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BRIEF REPORT

Open-Label Pilot Study to Compare the Safety and Immunogenicity of Pentavalent Rotavirus Vaccine (RV5) Administered on an Early Alternative Dosing Schedule with Those of RV5 Administered on the Recommended Standard Schedule

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This study compares the safety and immunogenicity of pentavalent rotavirus vaccine (RV5) administered on an alternative schedule (initiated at 2–5 weeks of age) with those of RV5 administered on the recommended standard schedule. Our findings support the future conduct of larger clinical trials to confirm the safety and efficacy of rotavirus vaccination in the neonatal period.

Keywords. adverse events; immunogenicity; pentavalent vaccine; rotavirus; safety.

Rotavirus is the leading cause of severe diarrhea in infants and young children worldwide [1]. In the United States, the peak rate of hospitalization attributable to rotavirus occurs between 6 and 11 months of age, but severe rotavirus disease also occurs in children younger than 2 months [2]. The pentavalent rotavirus vaccine (RV5) (RotaTeq, Merck & Co., Inc., Kenilworth, NJ) was licensed in the United States in 2006 and is safe and highly effective at preventing severe rotavirus gastroenteritis and reducing associated healthcare costs [2–4]. According to the manufacturer's prescribing information, RV5 should be administered in a 3-dose series starting at 6 to 12 weeks of age, with subsequent doses given at 4- to 10- week intervals and the third dose given no later than at 32 weeks of age. We evaluated the safety and immunogenicity of an alternative dosing schedule for RV5 in infants starting at less than 6 weeks of age with subsequent doses to be administered at 2 and 4 months of age. Administering an initial dose at a younger age might provide earlier protection from rotavirus infection and would allow additional opportunities for the timely completion of a 3-dose RV5 series, as recommended in the United States [5].

METHODS

This interventional open-label single-center study was conducted between February 2014 and July 2015 at Duke University Primary Care Pediatric Clinics, approved by the Duke University Health System Institutional Review Board, and registered with ClinicalTrials.gov (identifier NCT01960725). Approval for the off-label use of RV5 was obtained from the US Food and Drug Administration.

Sixty-six healthy infants were enrolled into 2 groups of 33 infants each. Group A included infants aged 2 months (range, 56–83 days) who were vaccinated with RV5 according to the standard schedule at 2, 4, and 6 months of age. Group B included infants aged 2 to 5 weeks (range, 14–41 days) who were given RV5 at 2 to 5 weeks and then at 2 and 4 months of age. This group was stratified further into subgroup B-1, which included 10 infants between 14 and 20 days of age, and subgroup B-2, which included 23 infants between 21 and 41 days of age. Subgroup B-2 included 11 infants ≤30 days old. Concomitant administration of other recommended vaccines was permitted.

The manufacturer supplied the licensed live oral RV5 expressing the G1, G2, G3, G4, and P1A[8] proteins from human strains on a backbone of the bovine (WC3) strain. To assess immune response to vaccination, sera were obtained 1 month after the final dose and assayed for anti-rotavirus immunoglobulin A (IgA) and rotavirus-neutralizing antibody responses against the G1, G2, G3, G4, and P1A[8] serotypes. Titer levels below the assay cutoff limit were assigned to 50% of the cutoff limit.

Reactogenicity data and adverse events were recorded on a report card by caregivers for 7 and 14 days, respectively, after

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each RV5 dose. Solicited adverse events included fever (axillary temperature, ≥100.4° F), diarrhea, vomiting (or spitting up), and hematochezia and were graded as mild, moderate, or severe. Serious adverse events were monitored for up to 6 months after the final RV5 dose. The proportions of subjects in each vaccine group for whom an adverse event was reported were determined. Descriptive analyses included frequencies and percentages for categorical data along with 2-tailed χ^2 or the Fisher exact test to compare proportions and to examine the associations between variables. Serum-neutralizing antibody (SNA) and IgA geometric mean titers (GMTs) and 95% confidence intervals (CIs) were determined for the study groups. Statistical analysis was performed using JMP 12 (SAS Institute, Inc., Cary, NC).

RESULTS

All subjects completed this study for safety outcomes. For the immunogenicity analysis, 27 infants in group A and 28 infants in group B were included. The proportions of girls were higher in both groups (58% and 64% in groups A and B, respectively). The majority of subjects in both groups were white (77%); fewer black (20%) and Asian (3%) subjects were enrolled. Distributions of sex and ethnicity/race were not significantly different between the groups. The mean ages at enrollment (and receipt of the first vaccine dose) were 27 ± 7 and 63 ± 5 days for groups B and A, respectively.

