Prospective Follow-up and Pulmonary Functions From a Placebo-Controlled Randomized Trial of Ribavirin Therapy in Respiratory Syncytial Virus Bronchiolitis

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Objective: To determine any long-term differences in adverse effects and pulmonary function between infants with respiratory syncytial virus and lower respiratory tract infection who were treated with ribavirin and a control group.

Study Design: Long-term follow-up included enumeration of episodes of respiratory illness, wheezing, and pneumonia and, ultimately, administration of pulmonary function tests (PFTs). Pulse oximetry was done at each visit. During the first 3 years we conducted follow-up in the fall and spring. In years 4 and 5 we conducted 1 visit per year. During years 5 through 7 we conducted PFTs, and starting with year 7 a methacholine chloride challenge was done if forced expiratory volume in 1 second (FEV₁) was greater than 70% of predicted value.

Results: We prospectively enrolled (December 1983 to February 1985) in a randomized trial of ribavirin vs placebo children who were previously healthy, were premature, or had chronic pulmonary disease. One pulmonologist (R.F.; blinded) scored and interpreted the results of the PFTs. We studied 42 patients aged 1 to 33 months; 2 patients died (1 receiving ribavirin and 1 receiving placebo) and 5 patients receiving placebo were lost to follow-up; 35 patients (24 taking ribavirin and 11 taking placebo) attended 212 visits. Four patients were premature (3 in the ribavirin and 1 in the placebo group), and 3 of these had bronchopulmonary dysplasia (2 in the ribavirin and 1 in the placebo group). From years 1 to 3, there was more reactive airway disease, wheezing, and pneumonia in the placebo than in the ribavirin group (mean score, 22.3 for 12 placebo-treated patients vs 15.8 for 23 ribavirin-treated patients; \( P = .07 \) by Kruskal-Wallis test); for all years, it was 22.0 for 11 placebo-treated patients vs 16.0 for 22 ribavirin-treated patients (\( P = .10 \)). After informed consent was given, 19 patients completed PFTs (13 receiving ribavirin and 6 receiving placebo); 7 of 13 ribavirin-treated patients (53%) had normal or mild PFT results vs 0 of 6 placebo-treated patients (\( P = .04 \) by Fisher exact test). On methacholine challenge (7 ribavirin-treated patients and 5 placebo-treated patients), there was more reactivity in the placebo vs the ribavirin group (exact \( P = .07 \)). Scoring done by weighting for severity for 19 patients (13 ribavirin-treated patients and 6 placebo-treated patients) (even after correcting for asthma) showed a significant difference in favor of previously ribavirin-treated patients (exact \( P = .02 \)).

Conclusions: No outward effects were identified from ribavirin exposure. We observed no increase in reactive airway disease, wheezing, and pneumonia in the ribavirin compared with the placebo group. Weighted severity scores suggest long-term beneficial effect of ribavirin therapy; however, larger numbers should be evaluated.


Editor’s Note: I’ve always been surprised that many (most?) physicians believe that the use of ribavirin is based on its safety, which has not been the case. Perhaps this study, added to several others, will convince them.

Catherine D. DeAngelis, MD

R espiratory syncytial virus (RSV) is a common cause of respiratory morbidity in infants around the world. In our experience in Washington, DC, approximately 1 of every 100 primary RSV infections has resulted in a hospital admission.1 Furthermore, approximately 1 of every 4 pediatric patients hospitalized with acute respiratory tract disease has had RSV infection. The outbreaks occur in yearly cycles. Currently, preventive therapy is available for some high-risk individuals, whereas ribavirin remains the only approved modality of therapy for selected patients.

In 1983, we initiated a randomized trial of ribavirin therapy compared with placebo in hospitalized patients aged 1 month and older. These patients were admitted to the hospital with RSV infection diagnosed by indirect immunofluorescence of respiratory tract secretions. They were randomized consecutively into treatment and placebo groups. We also anticipated, on clinical grounds, that
PATIENTS, MATERIALS, AND METHODS

The follow-up study consisted of the longitudinal evaluation of patients prospectively randomized to a ribavirin or a placebo control group.

