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Pentavalent Rotavirus Vaccine in Infants With Surgical Gastrointestinal Disease

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Abstract

Objectives—Pentavalent rotavirus vaccine (RV5) has been shown to be well-tolerated and efficacious in preventing rotavirus gastroenteritis in healthy infants. Safety and immunogenicity of RV5 in infants with surgical gastrointestinal disease have not been studied. The aim of the present study was to evaluate the safety and immunogenicity of RV5 in infants with a history of congenital or acquired intestinal disease requiring resection compared with healthy infants.

Methods—Infants with intestinal resection were matched by gestational age and chronological age to healthy infants (controls). Dose 1 of RV5 was given at 10 to 12 weeks of chronological age. Doses 2 and 3 were given at intervals of 4 to 10 weeks, with all 3 doses given by 32 weeks. All infants were monitored for adverse events (AEs) by telephone calls, clinic visits, and parental written reports during the first 42 days after each dose and monthly thereafter by telephone for 12 months. Serum anti-rotavirus immunoglobulin A (IgA) titers were measured prevaccination and 2 weeks after dose 3.

Results—A total of 5 infants with surgical gastrointestinal disease and 3 control subjects were enrolled. All participants (100%) mounted a 3-fold increase in serum anti-rotavirus IgA geometric mean titer postvaccination. RV5 administration to surgical infants was well tolerated with a majority of AEs being attributed to the underlying medical condition.

Conclusions—Postvaccination serum anti-rotavirus IgA levels indicate that RV5 is immunogenic in infants with a history of bowel resection, despite varying lengths of residual bowel. RV5 was well tolerated with few vaccine-related AEs.

Keywords

bowel resection; pediatric; pentavalent rotavirus vaccine; rotavirus; short bowel syndrome

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Rotavirus infection was a common pediatric illness and a leading cause of severe acute gastroenteritis in infants and young children (1) before the availability of effective vaccination in the United States (2). In February 2006 a pentavalent rotavirus vaccine (RV5; RotaTeq [Merck & Co, Whitehouse Station, NJ]) was licensed and recommended for use among infants in the United States. This vaccine was studied for safety, immunogenicity, and efficacy in large clinical trials before Food and Drug Administration (FDA) approval in the United States (3,4) and in postmarketing surveillance studies after approval (5–10). It was recommended by the US Advisory Committee on Immunization Practices (11,12) and became part of a successful national vaccine program (7,9). Since that time, and the FDA approval of an additional rotavirus vaccine, a substantial and sustained reduction in rotavirus activity has been observed (6,13–15).

In phase III studies, 92.9% to 100% of 439 participants (healthy infants) achieved a 3-fold increase in serum anti-rotavirus immunoglobulin A (IgA) after a 3-dose regimen (16). RV5 was also shown to be well tolerated and efficacious in preventing severe rotavirus gastroenteritis in healthy infants (4). Efficacy and safety data for RV5 in patients with a history of gastrointestinal (GI) disorders, congenital abdominal disorders, intussusception, or abdominal surgery are unavailable and remain largely unevaluated (16).

Serious neonatal GI disorders include necrotizing enterocolitis and congenital bowel abnormalities such as volvulus, intestinal atresia, and gastroschisis. Intestinal resection may be required as a standard surgical treatment in infants with these disorders and involves the surgical removal of affected portions of the intestinal tract. Resections can include portions or all of the stomach, small intestine (duodenum, jejunum, ileum), cecum, or large intestine. With extensive intestinal resection, short bowel syndrome can ensue, which is commonly defined as the need for prolonged parenteral nutrition (PN) in the setting of congenital or acquired GI disease (17).

Specific lymphoid tissues that line the small intestine, known as Peyer patches, are concentrated in the ileum. These tissues are known to be involved in the host immune response to substances passing through the GI tract, and may play a significant role in the development of immunity when oral vaccines are ingested (18). The presence and amount of these specific tissues in infants after intestinal resection depend on the portion and length of the GI tract excised or afflicted by ischemia or inflammation.

The safety and immunogenicity of RV5 in infants with surgical GI disease have not been studied previously, and RV5 administration to this group includes a precaution (16). It is unknown whether RV5, or any oral rotavirus vaccine, poses any additional safety concern for infants after intestinal surgery such as intussusception or worsening of underlying GI disease.

Herein, we report the results of a pilot study of RV5 in infants with surgical GI disease compared with chronological age- and gestational age-matched healthy controls.

