Palivizumab Use in Very Premature Infants in the Neonatal Intensive Care Unit

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ABSTRACT. *Objective.* **The purpose of this study was to determine the ability of young hospitalized premature (born ≤30 weeks' gestational age) infants to achieve serum levels of palivizumab that are protective against RSV infection.**

Methods. **Palivizumab, 15 mg/kg per dose intramuscularly, was administered every 28 days to stable premature infants who were hospitalized in the neonatal intensive care unit starting at 1 month of postnatal life. Palivizumab concentrations were assayed in serum samples that were drawn from infants who remained in the hospital at 14 days (midpoint concentration) and at 28 days (trough concentration) after each dose was administered.**

Results. **The gestational age of the 24 infants who were enrolled was 27.5 ± 1.8 weeks (mean ± standard deviation), and birth weight was 928 ± 159 g. Midpoint palivizumab concentrations in the 24 infants after the first dose were 45.6 ± 13.0 μg/mL; 71% (17 of 24) of the infants maintained optimal palivizumab concentrations (≥40 μg/mL). The concentrations dropped subsequently; trough concentrations just before the second dose were 32.2 ± 10.5 μg/mL, and only 23% (5 of 22) of the infants had concentrations in the optimal range. Sixteen infants were given 2 doses and 6 were given three doses of palivizumab while in the neonatal intensive care unit. Midpoint concentrations after the second dose were significantly higher than those after the first dose. Likewise, trough concentrations before the third dose were 51.9 ± 7.8 μg/mL and higher than those before the second dose; the concentrations were >40 μg/ml in all 6 infants tested.**

Conclusions. **Very premature infants had sustained optimal protective serum concentrations only after the second dose of palivizumab; 77% of infants tested had trough concentrations <40 μg/mL before the second dose. Additional studies are needed to establish the optimal timing of the initial dose and optimal dosing interval of palivizumab in this most vulnerable population.** *Pediatrics* **2004;114:e554–e556. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0226;** ***neonatal intensive care unit, respiratory syncytial virus.***

ABBREVIATIONS. RSV, respiratory syncytial virus; NICU, neonatal intensive care unit.

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Palivizumab (Synagis; MedImmune Inc, Gaithersburg, MD) has been shown to be effective in deterring respiratory syncytial virus (RSV)-associated lower respiratory tract infection in high-risk infants and young children.[1] Very premature infants are most vulnerable to severe RSV infection early in life; however, studies of palivizumab prophylaxis specifically targeting this population have not been reported.[2] Since October 1999, we have implemented palivizumab prophylaxis in preterm infants who remained hospitalized in our neonatal intensive care unit (NICU) during the RSV season.[3] We chose to use the dose of palivizumab 15 mg/kg per dose every 28 days, based on data obtained in older and heavier preterm infants.[4–6] The purpose of this study was to determine the ability of hospitalized very premature (≤30 weeks' gestation at birth) infants to achieve serum levels of palivizumab comparable to older infants.

METHODS

Patient Population

This prospective study was conducted in the NICU of John Stronger Jr. Hospital of Cook County during the November 1, 2001, to March 31, 2002, RSV season. The protocol was approved by the hospital's Institutional Review Board. Parental consent was obtained before enrollment. Infants who had gestational age ≤30 weeks at birth and remained in the NICU at 1 month of age were recruited. Infants with acute illness, multiple congenital anomalies, congenital heart disease, and known hepatic or renal dysfunction were excluded.

Medication

Protective concentrations of palivizumab have been extrapolated from a cotton rat model showing that concentrations of palivizumab of 25 to 30 μg/mL lead to a mean reduction of pulmonary RSV titers by 99% and at serum concentration of ≥40 μg/mL to a 99% reduction of RSV infection in all animals.[7] We chose 15 mg/kg monthly intramuscular injection as this dose has been shown to maintain concentrations of ≥40 μg/mL in the majority of patients and, thus, achieve maximal prevention of RSV infection.[1,5]

All hospitalized very premature infants were given RSV prophylaxis per our NICU standard protocol regardless of inclusion in the study. Palivizumab, 15 mg/kg intramuscularly, was given at 1 month of postnatal life and every 4 weeks thereafter during the RSV season. Patients were then followed in our high-risk infant follow-up clinic and received their prophylactic injections for the remainder of the RSV season.