INITIAL THERAPEUTIC STUDY

In December 1983, after obtaining informed consent, we enrolled infants (≥1 month old) admitted to the hospital with acute lower respiratory tract illness and proven RSV infection. The presence of RSV was confirmed in exfoliated respiratory tract cells present in combined nasal and oropharyngeal swab specimens with indirect immunofluorescent antibody methods. Only infants who were expected to stay 3 days or longer in the hospital were included in the research study. Although we excluded patients with congenital heart disease, patients with chronic pulmonary disease and prematurity were included.

After obtaining a complete history from the parent or legal guardian, a physical examination was done by a physician (W.J.R.) who did not know whether the infant was assigned to the drug or the placebo group. This blinded observer assigned severity rating values that ranged from 0 (normal) to +4 (more severe). Before the daily scoring the patient and the equipment were cleaned by hospital personnel not involved in the scoring. The preparation of the ribavirin and placebo was coordinated through the hospital pharmacy so that neither medical nor paramedical personnel were aware of the type of assignment.

FOLLOW-UP AFTER HOSPITAL DISCHARGE

The methods for randomization, administration of aerosol, collection of nasopharyngeal samples, and processing of viruses were described previously.2

Follow-up after hospital discharge consisted of scheduled visits to the pulmonary clinic, once in the fall and then again in the spring for the first 3 years after joining the study. Monthly telephone calls to assess health condition, including wheezing, were made to families throughout the study, and any significant information was recorded. During the first year of follow-up, children who developed wheezing and upper respiratory tract infection were instructed to come in for collection of respiratory tract secretions, which were tested for RSV by indirect immunofluorescent antibody techniques; viral cultures were also performed. Thereafter, indirect immunofluorescent antibody testing and viral cultures of a respiratory tract specimen were done only if the child developed wheezing during the time RSV was prevalent. During years 4 and 5, the visits were scheduled once a year. At each visit a pulse oximetry was done and a questionnaire was completed by the parent about the child’s health. Any other physician contact was also documented if it dealt with respiratory tract symptoms (no attempts were made to review the actual private physician records). In the fifth year, at an age when the patients were expected to be cooperative, a PFT battery was performed, and the results were analyzed by a member of the Department of Pulmonary Medicine who was unaware of the patient’s previous treatment status (the members of the Department of Pulmonary Medicine were unaware of the assignment status of the patients). Parents of the patients were also questioned about exposure of the child to smoking in the household. On the basis of the results from that PFT battery, patients were categorized into groups designated as normal, mild, moderate, or severe impairment. For evaluation of PFTs, the classification essentially was as follows: normal and mild, ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) greater than 80% and FVC greater than 80% predicted; moderate, FEV1/FVC less than 80% and FVC less than 80% predicted; and severe, FEV1/FVC less than 60%. Whereas patients 5 to 7 years old underwent PFTs, after 7 years of age a methacholine challenge was done by the procedure described by Chai et al.3 On the basis of their reactivity to methacholine administration, patients who underwent methacholine challenge testing were classified as follows: normal, nonreactive (ie, <20% decrease in FEV1) at all concentrations; mild, reactive (ie, 20% decrease in FEV1) at 25 mg/mL of inhaled methacholine; moderate, reactive (ie, 20% decrease in FEV1) at 1.25 to 10.00 mg/mL of inhaled methacholine (4 dose steps); and severe, reactive (ie, 20% decrease in FEV1) at less than 0.6 mg/mL of inhaled methacholine (4 dose steps). Patients with a baseline FEV1 less than 70% of predicted value were not tested. This aspect of the study also was approved independently by the Children’s National Medical Center institutional review board, and the informed consent form for this challenge was obtained separately from parents. Precautions were taken addressing medications that could affect the test with omission or modification of the medication schedule. Baseline spirometry was recorded measuring FVC, FEV1, FEV1/FVC, and forced expiratory flow, midexpiratory phase (FEF25%-75%), and the best of the 3 methods was recorded. Patients inhaled 5 breaths of 1 mL buffered isotonic sodium chloride solution, followed by spirometry testing for 1.5 minutes, and FEV1 was obtained as a control. If FEV1 decreased less than 20%, the methacholine challenge proceeded. Patients with a 20% or greater decrease were not tested. Dilutions of methacholine and isotonic sodium chloride solution of 0.075, 0.15, 0.30, 0.60, 1.25, 2.5, 5.0, 10.0, and 25.0 mg/mL of concentration were used. The provocative dose (PD) causing a 20% fall in FEV1 was designated PD20 FEV1. The provocative tests were also scored by a pulmonologist (R.F., blinded) who was unaware of the treatment group assignment.

