt Lake City): A.T.P. and John C. Christenson; University of Alabama at Birmingham: R.J.W., L.R., Lynette Sherrill, W.W., and Mark Carpenter; ICN Pharmaceuticals (Costa Mesa, CA): H.F.; University of Colorado (Denver): K.B.; Gallup Indian Medical Center (Gallup, NM): Bruce Tempest; Johns Hopkins University (Baltimore, MD): Ray Reid; Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health (Bethesda, MD): Catherine Laughlin, Walla Dempsey, and Thelma Gaither.

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References