

Ribavirin for respiratory syncytial virus bronchiolitis reduced the risk of asthma and allergen sensitization

Chen C-H, Lin Y-T, Yang Y-H, Wang L-C, Lee J-H, Kao C-L, Chiang B-L. Ribavirin for respiratory syncytial virus bronchiolitis reduced the risk of asthma and allergen sensitization.

Pediatr Allergy Immunol 2008; 19: 166–172.

© 2008 The Authors

Journal compilation © 2008 Blackwell Munksgaard

Respiratory syncytial virus (RSV) bronchiolitis in early life is a risk factor for later development of asthma and atopy. Ribavirin is the only effective drug currently available against acute RSV bronchiolitis. However, the long-term effects of ribavirin remain unclear. We investigated a cohort of children hospitalized with RSV bronchiolitis from when they were under 2 yr old until they reached a mean age of 6.2 yr. In total, we enrolled 175 children in this study. Both the group treated with ribavirin and the group not treated with ribavirin included high-risk young children with congenital heart disease or chronic lung disease. Their respective age-matched controls, that we labeled groups A and B, both without ribavirin treatment, consisted of previously healthy subjects. Wheezing was either verified by physicians or estimated by a questionnaire. Allergen sensitization was judged by serum allergen-specific IgE levels. The cumulative incidence of physician-diagnosed asthma or recurrent wheezing in the ribavirin group (15%) was significantly lower than its incidence in the non-ribavirin-treated group (34%, $p = 0.049$), and in the control A group (43%, $p = 0.005$). Allergen sensitization was also least frequent in the ribavirin group. Ribavirin therapy was an independent factor in reducing the risk of developing asthma, asthma/recurrent wheezing, and sensitization to *D. pteronyssinus*/*D. farinae*. The long-term value of ribavirin for acute RSV bronchiolitis and its underlying mechanisms deserves further research.

**Chien-Han Chen¹, Yu-Tsan Lin¹,
Yao-Hsu Yang¹, Li-Chieh Wang¹,
Jyh-Hong Lee¹, Chuan-Liang Kao² and
Bor-Luen Chiang¹**

Departments of ¹Pediatrics and ²Laboratory
Medicine, National Taiwan University Hospital and
National Taiwan University College of Medicine,
Taipei, Taiwan, Republic of China

Key words: allergen sensitization; asthma; respiratory
syncytial virus; ribavirin; high-risk young children

Dr Bor-Luen Chiang, Department of Pediatrics,
National Taiwan University Hospital, #7, Chung-Shan
South Road, Taipei 100, Taiwan, Republic of China
Tel.: +886 2 2312 3456 ext. 7302
Fax: +886 2 2397 2031
E-mail: gicmbor@ha.mc.ntu.edu.tw

Accepted 13 May 2007

Respiratory syncytial virus (RSV) is a prevalent infectious cause of lower respiratory tract disease in both infants and children. Most affected children are infected before the age of 2 yr (1). Several studies suggest that RSV bronchiolitis in early childhood is independently associated with the development of asthma/recurrent wheezing and allergen sensitization in later life (2–4). However, whether antiviral medication may prevent the development of asthma and atopy is still undetermined.

Ribavirin, approved in early 1986 (5), is the only effective antiviral agent currently available against acute RSV infection, but the cost is

relatively expensive. Increased morbidity and mortality have been observed in RSV-infected infants with underlying cardiopulmonary illness (6). Ribavirin is, therefore, most frequently used to treat these high-risk young children (5). Although the data supporting the immediate therapeutic effects of ribavirin are sufficient, its long-term benefits remain to be seen.

For our study, we followed up a cohort of children hospitalized because of RSV bronchiolitis before the age of 2 yr with or without ribavirin therapy, until a mean age of 6.2 ± 1.6 yr. All patients in the ribavirin-treated group were high-risk young children with either

chronic lung disease or congenital heart disease. We aimed at investigating if ribavirin therapy could reduce the risk of developing asthma and allergen sensitization.