STATISTICAL METHODS

Comparisons of groups and results were done by parametric t test or by nonparametric Fisher exact, Wilcoxon, Kruskal-Wallis, and χ2 tests.4,5 For an observation to be considered statistically significant, P ≤ .05 had to be obtained.

These patients would spend 3 days or more in the hospital. We excluded patients with congenital heart disease. This study, which examined whether ribavirin therapy would result in an earlier clinical cure, was conducted during a 2-year period, and the results of the therapeutic observations were previously published.2 At the completion of the trial, we were interested in long-term follow-up of the children who had been enrolled in the study, which also included an additional 10 children enrolled in the following season under the same protocol. During this phase of the study we wanted to determine whether there were any obvious adverse effects associated with the use of ribavirin, such as dif-
and never made a follow-up visit. Patients were lost to follow-up soon after hospital discharge during hospitalization. Their deaths were considered to be 1 in the placebo group and 1 in the treatment group, died chitis, and 8 had pneumonia. Two patients with severe BPD, length of hospital stay.2

Groups were comparable in terms of severity of illness, oxy-
copulmonary dysplasia (BPD). Of 17 patients in the pla-
were premature, and 2 of these 3 patients also had bron-
ribovirin. Four of the 42 original patients had under-

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To receive placebo and 25 patients were randomized to re-
ribavirin. Four of the 42 original patients had under-
25 patients were randomized to receive ribavirin. Four of the 42 original patients had underlying conditions. Of 25 patients in the ribavirin group, 3 were premature, and 2 of these 3 patients also had bronchopulmonary dysplasia (BPD). Of 17 patients in the placebo group, 1 was premature and also had BPD. The 2 patients with severe BPD, age 1 through 7 months (mean, 3.3 months; median, 2.0 months), comprised the placebo group. On entry, 16 ribavirin-treated patients (67%) and 8 placebo-treated patients (73%) were younger than 6 months. Four patients (17%) in the ribavirin-treated group had a diagnosis of pneumonia compared with 2 patients (18%) in the placebo group. Three ribavirin-treated patients (12%) had underlying conditions: 2 had BPD and 1 was premature. One patient (9%) in the placebo group had BPD. This report deals with the cumulative follow-up of 35 patients followed up longitudinally by our study team who completed at least 1 visit for a total of 212 clinic visits. Of the 24 ribavirin-treated patients, 17 (71%) being followed up lived in houses in which smoking was prevalent (no information was available for 2 patients). Of the 11 placebo-treated patients, 7 (64%) also lived in such environments.

The mean arterial oxygen percent saturation determined at the visits throughout follow-up was comparable in both groups (98%-99%). During follow-up, of 22 viral cultures from 16 different patients (12 from the ribavirin group and 4 from the placebo group), 13 were negative (8 in the riba-
virin group and 5 in the placebo group). Of the 9 positive cultures, 5 yielded parainfluenza virus, 1 yielded herpes simplex virus, and 3 (2 in the ribavirin group and 1 in the placebo group) were positive for RSV. Two of these RSV infections required hospitalization, 1 patient at 17 months of age (10 months after ribavirin therapy) and another at 19 months of age (1 year after placebo use). The third patient was managed with an emergency department visit 3 years after ribavirin treatment at about 40 months of age.