Geometric mean titers (GMTs) for serotype-specific SNA (G1, G2, G3, G4, and P1) were not significantly different between the 2 groups, except for the GMT of serotype G4, which was higher in group A than in group B (144.6 [95% CI, 105.1–198.8] vs 66.5 [95% CI, 50.7–87.1], respectively) (Table 1). Within group B, the G4 serotype GMT did not vary according to age at the time of study entry. The anti-rotavirus IgA GMT was higher for the standard-schedule group than for the alternative-schedule group; however, this difference was not significant. When we compared the serotype-specific SNA titers between the subgroups, the GMTs for all serotype-specific SNAs were higher in the younger age group (subgroup B-1) than in the older group (subgroup B-2); however, these differences were not statistically significant.

RV5 was well tolerated. Fever was reported for a total of 3 (5%) subjects, 2 (6%) in group A and 1 (3%) in group B [Table 2]. Of all the subjects, vomiting was reported for 20%, and diarrhea was reported for 30%. Vomiting and diarrhea were more common in group B than in group A, but these differences were not significant. However, within group B, vomiting was reported significantly more often in the younger-age subgroup (B-1) than in the older-age subgroup (B-2) (50% vs 13%, respectively; $P = .036$). These vomiting episodes reported for subgroup B-1 were mostly mild (4 of 5 episodes), and no severe episodes were reported. None of the parents/caregivers of the study subjects reported bloody stools.

Overall, 44 adverse events were reported for 27 (41%) of the subjects, 30 (68%) of which were vaccine related. The majority of the events (33 [75%]) occurred after the first dose. Adverse events did not significantly differ between groups A and B or between the group B subgroups. The most frequently reported adverse events were irritability, upper respiratory symptoms, and gastrointestinal symptoms. Fever was reported in 2 infants in the standard-schedule group and in both of them was considered to be caused by viral illness and unrelated to vaccination. All the vaccine-related adverse events in the alternative-schedule group (group B) were reported among children in the older subgroup. One serious adverse event occurred in an infant in group A. Four days after the third RV5 dose, the child developed vomiting and diarrhea and was hospitalized as a result of dehydration 10 days later. Testing for rotavirus was not performed. The event was deemed vaccine related and resolved without sequelae.

DISCUSSION

To our knowledge, this is the first trial of the RV5 administered on an alternative earlier schedule. Rotavirus SNA GMTs for the G1, G2, G3, and P1 serotypes were similar between the 2 groups; however, G4 GMTs were significantly lower in the alternative-schedule group. Furthermore, within the

Table 1. Immunogenicity Response (GMTs) of Study Groups 4 Weeks After the Last Dose of RV5

	GMTs (95% CI)			
Anti-rotavirus Titer	Group A (Standard Schedule) (N = 27)	Group B (Alternative Schedule) (N = 28)	Subgroup B-1 (14- to 20-day-olds) (N = 9)	Subgroup B-2 (21- to 41-day-olds) (N = 19)
Serotype G1	188 (117.9–299.7)	184.5 (117–290.8)	245.3 (90.8–662.4)	161.2 (93.7–277.2)
Serotype G2	38.7 (25–59.9)	33.1 (20.7–52.9)	77.6 (36.9–163.1)	22.1 (12.9–37.8)
Serotype G3	42.1 (27.5–64.6)	27.3 (17.3–43.2)	50 (19.2–130.2)	20.5 (12.2–34.3)
Serotype G4	144.6 (105.1–198.8)[a]	66.5 (50.7–87.1)[a]	83.9 (53.8–130.7)	59.6 (41.8–84.9)[a]
Serotype P1	114.7 (77.51–169.6)	136.5 (84.91–219.3)	298.0 (138.9–639.2)	94.3 (53.8–165.3)
Rotavirus IgA	318.3 (179.7–563.8)	183.7 (93.37–361.6)	173.9 (42.5–711.8)	188.6 (81–439.2)

Abbreviations: CI, confidence interval; GMT, geometric mean titer; IgA, immunoglobulin A; RV5, pentavalent rotavirus vaccine.
[a]Significant differences (no overlap of 95% CIs) between groups A and B and between group A and subgroup B-2 (21–41 days old).

Table 2. Solicited Adverse Events within the First Week After Vaccination with RV5 Vaccine

