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Use of Intravenous Gamma Globulin To Passively Immunize High-Risk Children against Respiratory Syncytial Virus: Safety and Pharmacokinetics

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Infants with cardiopulmonary disease develop severe illness from respiratory syncytial virus (RSV) infection. Safety, feasibility, and pharmacokinetics of intravenous gamma globulin (IVIG) to prevent RSV illness were studied in 23 high-risk infants in a phase I trial. IVIG with an RSV neutralizing antibody titer of 1:1,100 in 5% solution was given monthly over a 2- to 4-h period in a clinical setting during the RSV season. The first group ($n = 7$) received 500 mg/kg of body weight, the second group ($n = 9$) received 600 mg/kg, and the third group ($n = 7$) received 750 mg/kg. Serum was drawn prior to infusion and 2, 14, and 30 days after infusion. Total immunoglobulin G and RSV A2 and RSV B neutralizing antibody levels were obtained after the first IVIG infusion. Two children developed mild reversible pulmonary edema (group receiving 600 mg/kg per dose), and one developed hives and wheezing during one infusion (group receiving 500 mg/kg per dose). Twelve children developed subsequent RSV infection during two RSV seasons (November to April) over a 2-year follow-up period; 9 of 12 developed infection during the infusion year. Eleven illnesses were mild; one child died of progressive RSV illness (group receiving 500 mg/kg per dose). A cumulative infusion effect was not observed. IVIG appears safe and feasible in an outpatient setting, and at 750 mg/kg per dose, a target RSV antibody level of ≥1:100 was achieved.

Respiratory syncytial virus (RSV) is the most common cause of serious respiratory illness in young children (2, 8). Children at greatest risk of serious or fatal RSV lower respiratory tract illness include those with bronchopulmonary dysplasia and congenital heart disease (10–12, 21, 22). Because the level of morbidity is so great in these populations, prevention of serious RSV lower respiratory tract illness is an important goal.

It is unlikely that a live vaccine will be available in the near future to prevent high-risk young children from developing serious RSV infection. Vaccine development is proceeding cautiously because of the problem in developing a live vaccine which is safe, stable, and immunogenic and to avoid the serious pulmonary complications seen 20 years ago with the use of a formalin-inactivated vaccine (18). At the present time, passive immunization with intravenous gamma globulin (IVIG) is most likely to offer protection to high-risk children. Animal models demonstrated that sufficient IVIG can be administered to prevent RSV lower respiratory tract illness (17, 26–28) and that animals with high levels of neutralizing (Nt) antibody do not develop severe pneumonitis when challenged with large doses of RSV (29). In addition, epidemiologic studies of newborn infants suggest that passively acquired maternal immunoglobulin G antibody to RSV may protect against severe RSV illness in early infancy (9, 25). We therefore initiated a phase I trial to determine the feasibility and safety of monthly IVIG infusions, to define the pharmacokinetics of IVIG in this high-risk population, to assess whether a target RSV antibody titer could feasibly be achieved, and to demonstrate that unusually severe pulmonary disease would not occur if children given IVIG subsequently acquired RSV infection. If successful, a phase II efficacy trial utilizing an RSV-enriched immunoglobulin could be initiated.

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MATERIALS AND METHODS

This study was a prospective open trial. Patients less than 14 months of age were enrolled prior to the 1988 RSV season (November through April) at the following three clinical sites: University of Colorado Hospital (Denver), Strong Memorial Hospital (Rochester, N.Y.), and Children's Hospital National Medical Center (Washington, D.C.). Patients had moderate to severe bronchopulmonary dysplasia (defined as requiring oxygen currently or within the 6 months prior to study entry) or congenital heart disease (mostly among children under 1 year old). Exclusion criteria included immunoglobulin A deficiency or other immunodeficiency states. This study was approved by the Committee on Human Investigation at each clinical site. Written informed consent was obtained from each parent or guardian.

A baseline physical examination, respiratory assessment, and serum immunoglobulin level were obtained at enrollment. Children received monthly infusions between 1 De-

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cember 1988 and 30 April 1989. Two lots of a commercial IVIG preparation were infused (Gamimune-N, lots 40S74 and 40T013; Cutter Biological Laboratories, Miles, Inc., New Haven, Conn.). These were selected from several lots screened for RSV antibody by methods described previously (24) and contained (in a 5% solution) RSV Nt antibody at geometric mean titers of 1:1,125 and 1:1,075, respectively. The doses infused at the three clinical sites were as follows: 500 mg/kg of body weight (10 ml/kg) in New York, 600 mg/kg (12 ml/kg) in Washington, and 750 mg/kg (15 ml/kg) in Colorado. The initial dose was infused over 4 h; the time of subsequent infusions was shortened to 2 h if the first dose was well tolerated. Temperature, weight, and physical examination data were recorded at the beginning and end of each infusion; pulse and respiratory rate were obtained at half-hour intervals throughout the infusion.