During the first 3 years (Table 2) there was more RAD and wheezing in 11 placebo-treated patients compared with 24 ribavirin-treated patients, but the difference did not reach statistical significance at P<.05 (P = .10 by the Wilcoxon test). When one evaluates the total study period, the total frequency of wheezing decreased (Table 2). This was still not statistically significant for the total study (same number of individuals) (P = .10 by the Wilcoxon test). During those 6 years, we documented a mean of 44% episodes of wheezing per visit in the ribavirin group (range, 0%-100%) vs 65% in the placebo group (range, 33%-100%). During that same period (Table 3), 4 (17%) of 24 ribavirin-treated patients had 2 or more episodes of wheezing compared with 6 (55%) of 11 placebo-treated pa-

Table 1. Summary of Follow-up (F/U) of Patients Who Received Ribavirin or Placebo for RSV Bronchiolitis*

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>25</td>
<td>1</td>
<td>0</td>
<td>24</td>
<td>6</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Placebo</td>
<td>17</td>
<td>1</td>
<td>5</td>
<td>11</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>2</td>
<td>5</td>
<td>35</td>
<td>11</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>

* RSV indicates respiratory syncytial virus; PFTs, pulmonary function tests; and MC, methacholine challenge.

Table 2. Presence of Pneumonia, RAD, and Wheezing During the 6 Years After RSV Bronchiolitis*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Patients</th>
<th>Sum of Scores</th>
<th>Expected Under H0</th>
<th>SD Under H0</th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 1-3†</td>
<td>12</td>
<td>384.5</td>
<td>432</td>
<td>27.69</td>
<td>16.02</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>24</td>
<td>245.5</td>
<td>198</td>
<td>27.69</td>
<td>22.31</td>
</tr>
<tr>
<td>Placebo</td>
<td>11</td>
<td>244.0</td>
<td>198</td>
<td>27.69</td>
<td>22.18</td>
</tr>
<tr>
<td>Years 1-6‡</td>
<td>12</td>
<td>386.0</td>
<td>432</td>
<td>27.78</td>
<td>16.08</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>24</td>
<td>386.0</td>
<td>432</td>
<td>27.78</td>
<td>16.08</td>
</tr>
<tr>
<td>Placebo</td>
<td>11</td>
<td>386.0</td>
<td>432</td>
<td>27.78</td>
<td>22.18</td>
</tr>
</tbody>
</table>

* Determined from medical observation. RAD indicates reactive airway disease; RSV, respiratory syncytial virus; and H0, null hypothesis.
† Wilcoxon 2-sample test: Wilcoxon normal approximation S = 245.5, Z = 1.69, Probability of being greater than the standardized normal deviate (PROB) > Z = 0.09. Test—text approx. significance = 0.09. Kruskal-Wallis (χ² approximation) χ² = 2.94, PROB > χ² = 0.08.
‡ Wilcoxon 2-sample test: approximation cumulative 6 years, S = 244, Z = 1.64, PROB > Z = 0.10. Kruskal-Wallis test (χ² approximation) χ² = 2.74, PROB > χ² = 0.09.

ferences in the incidence of respiratory tract illness, wheezing, pneumonia, asthma, or reactive airway disease (RAD), and whether there was any difference in long-term outcome in pulmonary function test (PFT) results between the treated and control groups. The following is a report of long-term follow-up of these children.

RESULTS

During the therapeutic trial, 17 patients were randomized to receive placebo and 25 patients were randomized to receive ribavirin. Four of the 42 original patients had underlying conditions. Of 25 patients in the ribavirin group, 3 were premature, and 2 of these 3 patients also had bronchopulmonary dysplasia (BPD). Of 17 patients in the placebo group, 1 was premature and also had BPD. The 2 groups were comparable in terms of severity of illness, oxygen requirements, length of intensive care unit stay, and length of hospital stay.2

Of the initial 42 patients, aged 1 to 33 months, admitted to the hospital, 24 had a diagnosis of bronchiolitis, 9 had bronchiolitis and pharyngitis, 1 had laryngotracheobronchitis, and 8 had pneumonia. Two patients with severe BPD, age 1 through 7 months (mean, 3.3 months; median, 2.0 months), comprised the placebo group. On entry, 16 ribavirin-treated patients 67% and 8 placebo-treated patients 73% were younger than 6 months. Four patients 17% in the ribavirin-treated group had a diagnosis of pneumonia compared with 2 patients 18% in the placebo group. Three ribavirin-treated patients 12% had underlying conditions: 2 had BPD and 1 was premature. One patient 9% in the placebo group had BPD. This report deals with the cumulative follow-up of 35 patients followed up longitudinally by our study team who completed at least 1 visit for a total of 212 clinic visits. Of the 24 ribavirin-treated patients, 17 71% being followed up lived in houses in which smoking was prevalent no information was available for 2 patients. Of the 11 placebo-treated patients, 7 64% also lived in such environments.