Materials and methods

Inclusion and exclusion criteria

During a surveillance period of 4.5 yr (January 1997 to June 2001), 609 children aged ≤ 24 months were hospitalized because of RSV bronchiolitis in the National Taiwan University Hospital. RSV infection was confirmed by direct detection of the RSV antigen from sputum by immunofluorescent stain (7). Criteria to determine the need to administer ribavirin included the following: persistent respiratory distress even after adequate treatment; deteriorating cyanosis; respiratory failure with necessity for intubations; and concern regarding increased mortality and morbidity in high-risk young children. All of the high-risk young children with congenital heart disease or chronic lung disease during the surveillance period were included without selection into either the ribavirin-treated group or the 'no ribavirin' group. Exclusion criteria for these two groups were RSV bronchiolitis more than once, tracheo-bronchial anomalies, malignancy, and mortality during the follow-up period, because of heart failure, multiple congenital anomalies, or sepsis unrelated to ribavirin.

Those with neither underlying diseases nor ribavirin therapy were candidates for the control groups. To investigate if the possible age difference between the ribavirin and the no ribavirin group was a confounding factor, we assigned them their respective age-matched controls. The control A group consisted of RSV-infected subjects with both the dates and ages of hospitalization most matched to those in the ribavirin group. The control B group was composed of RSV-infected individuals with both the dates and ages of hospitalization most matched to those in the no ribavirin group. The investigator involved in the process of enrolling controls was blind to their family histories and personal atopic status.

In 2005, 54 subjects were eligible for the ribavirin group, 58 for the no ribavirin group, 54 for the control A group, and 58 subjects for the control B group. All of these RSV-infected subjects were invited to join our study. The study was approved by the ethics committee at the National Taiwan University Hospital. Informed consent was obtained from the parents of all participants.

Study tools, study population, and clinical definitions

The parents of all participants were requested to complete a written validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (8), to which we added questions about breast feeding, number of siblings, family history of atopy, current body weight, current therapy for asthma, current status of indoor furred pet-ownership, and smoking in the family. When filling in the questionnaire, all participants and their parents were blind to our specific aim and study design. Only children who later mailed back their questionnaires were enrolled. Of the 224 enumerated children, 175 (78%) mailed their questionnaires back so that they were enrolled; these included 40 in the ribavirin group, 44 in the no ribavirin group, 49 in the control A group, and 42 in the control B group.

The serum levels of allergen-specific IgE antibodies were measured by the Pharmacia CAP system (9) for eight common inhaled allergens, including *Dermatophagoides pteronyssinus*, *D. farinae*, *Blomia Tropicalis*, cat dander, dog dander, cockroach, Bermuda grass, and ragweed. Values of ≥ 0.35 IU/ml were considered positive.

Asthma was defined as questionnaire-reported physician-diagnosed asthma or physician-verified recurrent episodes of wheezing resulting in the diagnosis of asthma recorded in our medical charts, either in the past or in the current follow-up visits. Wheezing occurring at least three times but not verified by a physician was classified as 'recurrent wheezing'. Cumulative disorder was defined as symptoms ever happened in the past. Current disorder was defined as those during the last 12 months, which may or may not require maintenance medication. Heredity for atopy was defined as atopic/allergic diseases in parents or siblings. The occurrence of positive IgE antibodies was classified as allergen sensitization.

Follow-up visits

Among the 175 participants, 87 (50%) returned to our clinics for a further detailed evaluation and determination of serum IgE levels, including 23 in the ribavirin group, 24 in the no ribavirin group, 20 in the control A group, and 20 in the control B group.

Review of medical records

The medical charts were critically reviewed by one investigator, to obtain information including gestational age, type of delivery, sex, presence of underlying diseases, age of onset of RSV

bronchiolitis, fever duration, days of O₂ tent use and ventilator support, and hemogram. Ventilator support included conventional mechanical ventilators, nasal intermittent positive pressure ventilation, and nasal continuous positive airway pressure. Prematurity was defined as a gestational age of not more than 36 wk. The diagnosis of congenital heart disease was confirmed with a cardiac echo by a pediatric cardiologist. Chronic lung disease was defined as oxygen dependence in preterm infants for > 28 days after birth or at 36-wk post-conceptional age.

Statistical analysis

Chi-square test was used for comparison among the four groups. If $p < 0.05$ was found, the difference between any two groups was further examined by Fisher's two-tailed exact test. A value of $p < 0.05$ was considered to be statistically significant. Odds ratios (OR) and 95% confidence intervals (CI) were calculated in a univariate analysis to estimate, which hereditary and environmental factors predisposed to or had preventive effects on the development of asthma and allergen sensitization. A multivariate logistic regression was used to determine independent risk factors by the SAS logistic procedure.