METHODS

Study Design

The present study was a prospective, open-label, case-controlled, clinical trial conducted from July 17, 2009 to October 31, 2012 in a total of 3 medical centers. The Children's Hospital of Michigan in Detroit was the coordinating study center; William Beaumont Hospital in Royal Oak, MI, a referral center; and Boston Children's Hospital, a second study site that opened in March 2010 because of slow enrollment at the primary site. Healthy control participants were identified from patients receiving care in the Children's Hospital of Michigan General Pediatrics Clinic or Hutzel Women's Hospital, both in Detroit. The present study was conducted under an FDA Investigational New Drug (IND) protocol, 13843. The trial was registered at the national clinical trials Web site (NCT00767364).

The primary outcome of the present pilot study was to evaluate the safety and immunogenicity of RV5 in infants who had undergone intestinal resection compared with healthy infants (controls) matched by gestational age and chronological age (within 14 days). Secondary outcomes included quantification of serum anti-rotavirus IgA in infants before and after RV5 vaccination series and identification of any association between immunogenicity of vaccine series and the length or type of intestinal resection.

Ethics, Ethical Approval, and Data Monitoring

The protocol was approved by the investigational review board at each center. Written parental informed consent was obtained before enrollment. Infants with a history of GI surgery but no intestinal resection were not considered an ethical placebo control because of an inability to later immunize them if any benefit was discovered because the first dose must be administered by 12 weeks of age. Because the present study required an IND submission from the FDA, all adverse events (AEs) were communicated in triplicate to the FDA by Medwatch 3500 form, by the Vaccine Adverse Event Reporting System, and to the study sponsor. An independent Data and Safety Monitoring Board consisting of 4 physicians (pediatrician, pediatric infectious disease specialists [2], and a pediatric GI specialist) was assembled to review safety data with knowledge of the medical history after the first 6 enrollments and again at the end of the trial.

Participant Enrollment

Inclusion Criteria—Infants ages 6 to 12 weeks of chronological age with acquired or congenital surgical GI disease who had undergone intestinal resection were eligible for enrollment. Participants were required to be 10 to 12 weeks of chronological age to receive RV5 dose 1 (FDA recommendation) and be at least 10 days after any GI surgery at time of vaccine administration. Additionally, before vaccination, participants had to be afebrile (temperature $<38.0^{\circ}\text{C}$), be able to tolerate some enteral intake, have stable to increasing body weight, have stable electrolytes, and be clinically ready for home discharge. Infants had to have at least 30 cm of residual small intestine present with a whole colon and intact ileocecal valve or at least 45 cm of residual small intestine without an ileocecal valve (with or without a whole colon) to be included in the study.

Control group infants could be enrolled from 6 to 12 weeks of age, but were required to be 10 to 12 weeks of chronological age to receive RV5 dose 1. The control group participants were matched to the study infants in gestational age and chronological age within 14 days for more accurate comparison of immune responses. Control group infants could not be diagnosed as having any underlying GI conditions other than gastroesophageal reflux disease.

Exclusion Criteria—Potential participants were excluded from the study if they had a history of rotavirus infection or receipt of any rotavirus vaccine, were known to have a hypersensitivity reaction to vaccine components, could not have adequate follow-up for safety by telephone or home visit, were diagnosed as having a congenital or acquired immunodeficiency or neoplasm, were potentially immunosuppressed or received intravenous immunoglobulin, failed to have blood obtained by the third attempt, or were infants with immunodeficient household contacts.

Additional exclusions in study group infants included a diagnosis of portal hypertension, a need for bowel or liver transplant, imminent/evident liver failure, and a total serum bilirubin >7 mg/dL with associated stage 2 liver fibrosis (19).

Vaccination and Study Procedures

Dose 1 of RV5 was administered orally (2 mL) and was given at 10 to 12 weeks of chronological age. Doses 2 and 3 were given at a minimum interval of 4 weeks with all 3 doses given by 32 weeks of chronological age. All infants were monitored for AEs by telephone, clinic visits, and parental written reports during the first 42 days after each RV5 dose and monthly thereafter by phone for 12 months. Serum anti-rotavirus IgA titers were measured prevaccination and 2 weeks after dose 3 (20). Any patient with increased frequency of stools after vaccination (above baseline stool frequency in infants with surgical GI diseases) with other symptoms of possible GI infection (fever, vomiting) had their stool collected, frozen, and analyzed for rotavirus by rotavirus antigen detection assay (20). The baseline stool number was individualized per patient based on their normal daily bowel habits.