The mean arterial oxygen percent saturation determined at the visits throughout follow-up was comparable in both groups 98%-99%. During follow-up, of 22 viral cultures from 16 different patients 12 from the ribavirin group and 4 from the placebo group, 13 were negative 8 in the ribavirin group and 5 in the placebo group. Of the 9 positive cultures, 5 yielded parainfluenza virus, 1 yielded herpes simplex virus, and 3 2 in the ribavirin group and 1 in the placebo group were positive for RSV. Two of these RSV infections required hospitalization, 1 patient at 17 months of age 10 months after ribavirin therapy and another at 19 months of age 1 year after placebo use. The third patient was managed with an emergency department visit 3 years after ribavirin treatment at about 40 months of age.

During the first 3 years Table 2 there was more RAD and wheezing in 11 placebo-treated patients compared with 24 ribavirin-treated patients, but the difference did not reach statistical significance at P<.05 P = .10 by the Wilcoxon test). When one evaluates the total study period, the total frequency of wheezing decreased (Table 2). This was still not statistically significant for the total study (same number of individuals) P = .10 by the Wilcoxon test). During those 6 years, we documented a mean of 44% episodes of wheezing per visit in the ribavirin group (range, 0%-100%) vs 65% in the placebo group (range, 33%-100%). During that same period Table 3, 4 17% of 24 ribavirin-treated patients had 2 or more episodes of wheezing compared with 6 55% of 11 placebo-treated pa-
tients (P = .04 by Fisher exact test). There were no significant differences in the number of wheezing episodes between those who had subsequent positive viral cultures and those who did not (P = .30). The average number of wheezing episodes for those treated with ribavirin who had subsequent positive viral cultures was 1.33 (median, 1.00; range, 0.00-3.00). During the initial 3 years we observed more episodes of pneumonia in the ribavirin group. This difference was not statistically significant (P = .40 by Fisher exact test). Similarly, no statistical significance between groups was noted for the whole period (P = .39 by Fisher exact test).

**PULMONARY EVALUATION**

At various times during follow-up, a total of 11 patients, 6 taking ribavirin and 5 taking placebo, were lost to follow-up. Four patients in the ribavirin group moved and left no forwarding address or telephone numbers, 1 dropped out, and another repeatedly missed appointments for PFTs and methacholine challenge. The 19 patients lost to follow-up moved and left no contact information. Ultimately, 24 of the 35 patients (18 receiving ribavirin and 6 receiving placebo) were available for PFTs. Five of these patients, all in the ribavirin group, were unable to complete the tests for the following reasons: 3 patients had outright mental retardation, 1 patient was unable to cooperate because of immaturity, and 1 patient had a concurrent illness and the mother refused to bring back the child to the hospital. Thus, 19 of the original 35 patients were available for various function tests. Their mean entry severity scores before enrollment in the original treatment were 2.4 (median, 2.0; range, 2.0-3.5) for placebo-treated patients and 2.6 (median, 2.0; range, 1.0-4.0) for ribavirin-treated patients. The virus load before treatment (tissue culture infectious dose 50/0.2 mL) ranged between 1.0 and 4.0 (mean, 3.6; median, 3.0) for the placebo group and between 0.5 and 6.5 (mean, 2.9; median, 2.5) for ribavirin-treated patients. At enrollment in the study, the age of the 19 children who were ultimately available for PFTs ranged from 1 to 7 months (mean, 3; median, 2) in the placebo group and from 1 to 10 months (mean, 4 months; median, 3 months) in the ribavirin group. At the time of PFT administration ribavirin-treated patients had a mean age of 8.3 years (median, 9.0 years) compared with 7.0 years (median, 7.0 years) in the placebo group, and PFTs were corrected for age, lengths, and weights. Of the 19 patients who completed various PFTs (Table 4), 7 completed the PFT only and 12 completed the PFT and the methacholine challenge. The 19 patients were distributed as follows: 6 were in the placebo group and 13 were in the ribavirin treatment group.