Results

Characteristics of the patients

Demographic and background data were similar among the four study groups. For simplicity, only those of the ribavirin group and the no ribavirin group are shown in Table 1. The number of days that ventilator support was needed was longer in the ribavirin group. Follow-up durations and current ages were statistically different although there was no difference in the ages of RSV infection. Likewise, follow-up durations and current ages between the control A group (5 ± 1.4 yr, and 5.4 ± 1.4 yr-old) and control B group (6.1 ± 1.5 yr, and 6.7 ± 1.5 yr-old) were also different (both $p < 0.001$). However, the well-known genetic and environmental risk factors for the development of asthma, including heredity for asthma, heredity for allergic rhinitis, heredity for atopic dermatitis, the type of delivery, breast feeding, number of siblings, presence of indoor furred pets, and smoking in the family, did not differ among the four groups.

Corticosteroids were used to treat persistent wheezing during RSV bronchiolitis attacks in zero in the ribavirin group, in two (4.5%) in the

Table 1. Demographic and background data in the ribavirin group and the no ribavirin group

	Ribavirin (n = 40)	No ribavirin (n = 44)	p-value
Heredity atopy	32 (80)	32 (73)	0.456
Cesarean section	15 (38)	16 (36)	1
Male sex	29 (73)	24 (55)	0.115
Prematurity	8 (20)	14 (32)	0.321
CHD	36 (90)	37 (84)	0.526
CLD	5 (13)	9 (21)	0.389
Breast feeding	22 (55)	29 (66)	0.373
RSV age (months)	5.7 (5.7)	7.4 (4.9)	0.142
Fever (days)	3 (3)	5 (18)	0.533
O ₂ tent (days)	11 (11)	9 (5)	0.147
Ventilator (days)	2 (4)	0.4 (2)	0.010
Leukocyte (k/ μ L)	10 (4)	10 (4)	0.631
Eosinophil (%)	1.5 (2.1)	1.4 (1.9)	0.840
Current age (yr)	5.6 (1.3)	7 (1.5)	<0.001
Follow-up (yr)	5.1 (1.2)	6.4 (1.5)	<0.001
Body weight (kg)	19 (5)	20 (7)	0.291
Indoor furred pets	4 (10)	5 (11)	1
Smoking in family	22 (55)	21 (47)	0.521

Mean values (s.d.) or N (%) of subjects are given.

Continuous variables were analyzed by Student's *t*-test. Categorical variables were analyzed by Fisher's two-tailed exact test.

CHD, congenital heart disease; CLD, chronic lung disease; RSV, respiratory syncytial virus.

no ribavirin group (systemic steroid), in one (2%) in the control A group (systemic steroid), and in two (4.8%) in the control B group (systemic steroid in one and inhaled steroid in one). No subject ever received RSV immunoglobulin. Among the 87 subjects who returned to our clinics for the follow-up check up, heredity for atopy did not differ among the ribavirin (20/23, 87%), no ribavirin (17/24, 71%), control A (17/20, 85%), and control B (18/20, 90%) groups ($p = 0.323$).

Asthma, recurrent wheezing, and maintenance therapy

The cumulative prevalence of asthma in the ribavirin group (8%) was significantly lower than that (33%) in the control A group ($p = 0.004$; Table 2). To examine if the presence of congenital cardiopulmonary diseases confounded the outcomes, we compared the rates of recurrent wheezing and asthma between the no ribavirin group and its age-matched control B group. The results showed no difference between them (Table 2), implying that having or lacking cardiopulmonary diseases appeared not to be a significant confounding factor in this study.

As to the combined rate of cumulative asthma/recurrent wheezing, it was significantly decreased in the ribavirin group (15%), compared either with the control A group (43%, $p = 0.005$) or with the no ribavirin group (34%, $p = 0.049$;

Table 2. Comparison of recurrent wheezing/asthma between the ribavirin group and the control A group, and between the no ribavirin group and the control B group

	Ribavirin (n = 40)	Control A (n = 49)	p-value	No ribavirin (n = 44)	Control B (n = 42)	p-value
Recurrent wheezing, cumulative	3 (8)	5 (10)	0.726	6 (14)	4 (10)	0.739
Recurrent wheezing, current	2 (5)	4 (8)	0.687	1 (2)	4 (10)	0.197
Asthma, cumulative	3 (8)	16 (33)	0.004	9 (21)	15 (36)	0.151
Asthma, current	2 (5)	6 (12)	0.287	7 (16)	10 (24)	0.423

N (%) subjects are given.

