Experience of Pentavalent Human-bovine Reassortant Rotavirus Vaccine Among Healthy Infants in Taiwan

Chien-Chih Chang,1 Mei-Hwei Chang,1* Tzou-Yen Lin,2 Hong-Chang Lee,3 Wu-Shiun Hsieh,1 Ping-Ing Lee1

Background/Purpose: Rotavirus infection is the most common etiology of acute gastroenteritis in young children worldwide. The first rotavirus vaccine was licensed by the United States Food and Drug Administration in 1998 but was suspended soon after in 1999 because of the possibility of induced intussusception. This study evaluated the safety and immunogenicity of a newly developed pentavalent rotavirus vaccine in Taiwanese children.

Methods: This was a phase III global trial designed to evaluate the safety and immunogenicity of an oral, live pentavalent rotavirus vaccine (RotaTeq™). Taiwan was the only site in Asia enrolled in this trial. Normal healthy infants aged 6–12 weeks were enrolled, and each of the subjects received either three oral doses of the vaccine or placebo solution. The safety of the vaccine, particularly the risk of intussusception, and immunogenicity were studied.

Results: A total of 189 infants were enrolled. No increased risk of intussusception or other adverse reactions were noted following the vaccination. RotaTeq™ was immunogenic among subjects enrolled in Taiwan. At least a three-fold rise in serum antirotavirus IgA antibody was found among 93% of the vaccine group. The immunogenicity of RotaTeq™ in Taiwan was comparable to that in other areas.

Conclusion: The pentavalent human-bovine vaccine, RotaTeq™, was safe, generally well-tolerated, and immunogenic among Taiwanese infants. [J Formos Med Assoc 2009;108(4):280–285]

Key Words: RotaTeq, rotavirus, rotavirus vaccines, Taiwan

Rotavirus infection is the leading cause of acute gastroenteritis and is responsible for most diarrhea-related hospitalizations and deaths among infants and young children worldwide. Annually, it is responsible for approximately 50,000 hospitalizations and 20 deaths in the United States and 440,000 deaths worldwide. For this reason, the development of an effective rotavirus vaccine has been targeted as a public health priority.

Rotavirus commonly attacks children between the ages of 6 and 24 months, and virtually all children are estimated to be infected during the first 3–5 years of life. Longitudinal studies have demonstrated that naturally acquired rotavirus infections provide protection against subsequent rotavirus reinfection and protection is greatest against severe disease. This observation supports the concept that immunization can provide immunity against infection.

Rotaviruses are classified into types based on two outer capsid proteins: G protein and P protein. Both G and P proteins are immunogenic and...
correlated with protection against rotavirus disease. The four most prevalent genotypes that account for >80% of cases of human rotavirus diarrhea worldwide are: G1P[8], G2P[4], G3P[8], and G4P[8].

The first rotavirus vaccine, Rotashield, was licensed in the United States in 1998. However, the US Centers for Disease Control and Prevention recommended suspending its further use soon after because of a link between this vaccine and increased risk of intussusception.

RotaTeq™, a pentavalent rotavirus vaccine, is a live vaccine constructed from an attenuated bovine WC3 rotavirus, in which genes coding for serotype-specific surface protein have been replaced by genes from human rotavirus coding for the comparable serotypes G1, G2, G3, G4 or genotype P[8]. These reassortant viruses induced immune responses to the human capsid proteins while maintaining the attenuation properties of the parent strains. The safety, efficacy and immunogenicity of the vaccine have been evaluated in several phase I and II clinical trials.

Methods

Study design

This was a Phase III, multicenter, randomized, double-blind, placebo-controlled global trial designed to evaluate the safety and immunogenicity of the RotaTeq vaccine (Merck & Co., Inc., Whitehouse Station, NJ, USA). Taiwan was the only site in Asia in this vaccine trial. Healthy infants between 6 and 12 weeks of age were enrolled from three hospitals in Taiwan.

The aims of this study were: (1) to assess the safety of the rotavirus vaccine with respect to all adverse effects (AEs) within 42 days of any dose of vaccine; (2) to assess the incidence of intussusception occurring within 42 days of any dose of vaccine and 1 year after the first dose; and (3) to evaluate the immunogenicity of the three-dose regimen of oral rotavirus vaccine in Taiwanese children, and compare the results with those in other countries.

Vaccination

The live pentavalent rotavirus vaccine was composed of five human-bovine reassortant rotaviruses, each of which contained the WC3 bovine strain backbone with different human viral surface proteins G1, G2, G3, G4 and P[8]. An estimated final concentration of 6.5 × 10^7 IU to 1.2 × 10^8 IU was included in a 2 mL dose solution. Enrolled subjects were randomized to receive three oral doses of the vaccine or placebo at three separate visits scheduled 4–10 weeks apart. The first dose was administered between 6 and 12 weeks of age. Exclusion criteria are listed in Table 1. Subjects who were receiving oral poliovirus vaccine during the study or within 42 days prior to the first dose of vaccine/placebo were also excluded.