Serum was obtained prior to each infusion and 2 or 3 days and 14 days after each infusion. Sera were frozen at −20°C. RSV neutralization activity in serum was assayed with a virus plaque reduction test (22, 24). Serum specimens were inactivated at 56°C for 30 min, and fourfold dilutions were made in 96-well flat-bottomed plates (Costar, Cambridge, Mass.). Stock solutions of RSV were cultured and titered in HEp-2 monolayers. Stock solutions of RSV (strain A2, subgroup A, or 18537, subgroup B) were diluted in Hanks balanced salt solution containing gentamicin (25 mg/500 ml) and 10% guinea pig complement (Whittaker MA Bioproducts, Walkersville, Md.) to give a concentration of 100 PFU/50 μl. One-to-one mixtures of diluted RSV were made with each diluted specimen. After a 1-h incubation at room temperature, 50 μl of each RSV-serum mixture was inoculated onto confluent HEp-2 cell monolayers grown in 24-well culture plates (Costar). The HEp-2 cells and RSV-serum mixture were incubated at 37°C in 5% CO_2 for 1 h, washed once with Hanks balanced salt solution, and then overlaid with a medium containing methyl cellulose (5 g/500 ml of medium) in Eagle's minimum essential medium containing 2% fetal bovine serum (both from Whittaker Bioproducts). Titers at each serum dilution were run in triplicate. Positive controls (virus and diluent without serum) and negative controls (diluent alone) were prepared for each assay. The plates were covered and incubated in a 37°C, humidified, 5% CO_2 incubator until plaques developed in the positive control plates (usually 3 to 4 days). Plates were then stained with a 0.1% mixture of crystal violet in 5% glutaraldehyde, washed with tap water, and air dried. Plaques were counted on a Bellco plaque counting system (Bellco Glass Inc., Vineland, N.J.). For each serum dilution, the percentage of plaque reduction was calculated by comparing the mean plaque number with those of controls. To maintain linearity, positive controls must be maintained at a density of nearly 50 plaques per well. The percentage of plaque reduction was plotted, by utilizing a computer program supplied by David Alling, National Institute of Allergy and Infectious Diseases) versus the $\log_{10}$ dilution of the serum specimen (4) by the method of Mills et al. (23). A straight line was plotted, and the geometric mean titer or dilution (of the triplicate specimens) was calculated to give a 60% reduction in RSV plaques. All serological studies were run as a single batch in the laboratory of one of us (V.G.H.) to ensure quality control and consistent results.

Surveillance to detect RSV infection was carried out from December 1988 to May 1989 and from December 1989 to May 1990 (i.e., the RSV season during and one year following IVIG infusions). Surveillance consisted of weekly telephone calls and evaluation of ill children (11). If a study child developed rhinorrhea, wheezing, or cough during the months of November through April, a nasal wash was obtained for a rapid RSV antibody test (enzyme immunoassay). RSV illness severity was assessed by the investigators by a standardized respiratory scoring system (13). Decisions regarding hospitalization and medical management were made by the child's primary physician. If a child developed clinical RSV illness, no further infusions were given and a 3-week, convalescent-phase serum was obtained. These sera were not included in subsequent analysis.

TABLE 1. Underlying diagnosis by study site

Diagnosis[a]	No. of cases		
	New York (n = 7)[b]	Washington (n = 9)[c]	Colorado (n = 7)[d]
BPD	5	6	4
BPD + CHD	1	1	1
CHD	1	2	2

[a] Abbreviations: BPD, bronchopulmonary dysplasia; CHD, congenital heart disease.
[b] 500 mg/kg per dose.
[c] 600 mg/kg per dose.
[d] 750 mg/kg per dose.

Half-life analysis. We assumed that the time-response curve was approximated by a one-compartment model with resulting simple exponential decay (7, 20). Estimation of the rate constant was performed as follows. For each subject and each infusion, the antibody titers were converted to a log scale. The slopes were then computed by linear regression and averaged for each subject for each infusion. The half-life was computed by using the formula $RSV_{1/2} = -0.693/b$, where b is the slope of the regression line (7). Slopes were computed for each patient and then averaged, and the half-life was computed on the average slope.