Palivizumab Assay

Blood samples for palivizumab concentrations were obtained 14 and 28 days after each dose of palivizumab while the infants remained in the NICU. All samples were centrifuged immediately, and serum was separated and stored at −70°C. Serum palivizumab concentrations were measured using enzyme-linked immunosorbent assay methods (PPD, Inc, Richmond, VA).

TABLE 1. Patient Characteristics at the Time of Each Palivizumab Dose

	First Dose	Second Dose	Third Dose
Infants, *n*	24	22	6
Black	21	19	6
Hispanic	3	3	0
Male	11 (46%)	10 (45%)	3 (50%)
Postnatal age, d	30.8 ± 3.8*	59.2 ± 7.3	89.0 ± 2.0
IMV dependent	5 (21%)	1 (5%)	0
O_2 dependent	7 (29%)	4 (18%)	0
Room air	12 (50%)	17 (77%)	6 (100%)

IMV indicates intermittent mandatory ventilation.
* Mean ± SD.

Adverse Events

Infants were monitored closely for vomiting, redness at injection site, cough, rhinitis, diarrhea, rash, abnormal liver function tests, or other possible side effects, although these were rarely seen in previous multicenter studies.

Statistical Analysis

Data were analyzed with the SPSS statistical software (SPSS Inc, Chicago, IL). Results of continuous measures are expressed as mean ± SD. Differences between groups were tested for significance with use of 2-tailed *t* test. $P < .05$ was considered significant.

RESULTS

Fifty-nine infants met study criteria and were given palivizumab prophylaxis; all 59 received at least 2 doses before discharge. Parental consent for blood sampling was available in only 25 of the 59 infants. Consent was withdrawn before the first blood drawing in 1 child; thus, 24 infants had midpoint palivizumab concentration after the first dose. Two more infants were subsequently withdrawn from the study before the second dose; thus, 22 infants had trough concentrations before the second dose. Six study infants remained in the NICU for their third dose of palivizumab and had blood drawn for trough concentration. Patient demographic data are shown in Table 1. The mean birth weight was 928 ± 159 g (range: 772-1088 g); the gestational age was 27.5 ± 1.8 weeks (range: 24-30 weeks).

Serum concentrations after the intramuscular injections of palivizumab are shown in Table 2. Mean ± SD trough serum concentrations after first dose and second doses were 32.3 ± 10.5 μg/mL (range: 16.2-51.6 μg/mL) and 51.9 ± 7.8 μg/mL (range: 41.9-64.0 μg/mL), respectively. Seventy-one percent (17 of 24) of infants had optimal protective concentrations (≥40 μg/mL) at midpoint after the first dose. However, only 23% (5 of 22) of infants had optimal protective concentrations before the second dose. All infants who were tested after second dose maintained concentrations >40 μg/ml until the third dose. In addition, both midpoint and trough concentrations were significantly higher after the second dose as compared with the concentrations after the first dose ($P < .0001$ and $P < .001$, respectively).

We compared infants with high (≥40 μg/mL) and low (<40 μg/mL) trough concentrations after the first dose of palivizumab (Table 3). There were no significant differences between the 2 groups in gestational age and birth weight. However, percentage weight change between injections was significantly higher in infants with low trough concentrations as compared with infants with high serum concentrations ($P = .04$).

None of the patients had significant changes in hepatic and renal functions related to the palivizumab injection. No serious adverse events were observed. Local reactions such as indurations, erythema, and bruising at the site of injection were observed in 28%; all of these reactions resolved within 24 to 48 hours later. None of the study infants developed RSV infection.

DISCUSSION

This study is the first to report palivizumab concentrations in young, very premature infants (≤30 weeks at birth) who received RSV prophylaxis during the course of their hospitalization in the NICU. Serum levels of palivizumab in preterm infants were also studied in the larger multicenter IMpact-RSV trial; however, at the time of entry in that study, the mean age of infants was 5.7 ± 0.15 months (mean ± standard error) and the weight was 4.8 ± 0.1 kg.[1] In contrast, at the time of entry in our study, the mean age of infants was 30.8 ± 3.8 days and their weight was only 1293 ± 236 g (mean ± SD).