Evaluation of Adverse Events

All infants were studied for AEs with active safety surveillance for the first 42 days after each dose and also monthly afterward for a total of 12 months from the first vaccination date. Parents/guardians were asked to fill out a vaccination report card for 42 days after each dose. Contact was made with the parent/guardian by telephone at 48 to 72 hours after each vaccine dose to review whether any AEs had occurred and at 7, 14, and 42 days after each vaccine dose. Each infant was examined at 7 days after each vaccine dose, and the vaccine report cards were reviewed to assess for AEs. The parent/guardian was asked to record the child's temperature and any episodes of vomiting, diarrhea, hematochezia, or irritability for the first 7 days after the vaccine was administered. The parents/guardians were also asked to report the presence of other events from days 8 to 42 after the vaccine is administered, for example, fever ($>38.0^{\circ}\text{C}$), otitis media, bronchospasm (wheezing), and rhinorrhea. Participant parents were given a rectal thermometer for the purposes of the present study

with instructions on appropriate use. Participants were examined at 7 days after each vaccine dose, and a review of the vaccine diary/report card occurred at that time.

Participants in the present study were studied for 1 year from the date of their first rotavirus immunization. Parents were informed, before discharge from the initial enrollment day clinic visit, about signs and symptoms of an acute infectious gastroenteritis-type illness and intussusception.

Evaluation of Immunogenicity

An assessment of the percentage of infants who responded to the complete (RotaTeq) vaccine series with a 3-fold increase in serum anti-rotavirus IgA geometric mean titer (GMT) in the surgical GI disease group compared with that of normal infants was performed. There are no established immunogenicity correlates of protection for rotavirus IgA titers after vaccination (21).

Statistical Analysis

Mean anti-rotavirus antibody titers after vaccination were analyzed for any rise in GMT compared with prevaccination GMT. The percentage of participants with a 3-fold rise in titer in the study and control groups (because this was previously reported as successful seroconversion (4)) was calculated and compared using the 1-sample and independent samples *t* test. AEs were analyzed and reported using descriptive statistics. Data were examined using SPSS version 21.0 (IBM SPSS, Armonk, NY).

STUDY RESULTS

Enrollment

A total of 56 infants were screened for enrollment in the surgical GI disease study group during the study period. Of these, 5 met study group enrollment criteria. The other 51 who could not be enrolled were excluded for the following reasons: neonatal intensive care unit length of stay >12 weeks (14), no bowel resected despite abdominal surgery (11), little bowel remaining (7), declined participation (7), could not receive care at primary site (5), multiple congenital anomalies or concern for possible immunodeficiency (4), vaccine given by primary physician (2), or could not tolerate enteral intake (1). There were 117 infants screened to be suitable controls, of which only 10 were gestational and chronological age matched. Of these 10 infants, parental informed consent to participate in the study was obtained in 3 participants; 7 other parents declined to participate.

Participants and Immunogenicity

Eight participants were enrolled during the study period at the 2 study sites. Demographic information, details of surgical resections, vaccination details, and immunogenicity data are summarized in Table 1. No suitable age-matched infant could be identified for the infant with bowel resection born at 30 weeks. All vaccine was administered on the hospital day of discharge or after hospital discharge. All study group participants required PN postoperatively, and all, except subjects 1 and 3, were transitioned to full oral feedings before discharge.

Prevaccination and postvaccination antibody titers were transformed to GMT because of the non-normal distribution of the data. The 1-sample *t* test for significance across all of the postsample GMT (540.22 SD $\pm$ 316.03) compared with the constant, fixed prevaccination (GMT 1.56 SD $\pm$ 0.01) was greatly significant ($P < 0.001$; 95% CI 299.03–788.31). Therefore, all participants (100%) in both groups had a 3-fold rise in serum anti-rotavirus IgA GMT detected 2 weeks after dose 3. The mean difference between the prevaccination and postvaccination GMT found between the groups, bowel resection (618.61 SD $\pm$ 301.72) versus controls (431.02 SD $\pm$ 371.74), was not significant ($P = 0.462$ by Student *t* test).

Adverse Events

AEs in study group infants were similar to those previously reported in healthy infants with the exception of stoma site bleeding after RV5 dose 1 in 2 of surgical participants (with stomas), which was mild and resolved. Most AEs in the study group were related to their underlying medical problems such as confirmed or possible central venous catheter infection. All severe AEs were noted as such because of required hospitalization. There were no instances of intussusception, and no AE was deemed life threatening. In 1 surgical infant, diarrhea symptoms increased above participant baseline: stool antigen was negative for rotavirus. AEs in both study groups are summarized in Table 2.