Immunogenicity evaluation

Antibody response to this vaccine was evaluated in a subgroup of subjects recruited at the National Taiwan University Hospital. Two serum samples were collected for immunological evaluation.

### Table 1. Infants with one of the following conditions were excluded from this study

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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<tr>
<td>• Congenital abdominal disorders</td>
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<td>• History of intussusception or abdominal surgery</td>
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<td>• Impairment of immunological function</td>
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<td>• Known history of hypersensitivity to any component of the rotavirus vaccine</td>
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<td>• Prior administration of any rotavirus vaccine</td>
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<td>• Fever at the time of immunization</td>
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<td>• Prior rotavirus disease</td>
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<tr>
<td>• Chronic diarrhea</td>
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<tr>
<td>• Failure to thrive</td>
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<tr>
<td>• Active gastrointestinal illness</td>
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<tr>
<td>• Receipt of intramuscular, oral, or intravenous corticosteroid treatment</td>
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<tr>
<td>• Residence in a household with an immunocompromised person</td>
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<td>• Prior receipt of any blood transfusion or blood products</td>
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<tr>
<td>• Receipt of oral poliovirus vaccine during the course of the study or within 42 days prior to the first dose of vaccine/placebo</td>
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One was collected before dose 1 of RotaTeq/placebo, and the other was collected on day 42 after dose 3. Serological response was tested for antirotavirus IgA antibody against WC3 by ELISA, and for serum neutralizing antibody (SNA) against rotavirus serotypes G1, G2, G3, G4 and P[8] by an antigen-reduction enzyme immunoassay at Cincinnati Children’s Hospital Medical Center (Cincinnati, OH, USA), as reported previously.9–12 Seroconversion was defined as a greater than three-fold increase in the antibody titer of either antirotavirus IgA or NA.

Safety measurement
To evaluate the safety of the vaccine, all subjects were followed for AEs for 42 days after each dose. For the incidence of intussusception, they were followed for 42 days after each dose and for up to 1 year after the first dose. Intussusception was defined by radiographic or surgical confirmation, or evidence of intussusception at autopsy within 1 year of the first dose.

Results
From April 2003 to June 2004, a total of 189 infants (99 males, 90 females) were enrolled from three hospitals in northern Taiwan. Of these, 96 were in the vaccine group, and 93 were in the placebo group. Four children from the vaccine group were withdrawn from the study during follow-up (3 were lost to follow-up and the other was cross-treated).

The AEs of special clinical interest, such as fever, intussusception, diarrhea, vomiting, and irritable crying, are shown in Table 2. There were no cases of intussusception in this Taiwanese cohort. During the 42 days of follow-up after each vaccination and 1 year following the first dose, the vaccine did not increase the risk of any AE in comparison with the placebo group.

Seroconversion rates of antirotavirus IgA were 93.9% (95% CI, 83.1–98.7%) among 49 vaccine recipients and 12.5% (95% CI, 4.7–25.2%) among 48 placebo recipients (Table 3). Seroconversion rates of SNA to each human rotavirus serotype in the vaccine were significantly higher in the vaccine group than in the placebo group. At least a three-fold rise in SNA titer against serotypes G1, G2, G3, G4 and P[8] was found in 83.7%, 16.3%, 16.3%, 70.8% and 61.2% of patients, respectively, in the vaccine group. In contrast, the seroconversion rates were only 2.1–4.1% in the placebo group (Figure).

Discussion
According to the results of the large-scale Rotavirus Efficacy and Safety Trial (REST) of RotaTeq™, this vaccine was safe and efficacious in preventing rotavirus gastroenteritis, and decreasing severe diarrhea and health care-related contact.13 Its efficacy was 74% against G1 to G4 rotavirus gastroenteritis of any severity, and 98% against severe rotavirus gastroenteritis. The safety substudy of the present trial showed that the
rates of fever, vomiting and diarrhea within 42 days after any dose of vaccine were similar between the vaccine and placebo groups.

The results of our study demonstrate that the vaccine is generally well-tolerated among normal healthy infants in Taiwan. There was no case of intussusception found in this study. It is expected that the reassortant rotavirus vaccine will be safe and effective in the prevention of severe illness caused by rotavirus in Asia. However, the number of cases in this study was too small to conclude that this rotavirus vaccine was free from the risk of intussusception.