		No. (%) of Adverse Events			
				Subgroups	
Timing	Adverse Event	Group A (N = 33)	Group B (N = 33)	B-1 (14- to 20-day-olds) (N = 10)	B-2 (21- to 41-day-olds) (N = 23)
After dose 1	Fever[a]	0 (0)	0 (0)	0 (0)	0 (0)
	Vomiting	2 (6.1)	5 (15.2)	3 (30)	2 (9)
	Diarrhea	2 (6.1)	7 (21.2)	1 (10)	6 (27.3)
After dose 2[b]	Fever	1(3.6)	0 (0)	0 (0)	0 (0)
	Vomiting	1(3.6)	6 (18.8)	4 (40)	2 (9.1)
	Diarrhea	3 (10.7)	5 (15.6)	3 (30)	2 (9.1)
After dose 3[c]	Fever	1(3.6)	1(3.4)	0 (0)	1 (5)
	Vomiting	2 (7.1)	3 (10.3)	1 (11.1)	2 (10)
	Diarrhea	4 (14.3)	5 (17.2)	2 (22.2)	3 (15)
After any dose	Fever	2 (6.1)	1 (3)	0 (0)	1 (4.3)
	Mild[d]	1 (3)	0 (0)	0 (0)	0 (0)
	Moderate	1 (3)	1 (3)	0 (0)	1 (4.3)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)
	Vomiting[e]	5 (15.2)	8 (24.2)	5 (50)	3 (13)
	Mild[f]	3 (9)	5 (15.2)	4 (40)	1 (4.3)
	Moderate	1 (3)	2 (6)	1 (10)	1 (4.3)
	Severe	1 (3)	1 (3)	0 (0)	1 (4.3)
	Diarrhea[g]	7 (21.2)	13 (39.4)	4 (40)	9 (39.1)
	Mild	4 (12.1)	7 (21.2)	1 (10)	6 (26.1)
	Moderate	2 (6)	5 (15.2)	3 (30)	3 (13)
	Severe	1 (3)	1 (3)	0 (0)	0 (0)

Abbreviation: RV5, pentavalent rotavirus vaccine.

[a]Fever was defined as an axillary temperature of ≥100.4°F.

[b]Subjects with missing values were excluded from analysis (group A, n = 28; group B, n = 32).

[c]Subjects with missing values were excluded from analysis (group A, n = 28; group B, n = 29).

[d]Fever was graded as mild (100.4–100.9°F), moderate (101.0–101.6°F), or severe (≥101.7°F).

[e]Using the Fisher exact test, P = .54 for group A versus group B, whereas P = .036 for subgroup B-1 versus subgroup B-2.

[f]Vomiting and diarrhea were graded as mild (aware of symptoms, but easily tolerated), moderate (acting like something wrong), or severe (extremely distressed or unable to do usual activities).

[g]None of the subjects reported hematochezia.

alternative-schedule group, the GMTs for all serotypes, including G4, did not significantly differ between the 14- to 20-day age subgroup and the slightly older 21- to 41-day age subgroup. The difference in G4 GMTs is not clear and cannot be presumed to be a result of higher maternal antibodies in the alternative-schedule group, because the levels in subgroup B-1 (the younger subgroup) were higher than those in subgroup B-2. In addition, the clinical significance of this difference is unknown, because a true correlate of protection has not been identified.

Solicited adverse-event rates were similar between the 2 study groups. However, in the alternative-schedule subgroups, vomiting was more common in the youngest (14- to 20-day-old) age group, which might be a result of the usual increased incidence of spitting up and vomiting typically observed in the first weeks of life. We did not include an unvaccinated control group for comparison; however, in studies of other rotavirus vaccines administered during the neonatal period, the frequencies of vomiting and other adverse events were reportedly similar in vaccine and placebo recipients [6, 7].

The goal of a rotavirus vaccine is to provide protection before exposure to natural infection. One study predicted a reduction of rotavirus hospitalization rates when the first dose is administered 2 weeks earlier, at 6 weeks of age [8]. An early neonatal schedule would prolong the vaccination window, which might potentially expand vaccine coverage and improve regimen-completion rates. Starting vaccination at 1 month of age would be feasible, because it coincides with the timing of a preventative care visit recommended by the American Academy of Pediatrics [9]. Administration immediately after birth was not chosen, because a previous rotavirus vaccine (rhesus rotavirus tetravalent vaccine) was found to decrease vaccine immunogenicity when the vaccine series was initiated [10]. In the United States and other temperate-climate countries, vaccination of infants born in the fall or early winter [at 2 to 5 weeks of age] might offer protection during rotavirus season. Rotavirus circulates year-round in resource-limited countries, and a high burden of disease in the first 6 months of life exists [11]. For these infants, early priming of the immune response can potentially enhance protection by establishing immune response before encountering illnesses and other factors that might modify vaccine efficacy.

This pilot study was limited by its small sample size. We did not evaluate prevaccination antibody titers, and the study was not designed to evaluate the duration of protection or vaccine efficacy. Furthermore, by design, we administered the second and third doses of vaccine at 2 and 4 months of age in those who initiated the vaccine early. It is possible that early administration of subsequent doses rather than early administration of the first dose accounted for the changes observed in immune responses.

Our study provides supportive evidence that RV5 is generally well tolerated and immunogenic in the neonatal period, although the rotavirus SNA serotype 4 response was less robust than that with the standard schedule. Larger clinical trials are needed to confirm the safety and efficacy of early RV5 administration.

Notes

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