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ROTATEQ®: A PENTAVALENT HUMAN-BOVINE ROTAVIRUS VACCINE

Jennifer Gailey, Pharm.D. Candidate

Rotavirus infection is the primary cause of acute, dehydrating gastroenteritis worldwide, resulting in 500,000 deaths annually.¹ Nearly 100% of children are exposed by the fifth year of life. While rotaviruses are proven to be the cause of only 5% - 10% of gastroenteritis episodes in children less than 5 years of age, they are responsible for 20% - 60% of hospital admissions secondary to gastroenteritis.² The most severe of infections usually occur between 6 and 24 months of age. Infection rates are independent of socioeconomic status, sanitation, and geography. The majority of cases in the United States occur during late fall to early spring. The peak season begins in the Southwest during November and December, then travels sequentially towards the Northeast, ending in April and May. Treatment is limited to general supportive measures such as oral rehydration; therefore, developing a vaccine against rotavirus has been identified as high priority by the World Health Organization (WHO) and the Global Alliance for Vaccines and Immunizations (GAVI). Based on economic models on disease burden developed by the Centers for Disease Control (CDC), the total cost of rotavirus gastroenteritis disease is estimated to be between \$1 and \$1.3 billion annually in the United States.^{1,3}

RotaShield® (a tetravalent rhesus-human reassortant vaccine) was the first rotavirus vaccine approved in the United States to prevent rotavirus gastroenteritis. Created by Wyeth-Ayerst Pharmaceuticals, it was licensed in 1998 but voluntarily withdrawn from the market by Wyeth in 1999 due to an association with intussusception.⁴ The CDC conducted 2 large multi-state investigations to evaluate the connection between patients who received the vaccine and reported cases of intussusception. The CDC estimated RotaShield® increased the risk for intussusception by 1 or 2 cases among each 10,000 infants vaccinated.⁵ Risk of developing intussusception was greatest during days 3-14 after the first dose and 3-7 days after the second dose.⁶ Research into developing a human-bovine rotavirus vaccine continued due to the importance to public health.^{5,7}

In February of 2006, RotaTeq® (rō' tə tēk), manufactured by Merck & Co., was licensed in the United States as the only FDA approved rotavirus vaccine. RotaTeq® is a live, oral, pentavalent, human-bovine vaccine (R-HBV) that contains 5 live reassortant rotaviruses. R-HBV is indicated for the prophylaxis of gastroenteritis caused by rotavirus infection of the 4 serotypes (G1-4) in infants 6 to 32

INSIDE THIS ISSUE:

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weeks of age.⁸ This article will review the pharmacology, efficacy, safety profile, dosing, and clinical trials of this R-HBV.

Pharmacology

R-HBV contains 5 live reassortant rotaviruses (serotypes G1, G2, G3, G4, and P[8]) isolated from human and bovine hosts. The backbone of the 5 viruses within the vaccine is the bovine strain WC3. Each of the 5 strains incorporate either the VP4 gene from a P[8] human rotavirus or the VP7 gene from a G1, G2, G3, or G4 human rotavirus. The most common G and P serotypes of known human rotavirus are represented by the VP4 and VP7 genes.^{8,9}

The exact mechanism by which R-HBV immunologically protects against rotavirus gastroenteritis is unknown.¹⁰ This live viral vaccine replicates in the small intestine in villous epithelial cells. After 1-4 weeks, antibody stimulation occurs and immunity is induced.^{10,11} Vaccinated infants are resistant to developing a severe case of rotavirus caused by applicable serotypes during the next season after vaccination. Some protection exists for up to 2 seasons, but the true duration of immunity is unknown.¹² Viral shedding was observed 1-15 days after a dose; transmission was not evaluated.

Clinical Trials

Immunogenicity

During the 1993-1994 rotavirus season, an efficacy trial was carried out with a quadrivalent precursor to R-HBV that contained the G1, G2, G3, and P[8] elements. This study was a randomized 3-dose trial including 439 infants at 10 sites in the United States. During this study, infants 8 weeks of age received the first dose, and the following 2 doses were separated by 6 to 8 week intervals. ELISA technol-

ogy was used to measure serum IgA levels, the most sensitive indicator of vaccine efficacy. Seroconversion was defined as a ≥ 3 fold increase in serum rotavirus IgA levels between the time of the first vaccine dose and 2 to 4 weeks after the last dose, and was found to have occurred in 87.6% of vaccine recipients and 1.6% of placebo recipients. ELISA also measured stool rotavirus IgA levels, where 74.2% of vaccine recipients and 3.8% of placebo recipients were found to have ≥ 3 fold increases between the time of their first dose and 2 to 4 weeks after the final dose. One of the 10 study sites determined immunogenicity separately after each vaccine dose in 37 vaccine and 37 placebo recipients. In this substudy, stool samples were obtained before and 2 to 4 weeks after each dose and quantified by ELISA to determine how many vaccine recipients had a ≥ 3 fold increase in rotavirus IgA. In total, 16, 19, and 15 recipients had increases in IgA after 1, 2, and 3 doses, respectively. This indicates a 3-dose regimen to illicit an increased immune response by this vaccine.^{10,14}