Nineteen patients completed PFTs (Table 5). More patients in the placebo group (6 of 6 completed) had moderate or severe findings compared with patients in the ribavirin group (6 of 13) (P = .043 by Fisher exact test [2-tailed]).

Table 4. Distribution by Group of Those Who Completed Testing for Pulmonary Function

<table>
<thead>
<tr>
<th>Pulmonary Function Test (PFT)</th>
<th>Placebo</th>
<th>Ribavirin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFTs only</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>PFTs and methacholine challenge</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>13</td>
<td>19</td>
</tr>
</tbody>
</table>

*P = .04 by Fisher exact test.

Table 5. Score of the Pulmonary Function Test*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Normal or Mild</th>
<th>Moderate or Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>7</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

*P = .04 by Fisher exact test (2-tailed).

Table 6. Results of the Methacholine Challenge and Mean PD20*

<table>
<thead>
<tr>
<th>Interpretation†</th>
<th>FEV1, L</th>
<th>FEV1 at PD20, L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or Mild</td>
<td>Predicted</td>
<td>Actual†</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.67</td>
<td>1.36</td>
</tr>
<tr>
<td>Severe</td>
<td>1.79</td>
<td>1.43</td>
</tr>
</tbody>
</table>

*PD20 indicates the provocative dose causing a 20% decrease in forced expiratory volume in 1 second (FEV1).†Concentration, in milligrams, at which mean PD20 occurred.

Table 7. Results of the Methacholine Challenge Only (Weighing for Severity)*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Patients</th>
<th>Sum of Scores</th>
<th>Expected Under H0</th>
<th>SD Under H0</th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>7</td>
<td>34</td>
<td>45.50</td>
<td>5.50</td>
<td>4.85</td>
</tr>
<tr>
<td>Placebo</td>
<td>5</td>
<td>44</td>
<td>32.50</td>
<td>5.50</td>
<td>8.80</td>
</tr>
</tbody>
</table>

*H0 indicates null hypothesis. S = 44.0, Z = 2.0, probability of being greater than the standardized normal deviate (PROB) > Z/S = 0.045. Kruskal-Wallis test (χ² approximation) χ² = 4.38, PROB > χ² = 0.036 (exact P = .0707).

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In this small, prospective study, patients who had RSV bronchiolitis during infancy who were treated with ribavirin experienced fewer overt episodes of wheezing, RAD, and asthma than those in the placebo group the first 3 years after RSV bronchiolitis. The difference between groups waned further in the subsequent 3 years. At no time was the difference statistically significant. However, when patients were evaluated with PFTs and challenged at 7 years or older, there was more reactive and more severe airway disease response in the placebo group compared with those treated with ribavirin. Hiatt and co-workers evaluated the effect of ribavirin therapy on pulmonary function in 94 previously healthy children with RSV lower respiratory tract infection. Maximum flow at functional residual capacity was higher at discharge and at the 12-month follow-up visit in those treated with ribavirin (P<.01 for both).

On the other hand, our failure to demonstrate significant differences by pulmonary function variables (FVC, FEV₁, FEV₁/FVC, and FEF₂₅%-₇₅%) is based on the small and it did not reach statistical significance. A larger group may have answered the query about differences, if any. However, when the individual PFT (done blindly) results were scored and assigned to categories ranging from normal to severe, the magnitude of the difference between the treated and placebo groups was appreciated. Our patients were all enrolled under the same treatment protocol prospectively and were not selected for risk factors on the initial enrollment. They were randomized from the start; hence, they should have been exposed to the same viral strain(s) circulating in the community pool. Patients who had bronchiolitis and pneumonia during infancy have increased risk of recurrent wheezing by as much as 50%. These observations hold true during initial follow-up after hospitalization. Still others associate RSV bronchiolitis during infancy with subsequent sensitization to allergens (common) and development of asthma given predisposition to asthma or allergy. Our observations during the first 3 years of follow-up display a trend of airway reactivity after RSV, which has been noted by others. However, the trend for less episodes of reactivity observed in ribavirin-treated patients is of interest. Children who have bronchiolitis during infancy seem to have persistent pulmonary function abnormality later in life. These problems have been characterized in terms of their response to exercise-induced decreases in peak expiratory flow rates and in the higher predisposition to bronchial reactivity. These findings have also been noted in situations in which these patients have been challenged with histamine acid phosphate.