According to a previous study, the protection provided by primary rotavirus infection is serotype specific.14 G1 rotavirus is now more prevalent around the world;4,5 however, the predominant circulating strains still vary by year and location. The four G serotypes contained in the present vaccine are responsible for >80% of cases of rotavirus gastroenteritis worldwide.5 Serotype G9 (in association with P[8]) has become more prevalent during the past few years, especially in some developing countries of Asia and Africa.5 Serotype G8 rotavirus has also emerged as an important serotype in some Africa countries.15

A sentinel hospital surveillance for rotavirus diarrhea in Taiwan during 2001 to 2003 has demonstrated that rotavirus accounted for 43% of the hospitalizations for diarrhea among children aged ≤60 months.16 The novel genotype G9P[8] was detected most commonly (37% of strains), followed by G1P[8] (31%), G2P[4] (9.3%), and G4P[8] (3.7%).

The emergence of serotype G9 in Taiwan since 2001 is of concern because it is not known

Table 3. Immunogenicity for serum antirotavirus IgA response in 100 infants who received three doses of RotaTeq or placebo

<table>
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<tr>
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<th>Vaccine</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>number of subjects</td>
<td>49</td>
</tr>
<tr>
<td>GMT (U/mL) of serum antirotavirus IgA</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.2, 0.7</td>
<td>0.2, 0.8</td>
</tr>
<tr>
<td>Predose 1 vaccination</td>
<td>number of subjects</td>
<td>49</td>
</tr>
<tr>
<td>GMT (U/mL) of serum antirotavirus IgA</td>
<td>305.6</td>
<td>1.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>185.1, 504.4</td>
<td>0.6, 2.8</td>
</tr>
<tr>
<td>Postdose 3 vaccination</td>
<td>number of subjects</td>
<td>49</td>
</tr>
<tr>
<td>Number (%) of subjects with ≥3-fold rise</td>
<td>46 (93.9)</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>in serum antirotavirus IgA</td>
<td>83.1%</td>
<td>98.7%</td>
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*Excludes subjects with invalid data based on laboratory determinations, or with samples taken out of 37 to 61 postdose 3 day range. CI = confidence interval; GMT = geometric mean titer.

Figure. Seroconversion rates for serum neutralizing antibody (SNA) against human serotypes included in the vaccine. Seroconversion was defined as a greater than three-fold increase in the titer of SNA against each rotavirus serotype between baseline and 42 days after the third dose.
whether or not it can also be protected against by this pentavalent vaccine. A reassortant virus that contained P[8] protein was included in the vaccine because it is the most common circulating P protein and is usually combined with G1, G3, G4 and G9 serotypes. The REST study of RotaTeq™ has proven that the vaccine reduces related hospitalizations and emergency department visits caused by G9 rotavirus by 100%. The efficacy against G9 rotavirus gastroenteritis of any severity was 65.4%.13

However, because of the complexity and flexibility of viral genotype diversity and epidemiology, it is important that continued rotavirus strain surveillance programs are conducted throughout the world before and after the introduction of this new vaccine.17 Ongoing surveillance also allows for evaluation of vaccine impact once it has been introduced in a country.

Measurement of serum antibody titers is a common method for determining the immune status of humans or animals against particular microorganisms, including viruses. High titers of serum antirotavirus IgA have shown a good correlation with protection in children pre-exposed to natural infection. However, no such correlation of protection has been found for the oral rotavirus vaccine.18,19 In fact, no specific titer of any antibody analyzed has been established as an immunological marker of protection after vaccination.9,20,21 Their presence is a general indicator for the actual effector of local protection, e.g. virus-specific secretory IgA at the intestinal mucosal surface, which is a critical factor for protection.22

The seroconversion rates for SNA against G2 and G3 were low (both 16.3%) in comparison to G1 and G4 (83.7% and 61.2%) in the present study. A similar finding was also noted in the REST study.15 However, the clinical efficacy against rotavirus gastroenteritis of any severity according to G serotype in the REST study was 74.9%, 63.4%, 82.7% and 48.1% for G1, G2, G3 and G4, respectively. The serum antibody responses following vaccination are only partially related to protection.3 The relatively poor correlation between serotype-specific SNA and clinical vaccine efficacy may be a real problem in the future, when further evaluation of the vaccine effect on various virus serotypes is needed.

In Taiwan, rotavirus gastroenteritis still leads to significant morbidity in infants and children. One out of every two to five children aged <5 years old was estimated to require medical care for rotavirus infection in Taiwan in 2001, with an estimated annual medical expenditure of US$10–16 million.23 The application of rotavirus vaccine in infants should be advantageous in Taiwan. However, because of the high vaccine prices, further study to evaluate the health and economic benefits of universal infant rotavirus vaccination is needed.

In conclusion, the results of our study demonstrate that this vaccine is safe and immunogenic in healthy infants in Taiwan. Continued surveillance is recommended.

Acknowledgments

This study was funded by Merck & Co., Inc. The authors express their appreciation to Dr Li-Ming Huang, Miss Jin Hua Lin, Zhao-Ying Song, Xu-Chu Deng and Chun-Jing Chen for their kind assistance.

References