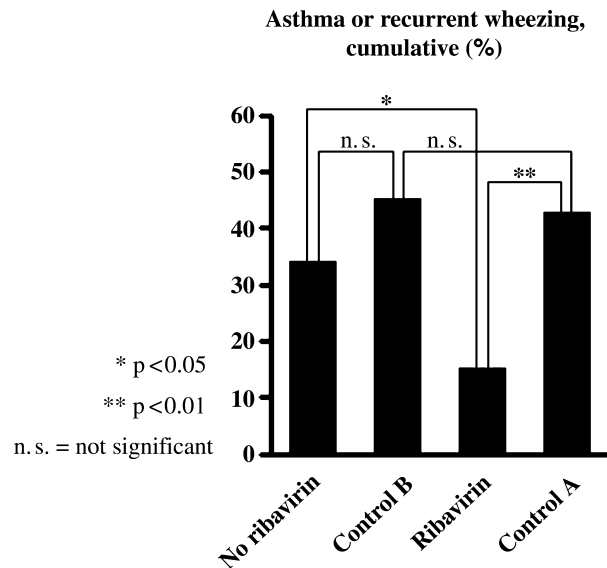


Fig. 1. The influence of ribavirin therapy on the development of asthma or recurrent wheezing. The combined rates of cumulative asthma or cumulative recurrent wheezing are shown for these four study groups, all of which included subjects hospitalized due to RSV bronchiolitis. The no ribavirin group (n = 44) and ribavirin group (n = 40) consisted of high-risk young children with congenital heart disease or chronic lung disease. The latter group enrolled children treated with ribavirin during an episode of RSV bronchiolitis, but the former group did not. Their respective age-matched control B (n = 42) and control A (n = 49) groups, both without ribavirin, included previously healthy subjects.

Fig. 1), while no difference existed between the no ribavirin group and the control B group, nor between the two controls either. The combined rates of current asthma/recurrent wheezing were 10% in the ribavirin group, 18.2% in the no ribavirin group, 20.4% in the control A group, and 33.3% in the control B group ($p = 0.069$).

Corticosteroids were used regularly as the maintenance therapy for current asthma in two of seven in the no ribavirin group (inhaled steroid), in three of six in the control A group (inhaled steroid in one, oral steroid in two), and in four of 10 in the control B group (inhaled steroid in three, oral steroid in one). None of the two children with current asthma in the ribavirin group needed corticosteroids regularly.

Allergen sensitization

All participants returning to our clinics agreed to have their serum IgE levels measured. We found that the rates of sensitization to any allergen were significantly different among the four study groups ($p = 0.004$), with the least frequent rate (26%) in the ribavirin group (Table 3). This rate was significantly lower in the ribavirin group than that in its age-matched control A group (26% vs. 75%, $p = 0.002$), while no significant difference existed between the no ribavirin group and its age-matched control B group (33% vs. 60%, $p = 0.128$). Furthermore, the percentages of sensitization to *D. pteronyssinus*, *D. farinae*, and *B. tropicalis* were significantly reduced in the ribavirin group in comparison to the control A group ($p = 0.001$, $p < 0.001$, and $p = 0.043$, respectively), while there was no difference in the rates of sensitization to each of the eight common inhaled allergens between the no ribavirin group and the control B group.

Preventive role of ribavirin

In the combined ribavirin, no ribavirin, control A and control B groups, ribavirin and several possible hereditary and environmental risk

Table 3. Comparison of allergen sensitization between the ribavirin group and the control A group, and between the no ribavirin group and the control B group

	Ribavirin (n = 23)	Control A (n = 20)	p-value	No ribavirin (n = 24)	Control B (n = 20)	p-value
Any positive	6 (26)	15 (75)	0.002	8 (33)	12 (60)	0.128
<i>D. pteronyssinus</i>	4 (17)	14 (70)	0.001	6 (25)	11 (55)	0.063
<i>D. farinae</i>	3 (13)	14 (70)	<0.001	6 (25)	10 (50)	0.08
<i>B. tropicalis</i>	3 (13)	8 (42)	0.043	5 (21)	10 (50)	0.059

N (%) subjects are given.