Statistical analysis. The assessment of the influence of dose and infusion on total immunoglobulin G, RSV A2, and RSV B Nt antibody titer was performed by repeated measures analysis of variance. Infusions were treated as repeated measurements on each patient. The comparisons of age and weight by study site were performed by one-way analysis of variance. Diagnosis by study site were compared with chi-square testing. For pairwise comparisons, the Bonferroni adjustment was utilized. All tests were executed at the $P < 0.05$ level of significance.

RESULTS

Twenty-seven children were initially enrolled; 23 completed the 4-month infusion period. The ages and weights were similar at the three clinical sites: ages (in months) averaged 8.3 ± 1.0 (New York), 9.2 ± 1.9 (Washington), and 11.6 ± 2.4 (Colorado); weights (in kilograms) averaged 5.32 ± 0.51 (New York), 6.91 ± 1.32 (Washington), and 6.42 ± 0.805 (Colorado) (P was not significant by analysis of variance). Underlying diagnoses, listed in Table 1, were also similar at each site (P was not significant by chi-square).

Adverse reactions were few, and most were mild. Two children who received 600 mg/kg per dose showed an increased respiratory rate and auscultatory findings suggestive of mild fluid overload during the first infusion. Both responded to diuretics and tolerated their subsequent infusions without incident. One child who received 750 mg/kg per dose had a local urticarial reaction at the intravenous site. The infusion was continued, and the rash resolved after 30 min.

TABLE 2. Mean RSV A2 Nt antibody titers[a]

Infusion	Day	Titer for following site: New York (n = 7)	Washington (n = 9)	Colorado (n = 7)
1	0[b]	10.1 ± 1.20	14.3 ± 2.87	28.1 ± 10.7
	2[c]	87.6 ± 23.9	46.0 ± 7.74	108.0 ± 29.4
	14[c]	31.7 ± 5.61	30.2 ± 3.99	90.0 ± 38.9
2	0[b]	25.0 ± 5.92	24.1 ± 2.60	69.7 ± 25.7
	2	88.0 ± 20.2	66.3 ± 8.78	136.0 ± 38.9
	14	67.9 ± 15.9	45.9 ± 7.18	83.1 ± 18.2
3	0[b]	23.8 ± 9.47	32.4 ± 3.5	49.5 ± 12.4
	2	81.0 ± 4.11	74.0 ± 10.7	90.8 ± 9.0
	14	56.6 ± 14.5	49.0 ± 7.97	87.0 ± 10.0
4	0[b]	33.0 ± 20.0	41.4 ± 6.80	70.0 ± 7.0
	2	81.0 ± 10.0	87.0 ± 8.33	122.0 ± 22.5
	14	53.0 ± 10.0	52.4 ± 3.58	105.0 ± 8.5

[a] Reciprocal of serum dilution resulting in 60% plaque inhibition; mean ± standard error. Doses were as follows: New York, 500 mg/kg; Washington, 600 mg/kg; Colorado, 750 mg/kg.
[b] For baseline differences, P was not significant.
[c] $P = 0.01$ when Colorado day 2 and day 14 titers are compared with those for New York and Washington (repeated measures analysis of variance).

TABLE 3. Mean RSV B Nt antibody titers[a]

Infusion	Day	Titer for following site: New York (n = 7)	Washington (n = 9)	Colorado (n = 7)
1	0[b]	13.3 ± 4.3	19.4 ± 10.4	141.0 ± 87.6
	2[c]	199.3 ± 75.0	134.6 ± 20.0	347.7 ± 76.9
	14[c]	113.8 ± 24.1	79.6 ± 10.0	285.6 ± 82.4
2	0[b]	72.7 ± 22.6	74.5 ± 21.0	206.7 ± 77.0
	2	194.4 ± 78.5	211.6 ± 7.7	417.0 ± 70.7
	14	156.7 ± 22.9	124.2 ± 22.3	340.1 ± 81.2
3	0[b]	73.2 ± 20.2	103.5 ± 11.9	249.5 ± 93.4
	2	144.6 ± 27.6	196.5 ± 21.6	370.0 ± 136.0
	14	123.4 ± 26.5	122.7 ± 19.9	277.0 ± 58.1
4	0[b]	93.8 ± 30.5	134.7 ± 24.4	207.8 ± 92.2
	2	192.8 ± 39.4	266.5 ± 44.3	410.8 ± 96.3
	14	151.0 ± 41.4	188.2 ± 26.7	245.0 ± 53.9

[a] Reciprocal of serum dilution resulting in 60% plaque inhibition; mean ± standard error. Doses were as follows: New York, 500 mg/kg; Washington, 600 mg/kg; Colorado, 750 mg/kg.
[b] For baseline differences, P was not significant.
[c] $P = 0.01$ when Colorado day 2 and day 14 titers are compared with those for New York and Washington (repeated measures analysis of variance).