We found that young, very premature infants who were enrolled in our study were unable to maintain sustained optimal protective serum concentrations (≥40 μg/mL) after the first dose of palivizumab. Although optimal serum concentrations were maintained in 71% of the infants at 2 weeks after the first injection, concentrations decreased subsequently and only 23% of infants tested had optimal trough concentrations before the second dose. This was in contrast to findings reported in older, heavier premature infants, in whom 66% of infants had optimal serum concentrations before the second dose.[5]

The failure of 77% of the infants in our study to maintain optimal trough concentrations after the first

TABLE 2. Serum Palivizumab Concentrations After the First, Second, and Third Doses

	n	Weight, g	Palivizumab, μg/mL	Range, μg/mL
At entry into study	25	1293 ± 236		
Midpoint after first dose	24	1587 ± 378	45.6 ± 13.0*	23.1–68.9
Trough before second dose	22	1880 ± 207	32.3 ± 10.5†	16.2–51.6
Midpoint after second dose	12	2169 ± 263	70.7 ± 13.8*	53.2–108
Trough before third dose	6	2655 ± 410	51.9 ± 7.8†	41.9–64.0

Values are mean ± SD.
* $P < .0001$ when midpoint concentrations after the first and second doses are compared.
† $P < .001$ when trough concentrations before the second and the third doses are compared.

TABLE 3. Comparison of Infants With High and Low Trough Palivizumab Concentrations After the First Dose

	Trough Level <40 μg/mL	Trough Level ≥40 μg/mL	*P* Value
No. of infants	17 (77%)	5 (23%)	
Gestational age at birth, wk	27.2 ± 1.7	28.2 ± 2.4	.29
Postnatal age at test, d	60.0 ± 3.8	57.2 ± 2.2	.7
Birth weight, g	927 ± 145	945 ± 233	.83
Weight at test, g	1884 ± 335	1956 ± 630	.90
% Weight gain between first and second doses	58 ± 15	41 ± 16	.04

dose of palivizumab may be attributable to their rapid weight gain during this time period or to the general hypercatabolic state of these infants. This was supported by the finding that infants with low trough concentrations had a significantly higher percentage weight change during the period between injections compared with infants with high serum concentrations.

If premature infants receive only 1 dose of palivizumab before discharge, as is the common practice, then a potentially significant number of infants may not sustain optimal protective concentrations until they receive the second dose. Our study demonstrates that young preterm infants are capable of achieving sustained optimal concentrations only after the second dose. Serum concentrations rose with repeated dosing in our infants; midpoint and trough concentrations before the third dose were significantly higher than those before the second dose.

CONCLUSIONS

Very premature infants were able to achieve sustained optimal protective concentrations of palivizumab only after the second dose; trough concentrations were suboptimal in three quarters of infants before the second dose. Additional studies are needed to determine optimal dosing and frequency in this population.

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REFERENCES

1. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics.* 1998;102:531–537
2. Holman RC, Shay DK, Curns AT, et al. Risk factors for bronchiolitis-associated deaths among infants in the United States. *Pediatr Infect Dis J.* 2003;22:483–489
3. Bonaparte J, Wu S-Y, Pyati S, et al. RSV: early palivizumab prophylaxis in the NICU. *Pediatr Res.* 2002;53:1571
4. Prescribing Information. Synagis (Palivizumab). MedImmune Inc; September 2003
5. Saez-Llorens X, Castano E, Null D, et al. and the MEDI-493 Study Group. Safety and pharmacokinetics of an intramuscular humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *Pediatr Infect Dis J.* 1998;17:787–791
6. Subramanian KNS, Weisman LE, Rhodes T, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *Pediatr Infect Dis J.* 1998;17:110–115
7. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI 493) with potent in vitro and in vivo activity against respiratory syncytial virus. *J Infect Dis.* 1997;176:1215–1224

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