Table 4. Univariate tests of various possible risk factors for cumulative asthma, cumulative asthma/recurrent wheezing, and sensitization to *D. pteronyssinus*, *D. farinae*, and dog dander

Risk factors	Asthma	Asthma/recurrent wheezing	Sensitization to <i>D. pteronyssinus</i>	Sensitization to <i>D. farinae</i>	Sensitization to dog dander
Ribavirin use	0.2 (0.1–0.7)**	0.3 (0.1–0.7)**	0.2 (0.1–0.7)*	0.2 (0.1–0.6)**	0.4 (0.1–3.9)
Heredity atopy	3.8 (1.2–11.4)*	2.6 (1.1–6.1)*	0.8 (0.3–2.5)	0.7 (0.2–2.2)	0.5 (0.1–3.0)
Male sex	1.7 (0.8–3.8)	1.8 (0.9–3.7)	1.1 (0.4–2.7)	1.2 (0.5–2.9)	3.1 (0.4–26.7)
Cesarean section	2.3 (1.1–4.6)*	1.5 (0.8–2.9)	0.8 (0.3–1.9)	0.9 (0.4–2.2)	2.4 (0.5–11.2)
Prematurity	1.2 (0.4–3.2)	2.1 (0.9–5.2)	0.9 (0.3–3.1)	1.1 (0.3–3.5)	5.3 (1.0–27.0)*
CLD	2.5 (0.8–7.7)	3.9 (1.2–12.2)*	0.4 (0.1–2.0)	0.4 (0.1–2.2)	1.5 (0.2–14.1)
Breast feeding	1.0 (0.5–2.1)	1.6 (0.9–3.2)	1.0 (0.4–2.4)	0.8 (0.3–2.0)	1.4 (0.3–7.5)
Fever >5 days	0.9 (0.4–2.3)	1.9 (0.8–4.2)	1.4 (0.5–4.1)	1.6 (0.5–4.7)	0.7 (0.1–5.9)
O2 tent >7 days	0.5 (0.2–1.1)	0.7 (0.4–1.4)	0.4 (0.2–1.1)	0.4 (0.2–1.0)	2.5 (0.5–11.9)
Ventilator >1 day	1.0 (0.3–3.4)	0.9 (0.3–2.6)	0.5 (0.1–2.4)	0.5 (0.1–2.7)	NA
Siblings <2	0.8 (0.4–1.7)	1.0 (0.5–1.9)	0.7 (0.3–1.7)	0.7 (0.3–1.8)	1.6 (0.3–8.7)
Current age >6 yr	1.1 (0.6–2.3)	1.3 (0.7–2.3)	0.6 (0.2–1.4)	0.6 (0.2–1.4)	0.8 (0.2–3.8)

Values are expressed as OR (95% CI).

CLD, Chronic lung disease; OR, odds ratio; CI, confidence interval; NA, not available.

* $p < 0.05$, ** $p < 0.01$.

Table 5. Multivariate analysis of various possible risk factors for cumulative asthma, cumulative asthma/recurrent wheezing, and sensitization to *D. pteronyssinus*, *D. farinae*, and dog dander

Risk factors	Asthma	Asthma/recurrent wheezing	Sensitization to <i>D. pteronyssinus</i>	Sensitization to <i>D. farinae</i>	Sensitization to dog dander
Ribavirin use	0.2 (0.1–0.6)**	0.2 (0.1–0.5)**	0.2 (0.1–0.7)*	0.2 (0.1–0.6)**	NS
Heredity atopy	4.6 (1.5–14.1)**	2.8 (1.1–6.6)*	—	—	—
Cesarean section	2.6 (1.2–5.4)*	—	—	—	—
Prematurity	—	—	NS	NS	5.6 (1.1–29.4)*
CLD	—	5.4 (1.5–19.5)*	—	—	—

Values are expressed as aOR (95% CI).