Efficacy

The RotaTeq[®] Efficacy and Safety Trial (REST) was randomized, placebo-controlled, and double-blinded (including sponsor), included 11 countries, and took place from 2001 to 2004. In total, it contained 69,274 infant subjects and measured efficacy by preventing rotavirus gastroenteritis (RGE) ≥ 14 days after completing the R-HBV series through the first rotavirus season. The vaccine was given as a 3-dose series to healthy infants with the first dose given between ages 6 and 12 weeks and the 2 additional doses given 4 to 10 weeks apart. All infants receiving the third dose were less than 32 weeks of age. Analyses were also conducted to

Table 1. Efficacy* of pentavalent rotavirus vaccine against G1-4 RGE in REST¹³

Disease severity**	Vaccine (N=2207)	Placebo (N=2305)	Efficacy % (95% Confidence Interval)	ITT Efficacy % (95% Confidence Interval)
Any	82	315	74.0 (66.8-79.9)	60.0 (51.5 - 67.1)
Severe	1	51	98.0 (88.8-100.0)	96.4 (86.2 - 99.6)

*Includes only cases that occurred at least 2 weeks after dose 3 in the clinical-efficacy substudy group

**Severity determined by scoring system of Clark HF, et al.¹⁶

Table 2. Efficacy of rotavirus vaccine in reducing G1-4 rotavirus-associated hospitalizations in REST¹³

	Vaccine (N=28,646)	Placebo (N=28,488)	ITT* vaccine (N=34,035)	ITT* placebo (N=34,003)
Number of Hospitalizations	6	144	10	187
Percent reduction in hospitalizations (95% CI)	95.8 (90.5 - 98.2)		94.7 (89.3 - 97.3)	

*ITT analysis includes all subjects who received at least one vaccine dose.

evaluate efficacy among infants who received at least one vaccination (Intent-to-Treat; ITT). Efficacy against any severity of RGE caused by serotypes G1-4 through the first rotavirus season was 74.0% and the ITT efficacy was 60.0%. Efficacy against severe RGE was 98.0% and ITT efficacy was 96.4% (**Table 1**). Efficacy of the vaccine against serious disease was also confirmed by a decrease in hospitalizations for RGE among all subjects enrolled in this trial. Hospitalizations in vaccinated infants were reduced during the first 2 years after the third dose by 95.8%. The efficacy of the ITT group reduced hospitalizations was 94.7% (**Table 2**).¹³

The efficacy of the R-HBV through a second rotavirus season was evaluated in REST. Efficacy against any grade severity RGE caused by serotypes G1-4 occurring through the two seasons after vaccination was 71.3% (95% CI = 64.7 - 76.9). The efficacy in preventing RGE only in the second season after vaccination was 62.6% (95% CI = 44.3 - 75.4). The efficacy of the vaccine beyond this time frame was not evaluated.¹³

Dosing and Administration

The oral R-HBV should be given at least 1 month apart from any other live vaccine if possible. Efficacy is not proven if the patient does not receive all 3 doses, nor if administered with a pertussis vaccine. Data and efficacy are not established in immunocompromised infants or those with blood

dyscrasias. The R-HBV is indicated for infants 6 to 32 weeks of age and all three oral doses should be given in that time frame. The first dose of 2 ml should be given between 6 and 12 weeks of age. The next two doses of 2 ml each will be administered at intervals of 4 to 10 weeks, and the final dose should be given before infant is 32 weeks old. Repeat dosing is not necessary if an infant regurgitates the dose and any remaining doses in the series should be given.^{12,13}

Toxicity and Safety

Due to the withdrawal of RotaShield[®], it was pertinent to conduct proper safety investigations regarding intussusception during the develop of new rotavirus vaccines. Of the 68,038 subjects who received at least one dose of vaccine or placebo, 67,756 (99.6%) were followed for 42 days after receiving their last dose, and 56,310 (81.3%) were followed for at least 1 year after their first dose. Within the 42-day period after any dose of the vaccine, 6 vaccine recipients and 5 placebo recipients had confirmed cases of intussusception. Within the first year after any dose, there were 12 reported cases of intussusception in the vaccine group and 15 confirmed cases in the placebo group. Neither of these figures are statistically significant (**Table 3**). Serious adverse events (SAE) occurred in 2.4% of vaccine recipients and 2.6% of placebo recipients within the 42-day period of any dose in phase III studies. The