A more serious reaction occurred in one infant who manifested generalized urticaria and wheezing 20 min after beginning her first infusion of 500 mg/kg per dose. The symptoms disappeared promptly after the infusion was stopped. This child, and three others who had poor venous access (one child from each clinical site), received no further IVIG infusions. Data from the 23 patients who completed four infusions are presented below.

The geometric mean RSV A2 Nt antibody titers for the 4-month infusion period are shown in Table 2 and Fig. 1. The baseline RSV A2 Nt antibody levels at the time of first infusion were similar at all sites (10.1 ± 1.2 mg/dl in New York, 14.3 ± 2.87 mg/dl in Washington, and 28.1 ± 10.7 mg/dl in Colorado; P is not significant when data for Colorado are compared with data for New York). Patients receiving 750 mg/kg per dose achieved peak A2 Nt antibody titers of 1:90 to 1:136. These were significantly higher than those for children receiving 500 or 600 mg/kg per dose (P = 0.01). Titers to RSV B (Table 3; Fig. 2) paralleled the RSV A2 titers. Although it appeared that preinfusion antibody titers rose somewhat with successive infusions, this was not statistically significant over successive doses. The half-lives of the anti-RSV A2 infusions were 21 days (New York), 24 days (Washington), and 28 days (Colorado).

RSV infection occurred in 12 children over two respiratory seasons. During the 1988–1989 season, nine cases of RSV illness occurred, one in the New York group, five in the Washington group, and three in the Colorado group. During the 1989–1990 season, three infections occurred, all in the Colorado group. Eleven infections were documented by RSV rapid antigen testing; the infection in one asymptomatic child was documented only by seroconversion. Clinical features of 10 episodes were relatively mild; these children were treated at home with increased oxygen and medical management. One moderately ill child in Washington required hospitalization but not intensive care. The 12th child, a ventilator-dependent, severely compromised infant, developed a nosocomial RSV infection immediately following an influenza A illness. Despite two infusions of IVIG at 500

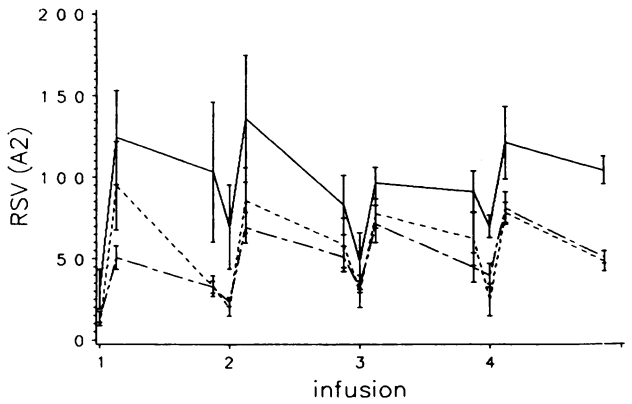

FIG. 1. Composite sequential RSV A2 Nt antibody titers in serum (in milligrams per deciliter) seen over a 4-month period for New York patients (– – –) (n = 7, 500 mg/kg or 10 ml/kg per dose), Washington patients (-—-) (n = 9, 600 mg/kg or 12 ml/kg per dose), and Colorado patients (——) (n = 7, 750 mg/kg or 15 ml/kg per dose).