CLD, chronic lung disease; aOR, adjusted odds ratio; CI, confidence interval; NS, not significant.

* $p < 0.05$, ** $p < 0.01$.

factors for the development of asthma and allergen sensitization were evaluated by a univariate analysis (Table 4). The result showed that ribavirin therapy was an important negative regulator for the development of asthma ($p = 0.0088$), asthma/recurrent wheezing ($p = 0.0053$), and sensitization to *D. pteronyssinus* ($p = 0.0133$) and *D. farinae* ($p = 0.008$). Significant risk factors included heredity atopy for asthma and asthma/recurrent wheezing ($p = 0.0171$ and 0.0261 , respectively), cesarean section for asthma ($p = 0.0197$), pre-maturity for sensitization to dog dander ($p = 0.047$), and chronic lung disease for asthma/recurrent wheezing ($p = 0.02$).

The factors with $p < 0.05$ in the univariate test were included in a multivariate logistic regression analysis (Table 5). The results showed that ribavirin therapy was an independently good prognostic factor to reduce the risk of developing asthma ($p = 0.0064$), asthma/recurrent wheezing ($p = 0.0018$), and sensitization to *D. pteronyssinus* ($p = 0.0134$) and *D. farinae* ($p = 0.0079$).

Independent risk factors included heredity atopy for the development of asthma ($p = 0.0085$) and asthma/recurrent wheezing ($p = 0.0232$), cesarean section for asthma ($p = 0.0126$), chronic lung disease for asthma/recurrent wheezing ($p = 0.0105$), and prematurity for sensitization to dog dander ($p = 0.0421$).

Discussion

In this study, we demonstrated that ribavirin therapy for children hospitalized with RSV bronchiolitis decreased the risk of asthma development and allergen sensitization. This is the first-time the long-term benefits of ribavirin has been disclosed. The effect of ribavirin on asthma development was unknown in the past. When compared with the prevalence of physician-diagnosed asthma (12.2%) in schoolchildren aged 6–8 in northern Taiwan in 2002 (10), it was much elevated in our control groups (33% in control A, 36% in control B), which enrolled the RSV-infected subjects. However, in the

ribavirin-treated group, it returned to a level (8%) close to that in the schoolchildren just mentioned. Furthermore, the prevalence of cumulative asthma/recurrent wheezing in the ribavirin group was much lower than that in the no ribavirin group. This is the first-time these findings have been reported. The literature concentrated on the influence of ribavirin on the development of wheezing disorders but not asthma (11–15). Two studies exclusively enrolled previously healthy children (13, 15), while three others included a mixed population of children with or without underlying diseases (11, 12, 14). As to the results, three studies declared the beneficial effect of ribavirin on preventing wheezing illness (13–15), but the other two did not (11, 12). A small case number was the major limitation of these studies, resulting in preliminary and conflicting results. On the contrary, our study included the largest case numbers for follow-up (175 children totally). Every child in the ribavirin-treated and no ribavirin groups had underlying diseases. Furthermore, physician-confirmed asthma was a key outcome measurement, more specific than describing a wheezing illness only.

The link between RSV infection and allergen sensitization has been controversial for decades (16). Some studies agreed with this link (3, 4, 17), but some did not (18, 19). Despite this debate, no one has ever investigated the outcome after ribavirin therapy. In our study, IgE data on admission were not available to confirm the initial atopic status of individuals. However, the percentages of heredity for atopy were similar among the four study groups. Our results showed that ribavirin therapy could decrease the risk of allergen sensitization (OR = 0.2).

Whether the presence of congenital heart disease contributes to the development of asthma or atopy remains unclear. In the literature, only two studies (20, 21) were interested in the relationship between congenital heart disease and asthma. The results showed that high pulmonary flow, pulmonary hypertension, or pulmonary congestion in infants with congenital heart disease may enhance the manifestation of atopic asthma in later life. However, these two studies only enrolled patients with congenital heart disease, without normal controls included. In our study, the frequency of congenital heart disease in the non-ribavirin treated patients was as high as 84%, while their rates of asthma, recurrent wheezing, and allergen sensitization were similar to those in the control group.