DISCUSSION

In the present study, RV5 was administered to infants with surgical GI disease with intestinal resection and healthy age-matched controls. The present pilot study showed a diverse group of infants with variable residual bowel length and anatomy were able to tolerate oral RV5 and mount an immune response with a statistically significant 3-fold rise in anti-rotavirus serum IgA GMT from baseline, a response similar to their age-matched controls. Although it has been noted that the exact immunologic mechanism by which rotavirus vaccines protect against clinical gastroenteritis is not clear (20,22) and that there is no definitive correlate of protection for rotavirus (4,21), a 3-fold rise in serum IgA anti-rotavirus titers has been deemed successful seroconversion (4). Our findings are in agreement with a recent publication in which infants with intestinal failure caused by various underlying GI disorders who had undergone surgery and received monovalent rotavirus vaccine (Rotarix, GSK Biologicals, London, UK) seroconverted (23). As written, it is not clear how many of those infants had intestinal resection.

Neonatal short bowel syndrome can be a devastating condition, but mortality rates in more recent literature have decreased to 7% to 11% because of new advances in the care of these patients (24–26). Common causes of death include liver failure or sepsis within 1 year postsurgery. In addition, rotavirus infections have been reported to cause setbacks in infants transitioning from PN to enteral feedings, as the intestinal adaptation phase of the disorder progresses (27,28). These fragile patients may have even more benefit than the general population from receiving the protection afforded by the vaccine to prevent wild-type infection with rotavirus. Administration of RV5 to 9 infants with high-output ileostomy was tolerated and did not alter weight gain, temperature, or urinary sodium (29). Only 1 infant developed severe stomal fluid loss postvaccination requiring fluid resuscitation (29).

In our study population, RV5 was well tolerated with few vaccine-related AEs. Hematochezia reported as an AE was seen equally in both vaccine and placebo recipients in the large clinical trials summarized in package insert information (16). Therefore, the finding of stoma site bleeding noted in 2 of the infants in the study group may or may not be related to receipt of RV5. Because parents filled out vaccine report cards for any AEs for 42 days after each dose and were called monthly by phone for safety checks for 12 months after the first dose to assess for late AEs, the report is comprehensive.

The majority of AEs reported in study group infants were categorized by the principal investigator as not related to RV5. The assignment of AE relatedness to vaccine receipt was complex in these patients because of many concurrent variables. These AEs are more likely to be reflective of the underlying medical conditions related to surgical GI disease or chronic PN use. Additionally, elevated bilirubin levels were noted in 1 study infant receiving long-term PN. The patient's bilirubin rise noted during the study was not thought to be caused by receipt of RV5.

Differences in specific serum anti-rotavirus IgA levels within the surgical group were initially postulated to be because of the presence of an intact terminal ileum: a higher serum antibody level was found in participants 1, 3, and 8, each with an intact terminal ileum compared with participant 5 with a terminal ileum resection. Participant 6 also had terminal ileum resection, and the postvaccination titer was the highest in the study participants. The impact of terminal ileum resection on immunity from RV5 requires further study; our study's limited sample size precludes firm conclusions with respect to the type of bowel resected and the vaccine's immunogenicity.

The small sample size of the present study is likely the largest limitation with regard to the ability to generalize the information learned from the present study. Slow initial enrollment led to the opening of a secondary site at Boston Children's Hospital to help to screen and enroll participants. During the study period, >50 patients who had undergone bowel surgery were approached for enrollment between the 2 study sites. The greatest number of screen failures were in those who required hospital stays >12 weeks, which was the latest the FDA, under this IND, would allow administration of the first dose of vaccine despite a harmonization recommendation by the US Advisory Committee on Immunization Practices that allowed the first dose to be given up to 14 weeks, 6 days (30). In another recent publication the present age restrictions for rotavirus immunization resulted in more than half of extremely-low-birth-weight infants being ineligible for vaccination at the time of neonatal intensive care unit discharge (31). Present age restrictions make infant groups with vulnerability to wild-type rotavirus infection, such as many premature and medically complex infants, ineligible to receive rotavirus vaccination. Additionally, many parents voiced concern over the possibility of vaccine's adverse effects in their already medically fragile infants in the study group. This concern was echoed in the article by Javid et al, with 40% of the families offered participation declining study enrollment (23).