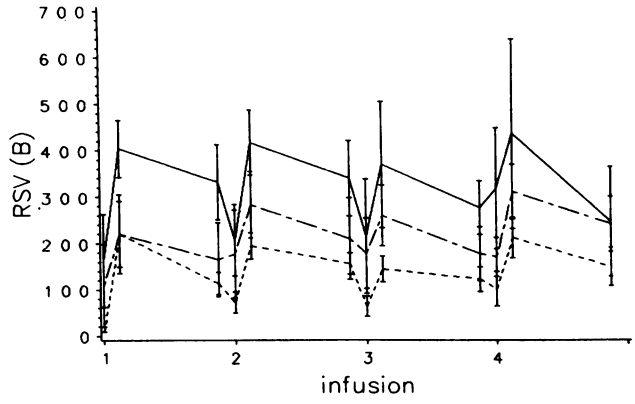

FIG. 2. Composite sequential RSV B Nt antibody titers in serum (in milligrams per deciliter) seen over a 4-month period for New York patients (– – –) (n = 7, 500 mg/kg or 10 ml/kg per dose), Washington patients (-—-) (n = 9, 600 mg/kg or 12 ml/kg per dose), and Colorado patients (——) (n = 7, 750 mg/kg or 15 ml/kg per dose).

mg/kg per dose and aggressive medical management which included ribavirin therapy, she continued to shed RSV and died. Permission for an autopsy was denied. This child was the only child in the New York group who developed RSV.

DISCUSSION

Children at high risk for serious or fatal RSV illness include those with bronchopulmonary dysplasia and other forms of pulmonary disease or with severe congenital or acquired heart disease, very young infants (particularly those born prematurely), and children with certain immunodeficiency states (1, 11, 12, 14–16, 21, 22). In the absence of a safe and effective RSV vaccine, passive immunization with IVIG presently holds the greatest promise for prevention of serious RSV illness in these children. Studies in animal models demonstrate that IVIG containing adequate RSV antibody protects against RSV lower respiratory tract infection. Prevention of pulmonary disease appears to correlate with RSV Nt antibody titers in serum of approximately 1:200 (17, 26, 27). Human epidemiologic studies are less clear; however, they also suggest that maternal RSV Nt antibody titers (as determined by microneutralization assay) ranging between 1:200 and 1:400 correlated with less severe pulmonary disease or evidence of clinical illness in very young infants (9, 25).

Monthly IVIG doses were safe and well tolerated over a 2-h infusion period in the oupatient setting. Adverse reactions were for the most part mild and easily reversible. One significant anaphylactoid reaction occurred; this was resolved by stopping the infusion. The major difficulty was venous access. This problem may be averted in the future if an intramuscular RSV-enhanced IVIG preparation can be developed.

An important goal of this study was to determine whether a target level of RSV antibody could be achieved and maintained with monthly IVIG infusions. While there is a growing body of literature on the use of IVIG in preterm and newborn infants (3, 5, 7, 24), little pharmacokinetic information exists for young children. We utilized a noncompartmental model and assumed that IVIG followed linear pharmacokinetics; this model has been validated in other studies (3, 5, 9, 24). Assuming a volume of distribution of 26%, we calculated that IVIG with an RSV Nt antibody titer of 1:1,100 given in doses ranging between 500 and 750 mg/kg should achieve a titer of 1:100. We were able to achieve and maintain this antibody level with a dose of IVIG of 750 mg/kg. While a titer of 1:100 is probably too low for prophylaxis against RSV, we believe that 750 mg/kg per dose of an adequately enriched RSV immunoglobulin (RSV titers of 1:4,000 or greater) would produce titers potentially adequate to prevent RSV illness. Such an immunoglobulin is currently being developed.

The high titers of RSV antibody described in previous work were not found in over 40 lots of commercial IVIG from three different manufacturers screened for this study. We speculate that the current use of larger donor pools and broader geographic locations dilute out the high individual titers seen previously. It is also unclear why the RSV B Nt antibody titer in commercial lots is higher than the A2 titer. This has been a reproducible phenomenon in animal model experiments. The clinical significance, however, is presently unknown.

No evidence of enhanced pulmonary disease, such as that described 20 years ago following immunization with formalin-inactivated vaccine (6), was seen in 12 documented episodes of RSV infection over a 2-year follow-up period. One would not expect to see this with a preparation of natural antibody. In this study, 10 of the 12 study children developed mild RSV illness; the one child who died was severely compromised and ventilator dependent. She received IVIG in the lowest dose (500 mg/kg). Our presumption was that her serious underlying lung disease prevented the clearing of RSV despite aggressive medical management and that her preceding influenza A illness may have additionally compromised both her pulmonary and her immune status (19). Larger numbers of unprimed children need to be studied, however, to fully access this potential risk of IVIG.

This pilot study demonstrated that monthly IVIG infusions were feasible and safe and that a target level of antibody could be predicted and attained. A phase II trial is currently under way to determine whether RSV-enriched IVIG can produce levels of RSV antibody sufficient to prevent the development of severe RSV lower respiratory tract illness in this high-risk population of children.

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