Ribavirin was not available in our hospital until 1996. Initially, pediatricians did not use this

drug unless the illness was unusually severe. After a transition period, now ribavirin is prescribed routinely in our hospital to every RSV-infected high-risk child. This is probably the reason why the ribavirin group needed more days of ventilator support and had shorter follow-up durations and younger current ages than the no ribavirin group. However, these differences were not significant enough to affect the outcomes. As shown in Table 4, ventilator support > 1 day and current age > 6 yr in this study did not increase the risk of developing asthma and allergen sensitization. In addition, the prevalence of asthma/recurrent wheezing and allergen sensitization between the control A and control B groups did not differ (Fig. 1; Table 3), although the gap of their current ages was very close to that between the ribavirin and no ribavirin groups. This result once again documented that the difference of current age was not a confounding factor.

A study on the long-term effects of ribavirin helps to understand more about the role of RSV bronchiolitis in the inception of asthma and atopy. Two hypotheses have been proposed (22). One is the consequential hypothesis, stating that early RSV infections damage the growing lung and alter the host's immune regulation. The other one is the common causal hypothesis, holding that RSV infections get worse in infants and children with certain underlying predispositions to lung disease and/or atopy. In this ongoing debate, our study showed the long-term benefits of ribavirin, thus supporting the standpoint of the consequential hypothesis.

How ribavirin therapy prevents the occurrence of asthma and allergen sensitization is unknown. We suggest that the exact mechanisms may be a direct anti-viral effect, immunomodulatory effect, or both. Rosner et al. (23) demonstrated that ribavirin-treated patients had fewer RSV-specific IgE in their airway secretions. The primary antiviral mechanism was via lethal mutagenesis (24). Ribavirin could also potentiate the antiviral interferon-stimulated response genes (25). Moreover, Foster et al. (26) found the expression of high-affinity IgE receptor in dendritic cells was higher in patients with allergies and/or asthma. Our previous *in vitro* and *in vivo* studies showed ribavirin could downregulate the Th₂-type immune response by modulating dendritic cells (27). To our knowledge, we are the first to demonstrate the long-term benefits of ribavirin in preventing asthma and allergen sensitization. The long-term effects of ribavirin therapy and its underlying mechanisms deserve further studies.

Acknowledgments

The authors thank W. L. Shih, K. H. Chu, S. T. Shin, C. T. Hsieh, K. L. Chang, Y. C. Lin for their contributions to this study. This work was funded by a grant from National Taiwan University Hospital, Taipei, Taiwan, Republic of China.