Table 3. Intussusception cases in rotavirus vaccine recipients vs. placebo during REST¹³

	Vaccine (n=34,035)	Placebo (n=34,003)
Confirmed cases within 42 days of any vaccine dose	6	5
Confirmed cases within 365 days of first vaccine dose	12	15

Table 4. Adverse events occurring within 42 days⁸

Adverse event	Vaccine (N=6,138) (n %)	Placebo (N=5,573) (n %)
Diarrhea	1,479 (24.1%)	1,186 (21.3%)
Vomiting	929 (15.2%)	758 (13.6%)
Otitis media	887 (14.5%)	724 (13.0%)
Nasopharyngitis	422 (6.9%)	325 (5.8%)
Bronchospasm	66 (1.1%)	40 (0.7%)

only SAE that occurred more commonly in the vaccine group is bronchiolitis. Rates of pneumonia, fever, and urinary tract infections were similar or higher with placebo. Overall, 44 deaths in 68,038 subjects occurred in the study; 24 in the vaccine group and 20 in the placebo group. The most common cause of death in both groups was sudden infant death syndrome. A substudy of 11,711 participants of REST were asked to record any adverse events occurring 42 days after each dose.^{12, 13} Non-serious adverse events in both groups include irritability, fever, vomiting, diarrhea, otitis media, nasopharyngitis, and bronchospasm. The adverse events associated with the use of R-HBV more frequently than placebo are detailed in **Table 4**.

Cost

The catalog price for RotaTeq[®] is \$62.50 per dose when purchased as a pack of 10 single-dose tubes, making a complete series of doses \$187.50.¹⁵

Summary

Rotavirus infections are the leading cause of severe gastroenteritis in young children. R-HBV vaccine, when administered during the first few months of life, can greatly reduce the morbidity and mortality associated with RGE caused by serotypes G1-4 during the first rotavirus season after vaccination. The 3-dose series can be easily incorporated into already-existing vaccination regimens. Serious adverse events occurred less frequently in the vaccine group than in the placebo group, including intussusception, which caused RotaShield[®] to be withdrawn from the market. Additional studies would be beneficial to further evaluate the safety and efficacy of R-HBV.

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RECENT DRUG APPROVALS

Levocetirizine (Xyzal®) - UCB Inc.

Levocetirizine is the levo isomer of cetirizine that has twice the affinity for H₁ receptors than cetirizine. Levocetirizine received FDA approval on May 29, 2007 for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in adults and children 6 years of age and older. The most common adverse reactions during the clinical trials were somnolence, nasopharyngitis, pharyngitis, fatigue, and dry mouth. The recommended dose for children ages 6-11 years is 2.5 mg daily and 5 mg daily for patients 12 years or

Lybrel™ (90 mcg levonorgestrel and 20 mcg ethinyl estradiol) - Wyeth Pharmaceuticals Inc.

Lybrel™ is low-dose combination oral contraceptive regimen that suppresses the hypothalamic-pituitary system ultimately suppressing ovulation and menstration. This combination is designed to be taken daily without interruption for as long as the woman wishes to suppress her periods. The long-term safety of continuous oral contraception is unknown beyond three years and many women still experience breakthrough bleeding and spotting. 28 day packs are expected to be available in July 2007.

Rotigotine (Neupro®) - Schwarz Pharma Inc.

Rotigotine is a lipid-soluble, selective dopamine (D₂) receptor agonist approved on May 9, 2007 for the symptomatic treatment (hypokinesia, rigidity) of Parkinson's disease. Rotigotine is a non-ergot derivative available as a transdermal patch that delivers continuous dopaminergic stimulation over 24 hours. This delivery system may reduce motor complications associated with advancing Parkinson's disease. 2, 4 and 6 mg/24 hour patches are expected to be available in June 2007. The starting dose is 2 mg/24 hours and may be increased as tolerated.

Retapamulin (Altabax®) - GlaxoSmithKline

Retapamulin is a semisynthetic antibiotic similar to pleuromutilin that binds to the 50S ribosomal subunit thereby preventing protein synthesis. Retapamulin is available as a 1% topical ointment for the treatment of impetigo due to methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes* in patients greater than 9 months of age. Treatment consists of application of a thin layer to affected area twice a day for 5 days.

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