Second-Year Follow-up Evaluation of Live, Attenuated Human Rotavirus Vaccine 89-12 in Healthy Infants

David I. Bernstein,1 David A. Sack,2 Keith Reisinger,3 Edward Rothstein,4 and Richard L. Ward1

Rotavirus vaccine development is a high priority. The association between the tetravalent rhesus-human reassortant rotavirus vaccine and intussusception has increased the need to develop new vaccines. In a small efficacy trial, the human rotavirus vaccine 89-12 recently has been shown to be safe and effective; 184 of the 215 healthy infants initially enrolled in this trial were followed for a second year. Vaccine efficacy during the second year was 59% (P = .047). For the 2 years of observation, vaccine efficacy was 76% against rotavirus gastroenteritis, 83% against severe rotavirus gastroenteritis, and 100% against rotavirus illnesses requiring medical intervention (P < .001 for each). These encouraging results have led to continued evaluation, in several countries, of a vaccine candidate derived from strain 89-12.

Subjects and Methods

Subjects. During August–December 1997, 215 healthy 10–16-week-old infants were enrolled in a randomized, double-blind, placebo-controlled, multicenter study of human rotavirus vaccine 89-12 [11]. The study protocol and informed consent, including the extension to the second year, were approved by the Institutional Review Board at each site.

Study design. Human rotavirus vaccine 89-12 is a multi-passaged preparation of a G1 [P8] isolate obtained from a stool collected from a child with rotavirus illness [10,11]. Subjects received 2 oral doses of either 1.0 mL of vaccine (1 × 10^6 focus-nerforming units) or placebo, immediately after an oral dose of 2.0 mL of antacid; the second dose was administered 6–10 weeks after the first dose. Parents were instructed to telephone the study personnel to report each suspected episode of gastroenteritis. Parents were called weekly during the rotavirus season and every other week between seasons. When an episode of gastroenteritis occurred, 2 stool specimens were collected on consecutive days and were frozen and sent to the central laboratory (Cincinnati Children’s Hospital), for rotavirus identification by ELISA and for serotyping by use of monoclonal antibodies, as described elsewhere [11]. A scoring system with a 20-point scale, as detailed by Rennels et al. [12] and used by

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Informed consent was obtained from the parents or guardians of participating children. Human experimentation guidelines of the US Department of Health and Human Services and/or those of the authors’ institutions were followed in the conduct this research.

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Commercial and other associations: D.I.B. and R.L.W. are inventors of human rotavirus vaccine 89-12 (patent “Human Rotaviruses, Vaccines and Methods” [issued 12 December 1995]) and were consultants to Avant Therapeutics and SmithKline Biologicals.

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Results

Vaccine efficacy reported for the first year was 89% against any rotavirus gastroenteritis, 78% against severe gastroenteritis, and 100% against very severe gastroenteritis [11]. After the first year, the randomization code was unblinded. During the second year, 93 of 107 placebo recipients and 91 of 108 vaccine recipients were available for follow-up through the next rotavirus season (January–May 1999). During this season, a total of 127 episodes of gastroenteritis were reported for these 184 subjects. Stool specimens for rotavirus-antigen evaluation were available from 91% of these episodes. Rotavirus was detected in samples of 84% of these episodes. Rotavirus was detected in samples obtained during 21 episodes; of these 21 episodes, 17 were serotype G1, and 4 could not be typed.

Table 1. Protective efficacy of human rotavirus vaccine 89-12 in the second year after immunization.

<table>
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<tr>
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<th>No. (%) of individuals</th>
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<tbody>
<tr>
<td></td>
<td>Vaccine (n = 91)</td>
<td>Placebo (n = 93)</td>
<td>Efficacy (95% CI), %</td>
</tr>
<tr>
<td>Rotavirus gastroenteritis</td>
<td>6 (6.6)</td>
<td>15 (16.1)</td>
<td>59 (3–83)¹</td>
</tr>
<tr>
<td>Severe (&gt;8 points)</td>
<td>1 (1.1)</td>
<td>10 (10.8)</td>
<td>90 (48–98)⁵³</td>
</tr>
<tr>
<td>Very severe (&gt;14 points)</td>
<td>0</td>
<td>1 (1.1)</td>
<td>100</td>
</tr>
<tr>
<td>Medical intervention</td>
<td>0</td>
<td>2 (2.2)</td>
<td>100</td>
</tr>
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NOTE. CI, confidence interval.

¹ P = .047.
³ P = .006.

Vaccine recipients had significantly fewer episodes of rotavirus gastroenteritis during the second year (efficacy, 59%; P = .047; see table 1) and had significantly fewer episodes of severe rotavirus gastroenteritis (i.e., score >8, as defined elsewhere [3]) (efficacy, 90%; P = .006; see table 1). During the 2 years, efficacy was 76% against rotavirus gastroenteritis (95% confidence interval [CI], 54–87) (P < .001) and 85% (95 CI, 53–94) against severe rotavirus disease (P < .001; see table 2); no vaccine recipients required medical intervention for rotavirus gastroenteritis, whereas 12 placebo recipients required such intervention (P < .001).

Table 2. Protective efficacy of human rotavirus vaccine 89-12 in the 2 years after immunization.

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of individuals</th>
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<tbody>
<tr>
<td></td>
<td>Vaccine (n = 108)</td>
</tr>
<tr>
<td>Rotavirus gastroenteritis</td>
<td>8 (7.4)</td>
</tr>
<tr>
<td>Severe (&gt;8 points)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Very severe (&gt;14 points)</td>
<td>0</td>
</tr>
<tr>
<td>Medical intervention</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

² P = .001.

Discussion

Results of this 2-year efficacy study compare favorably with those previously reported for RRV-TV [12, 13]. In a Finnish study of RRV-TV, efficacy against rotavirus gastroenteritis was 83% during the first year, 63% during the second year, and 68% for the 2 years combined [14]. In a study conducted in the United States, which used a lower dose of RRV-TV (i.e., 4 × 10⁷ plaque-forming units) than was provided by the licensed product (i.e., 4 × 10⁹ plaque-forming units), efficacy against rotavirus gastroenteritis was 64% during the first year, 48% during the second year, and 57% for the 2 years combined [13]. During that study’s 2 years of observation, protection against severe disease was 59%, and protection from episodes requiring medical intervention was 78%. Both studies used the same scoring system and definition.

The equivalent-to-superior efficacy of human rotavirus vaccine 89-12 compared with RRV-TV has led to expanded evaluation, in several countries, of a vaccine derived from strain 89-12. The main issues to be determined in ongoing trials are the safety of the vaccine, including its relationship to intussusception, and the protection provided against non-serotype G1 rotavirus strains.

Acknowledgments

We thank all the parents and infants who participated in the study, as well as the nurses and physicians who helped conduct the study.

References