References

1. SIMOES EA. Respiratory syncytial virus infection. *Lancet* 1999; 354: 847–52.
2. KORPPI M, KUIKKA L, REIJONEN T, REMES K, JUNTUNEN-BACKMAN K, LAUNIALA K. Bronchial asthma and hyperreactivity after early childhood bronchiolitis or pneumonia. An 8-year follow-up study. *Arch Pediatr Adolesc Med* 1994; 148: 1079–84.
3. SIGURS N. A cohort of children hospitalised with acute RSV bronchiolitis: impact on later respiratory disease. *Paediatr Respir Rev* 2002; 3: 177–83.
4. SIGURS N, GUSTAFSSON PM, BJARNASON R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005; 171: 137–41.
5. OHMIT SE, MOLER FW, MONTO AS, KHAN AS. Ribavirin utilization and clinical effectiveness in children hospitalized with respiratory syncytial virus infection. *J Clin Epidemiol* 1996; 49: 963–7.
6. GILCHRIST S, TOROK TJ, GARY HE Jr, ALEXANDER JP, ANDERSON LJ. National surveillance for respiratory syncytial virus, United States, 1985–1990. *J Infect Dis* 1994; 170: 986–90.
7. GARDNER PS, MCQUILLIN J. Application of immunofluorescent antibody technique in rapid diagnosis of respiratory syncytial virus infection. *BMJ* 1968; 3: 340–3.
8. ASHER MI, KEIL U, ANDERSON HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–91.
9. BOUSQUET J, CHANEZ P, CHANAL I, MICHEL FB. Comparison between RAST and Pharmacia CAP system: a new automated specific IgE assay. *J Allergy Clin Immunol* 1990; 85: 1039–43.
10. KAO CC, HUANG JL, OU LS, SEE LC. The prevalence, severity and seasonal variations of asthma, rhinitis and eczema in Taiwanese schoolchildren. *Pediatr Allergy Immunol* 2005; 16: 408–15.
11. KRILOV LR, MANDEL FS, BARONE SR, FAGIN JC. Follow-up of children with respiratory syncytial virus bronchiolitis in 1986 and 1987: potential effect of ribavirin on long term pulmonary function. The Bronchiolitis Study Group. *Pediatr Infect Dis J* 1997; 16: 273–6.
12. LONG CE, VOTER KZ, BARKER WH, HALL CB. Long term follow-up of children hospitalized with respiratory syncytial virus lower respiratory tract infection and randomly treated with ribavirin or placebo. *Pediatr Infect Dis J* 1997; 16: 1023–8.
13. EDELL D, BRUCE E, HALE K, EDELL D, KHOSHOO V. Reduced long-term respiratory morbidity after treatment of respiratory syncytial virus bronchiolitis with ribavirin in previously healthy infants: a preliminary report. *Pediatr Pulmonol* 1998; 25: 154–8.
14. RODRIGUEZ WJ, ARROBIO J, FINK R, KIM HW, MILBURN C. Prospective follow-up and pulmonary functions from a placebo-controlled randomized trial of ribavirin therapy in respiratory syncytial virus bronchiolitis. Ribavirin Study Group. *Arch Pediatr Adolesc Med* 1999; 153: 469–74.
15. EDELL D, KHOSHOO V, ROSS G, SALTER K. Early ribavirin treatment of bronchiolitis: effect on long-term respiratory morbidity. *Chest* 2002; 122: 935–9.
16. PEEBLES RS Jr. Viral infections, atopy, and asthma: is there a causal relationship? *J Allergy Clin Immunol* 2004; 113: S15–8.
17. SCHAUER U, HOJAN S, BITTSCHIEDT J, et al. RSV bronchiolitis and risk of wheeze and allergic sensitisation in the first year of life. *Eur Respir J* 2002; 20: 1277–83.
18. PULLAN CR, HEY EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J (Clin Res Ed)* 1982; 284: 1665–9.
19. PEEBLES RS Jr, HASHIMOTO K, COLLINS RD, et al. Immune interaction between respiratory syncytial virus infection and allergen sensitization critically depends on timing of challenges. *J Infect Dis* 2001; 184: 1374–9.
20. MATSUOKA S, TATARA K, USIROGUCHI Y, KUBO M, AKITA H, KURODA Y. Contribution of pulmonary hemodynamics on manifestation of allergic asthma in patients with congenital heart disease. *Acta Paediatr Jpn* 1993; 35: 508–12.
21. MATSUOKA S, TATARA K, USIROGUCHI Y, KUBO M, KURODA Y. Development of atopic asthma in infants with pulmonary congestion caused by congenital heart disease. *J Pediatr* 1994; 124: 597–9.
22. OPENSHAW PJ, DEAN GS, CULLEY FJ. Links between respiratory syncytial virus bronchiolitis and childhood asthma: clinical and research approaches. *Pediatr Infect Dis J* 2003; 22: S58–64.
23. ROSNER IK, WELLIVER RC, EDELSON PJ, GERACI-CIARDULLO K, SUN M. Effect of ribavirin therapy on respiratory syncytial virus-specific IgE and IgA responses after infection. *J Infect Dis* 1987; 155: 1043–7.
24. CROTTY S, CAMERON C, ANDINO R. Ribavirin's antiviral mechanism of action: lethal mutagenesis? *J Mol Med* 2002; 80: 86–95.
25. ZHANG Y, JAMALUDDIN M, WANG S, et al. Ribavirin treatment up-regulates antiviral gene expression via the interferon-stimulated response element in respiratory syncytial virus-infected epithelial cells. *J Virol* 2003; 77: 5933–47.
26. FOSTER B, METCALFE DD, PRUSSIN C. Human dendritic cell 1 and dendritic cell 2 subsets express FcεpsilonRI: correlation with serum IgE and allergic asthma. *J Allergy Clin Immunol* 2003; 112: 1132–8.
27. CHIANG DJ, YE YL, CHEN WL, LEE YL, HSU NY, CHIANG BL. Ribavirin or CpG DNA sequence-modulated dendritic cells decrease the IgE level and airway inflammation. *Am J Respir Crit Care Med* 2003; 168: 575–80.