Results from the present small, prospective pilot study show that the vaccine is well tolerated and can be immunogenic in infants with surgical GI disease. The present study focused on a specific group of infants, namely, those with GI resection, but because there

are an increasing number of extremely premature infants being delivered, the potential for an increase in the number of bowel resections and infants with intestinal failure is emerging. Larger, multicenter studies are needed to confirm these findings and help to shed light on any increased risk for intussusception or other AEs in this population when administered RV5.

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TABLE 1

Participant demographics, surgical information, and immunogenicity

No.	Gestational age, wk, sex	Surgical indication	Length, cm, type of bowel resected, age at procedure, days	Vaccine (V) dose and age, days	Prevaccine serum IgA anti-rotavirus, U/mL	Postvaccine serum IgA anti-rotavirus, U/mL*
1 [†]	36, female	Gastroschisis with intestinal infarction	All but 23 cm jejunum and 7 cm of ileum with jejunostomy, [‡] (1); anastomosis, (105)	V1: 73; V2: 129; V3: 197	<1.56	916.4
3	40, male	Meconium ileus; intestinal perforation with abscess	2 cm ileum with ileostomy, (1); 6 cm ileum, anastomosis, (90)	V1: 73; V2: 132; V3: 185	<1.56	679.48
5	30, male	NEC with perforation	14.5 cm colon with ileostomy, (20); ileocolic anastomosis, (114)	V1: 74; V2: 131; V3: 191	<1.56	259.65
6	39, male	Total colonic Hirschsprung disease	Total (31 cm) colon w/ ileostomy (8 cm ileum), (7); anastomosis (211)	V1: 70; V2: 134; V3: 190	<1.56	1018.78
8	38, male	Malrotation, midgut volvulus	80 cm small intestine (including duodenum), (3); anastomosis (49)	V1: 76; V2: 107; V3: 205	<1.56	549.97
2	37, female	Control	Control	V1: 73; V2: 135; V3: 205	<1.56	935.62
4	39, male	Control	Control	V1: 71; V2: 134; V3: 199	<1.56	314.05
7	40, male	Control	Control	V1: 70; V2: 119; V3: 161	<1.56	272.51

IgA = immunoglobulin A; NEC = necrotizing enterocolitis.

* A definitive correlation between immunogenicity and clinical efficacy has not been established.

[†]Number indicates sequence of enrollment.[‡]The surgical team reported only residual bowel length in this subject.

TABLE 2

Study adverse events

Adverse event	Total AE, group(s)	Days postvaccine dose, vaccine (V) dose	Body system	Severity	Related	Outcome
Stomal bleeding–hematochezia	2 SGD	2, V1; 5, V1	GI	Mild; moderate	Possibly related; possibly related	Resolved
Hematochezia	1 SGD	12, V2	GI	Moderate	Not related*	Resolved
Bowel obstruction: Hirschsprung enterocolitis	1 SGD	198, V3	GI	Severe	Not related	Resolved
Gastrostomy-tube drainage after removal	1 SGD	62, V2	GI	Mild	Not related	Resolved
Loose stools	1 control	4, V1	GI	Moderate	Possibly related	Resolved
Diarrhea [†]	1 SGD	183, V3	GI	Mild	Not related	Resolved
Vomiting	1 SGD	167, V3	GI	Mild	Not related	Resolved
Vomiting, diarrhea [†]	2 SGD	59, V3; 110, V3	GI	Mild	Probably not related; probably not related	Resolved
Fever (alone)	1 SGD; 1 control	20, V2; 1, V3	Gen.	Mild; mild	Possibly related; not related	Resolved; resolved
Fever with URI	1 SGD	98, V3	Gen.	Mild	Not related	Resolved
Central line sepsis	1 SGD	2, V1	Gen.	Severe	Not related	Resolved
Fever, rule out line infection	3 SGD	17, V2; 9, V1; 15, V1	Gen.	Severe	Not related	Resolved
Low hemoglobin	1 SGD	10, V2	Heme.	Severe	Not related	Resolved
Elevated bilirubin level	1 SGD	39, V2	Heme./GI	Severe	Not related	Ongoing
Fussiness	1 SGD; 1 control	60, V1; 1, V3	CNS	Mild; mild	Possibly related; possibly related	Resolved, resolved

AE = adverse event; CNS = central nervous system; Gen. = general; GI = gastrointestinal; Heme. = hematologic; SGD = surgical gastrointestinal disease infant; URI = upper respiratory infection.

* AE related to infant formula change, resolved with change to different formula.

[†] Diarrhea was above individual baseline level for stool frequency.