The possibility that these subsequent pulmonary findings result from the early damage caused by RSV seems to be supported by some of the earlier long-term observations. However, a recent report categorizes early wheezing as falling into 2 major groups that differ in predisposing factors at birth and in their outcomes. These predisposing factors are considered unrelated to viral infections. Whether viral infections during infancy lead later to RAD is still to be determined. Observations from the basic work by Welliver and colleagues support the role of mediators in RSV-induced acute disease and suggest a subsequent association. These investigators noted that the degree of hypoxia correlated significantly with the titers of RSV IgE and the concentration of histamine. Respiratory syncytial virus lower respiratory tract infection is implicated with IgE elevations. Similarly, Volovitz et al noted leukotriene C₄ in approximately 4 of 5 children who had...
the RSV IgE-specific detection compared with 1 of 4 of those without it. Rosmer and associates,20 in studying the effects of ribavirin therapy on the production of RSV-specific IgE, noted that patients treated with ribavirin had in their respiratory tract secretions lower amounts of RSV-specific IgE compared with controls.

The difference in the severity of response to challenge with methacholine and the difference in the PFT results favoring treated patients over controls that we observed need further study. Our sample sizes were small. Our observations were limited to pulmonary functions and wheezing during follow-up because we did not evaluate for cytokines, IgE, or other mediators. Our original goal was to observe treated patients for long-term safety. The loss of patients initially and during follow-up, beyond our control, affected the strength of the study. Although the initial severity assessment and viral titers remained balanced between groups, as patients dropped out, a tendency developed for those 6 placebo-treated patients who completed PFTs to be initially younger than the 13 patients in the ribavirin group (mean age, 2.3 vs 4.3 months). Also, at the time of testing, the mean age of the placebo group was 7.0 years vs 8.7 in the ribavirin group. In addition, potential bias may have been introduced by the fact that 24 of 25 ribavirin-treated patients compared with 11 of 17 placebo-treated patients participated in the longitudinal follow-up (P < .02 by the Fisher exact test). All of these differences could again affect the final observed results. Furthermore, because differences in RAD and wheezing episodes did not achieve statistical significance, we are left with speculation about the significance of the differences observed in pulmonary function, which is of interest in light of the comparable oxygen saturation in each group. A study with larger samples with pulmonary function evaluation of ribavirin-treated patients matched to controls of the same age challenged with methacholine might help answer this query. Finally, 2 recent publications must be addressed.21,22 Krilov and coworkers21 reported a comparison of ribavirin-treated patients and age-matched controls. These investigators conducted PFTs of the participants and did not demonstrate either beneficial or untoward adverse effects associated with ribavirin use. The results of our study, with a limited number of patients, support the safety findings. However, there are inherent differences between both studies, including the fact that our randomized patients were all part of a prospectively enrolled cohort from a single center (vs 6 centers); our patients’ illnesses were comparable in severity at enrollment and furthermore presumably represent balanced exposure to the strains prevalent in the community. On the other hand, the study by Long and colleagues22 is similar to ours in representing a randomized cohort follow-up of patients initially enrolled in a treatment trial. The mean age of ribavirin-treated patients vs controls at enrollment was 2.4 vs 4.1 months, and 70% of the ribavirin-treated patients were boys. Long and coworkers22 noted a difference in peak expiratory flow rates between ribavirin-treated patients and controls of 113% vs 102% (P = .17). Although they noted a trend in better PFT results between ribavirin-treated patients and controls, this was not significant. Neither of the 2 studies21,22 used methacholine challenge to detect reactivity. Hence, to date, there are reports with findings at odds with each other. Our observations, if confirmed by larger studies, may support the use of ribavirin, regardless of its antiviral effectiveness, for its long-term effect on outcome of patients infected with RSV during infancy.

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