Efficacy of the Human Rotavirus Vaccine RIX4414 in Malnourished Children

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The effect of nutritional status on protective efficacy of a live attenuated human rotavirus vaccine (RIX4414) was studied. Vaccine protection was evaluated through a secondary analysis of data from an efficacy study conducted in Brazil, Mexico, and Venezuela. Vaccine efficacy against rotavirus gastroenteritis (RVGE) was similar in well-nourished and malnourished infants: 74.1% (95% confidence interval [CI], 52.2%–86.2%) and 73% (95% CI, 11.2%–92.3%) for severe RVGE and 60.9% (95% CI, 37.4%–75.4%) and 61.2% (95% CI, 10.4%–83.1%) for RVGE of any severity, respectively. RIX4414 significantly decreased the rate of RVGE regardless of nutritional status, which suggests that this patient group can also benefit from rotavirus vaccination.


Vaccination is a powerful tool to reduce the enormous worldwide burden due to rotavirus illness, which is estimated to cause >600,000 deaths and 2 million hospitalizations annually in children <5 years of age [1]. One of the rotavirus vaccines recently licensed in >80 countries is the live attenuated human rotavirus vaccine (RIX4414) containing the G1P[8] strain [2] that was developed from the parent vaccine strain 89-12 [3]. In phase II and III efficacy and safety trials, RIX4414 vaccine was shown to be well tolerated and immunogenic while providing broad cross-protection against other nonvaccine strains [4, 5].

Malnutrition is a common and well-recognized public health problem in developing countries [6, 7]. It has also been associated with a high proportion of hospitalizations and deaths caused by diarrhea [7, 8]. In addition, it has been described that an impaired nutritional condition affects the immune system [9]. As a consequence, the interaction between nutrition and the immune system could interfere with the efficacy of rotavirus immunization, a phenomenon that had been described for another rotavirus (rhesus rotavirus tetravalent vaccine [RRV-TV]) candidate vaccine [10]. To determine whether malnutrition affects the efficacy of RIX4414 vaccine, a secondary analysis of data from the efficacy study was conducted in Brazil, Mexico, and Venezuela [4]. The results of that analysis are presented here.

Materials and methods. The methodology of the phase II study conducted in Belem (Brazil), Mexico City (Mexico), and Valencia (Venezuela) has been described elsewhere [4]. Briefly, healthy full-term infants (gestational age, 36–42 weeks), who weighed >2000 g at birth and who were 6–12 weeks (42–90 days) old at the time of the first vaccination, and whose parent or legal guardian signed an informed consent form were enrolled to receive 2 oral doses of the RIX4414 vaccine (GlaxoSmithKline Biologicals) or placebo according to a 0, 2-month schedule. Three concentrations (104, 105, and 106 focus-forming units [ffu]) of RIX4414 were tested. Routine childhood vaccines were administered (diphtheria–tetanus toxoid–whole-cell pertussis, Haemophilus influenzae type b, and hepatitis B virus) concomitantly with each study vaccine dose. Oral poliovirus vaccine was given at least 14 days before or after administration of study vaccine. The study was approved by the ethics committee of each study center and was conducted according to good clinical practice guidelines and the 1996 version of the Declaration of Helsinki.

All vaccinated infants were actively monitored for the occurrence of acute gastroenteritis episodes through weekly visits by health care workers starting from the administration of dose 1 until they were 1 year old, as described elsewhere [4]. Gastroenteritis was defined as diarrhea characterized by ≥3 looser than normal stools within a 24-h period. The widely accepted Ruuska and Vesikari 20-point scoring system was used to grade...
the severity of rotavirus gastroenteritis episodes [4]. An episode with a score of ≤6 was defined as mild, 7–10 as moderate, and ≥11 as severe [4].

Stool specimens were collected within 7 days of the onset of diarrhea and were first tested for rotavirus using ELISA [4] at the laboratory of Dr. R. Ward, Children’s Hospital Medical Center (Cincinnati, OH). All rotavirus-positive specimens were tested by reverse-transcription polymerase chain reaction at GlaxoSmithKline Biologicals (Rixensart, Belgium) for determination of the G type [4]. All G1 rotaviruses detected until the day of each vaccine/placebo administration. There were no restrictions on feeding the infants before or after vaccine/placebo administration. There were no restrictions on feeding the infants before or after vaccine/placebo administration. Nutritional status of the infants at the time of dose 1 was assessed by using World Health Organization growth charts weight for age (for both girls and boys) based on the following criterion: infants presenting a weight for age on the day of the first dose of study vaccine or placebo; who received 2 doses of study vaccine or placebo according to the protocol; who had no randomization code broken; who had no rotavirus other than vaccine strain in stool samples collected from first dose until 2 weeks after the second dose; and who entered the surveillance period and had follow-up data >15 days after the second dose. The 2-sided Fisher’s exact test (5% significance level) was used to compare rates between groups.

**Results.** When we examined the weight for age at dose 1 for the 1846 infants (1392 in the pooled vaccine group and 454 in the placebo group) included in the primary efficacy analysis, we observed that 287 infants fulfilled the criteria for malnutrition and 1559 infants were considered to be well nourished. The distribution of infants by group (vaccine or placebo) and nutritional condition was 1181 pooled vaccinees and 378 placebo recipients in the well-nourished group and 211 pooled vaccinees and 76 placebo recipients in the malnourished group. All malnourished infants were categorized as being mildly malnourished. The majority of well-nourished and malnourished infants was exclusively breast-fed or breast-fed complemented with infant formula. At the first dose, 96.7% of well-nourished and 93.4% of malnourished infants were breast-fed or breast-fed complemented with infant formula. At the second dose, 91% of well-nourished and 84.3% of malnourished infants were breast-fed or breast-fed complemented with infant formula.

Tables 1 and 2 present VEs in the ATP cohort against all and severe rotavirus gastroenteritis (RVGE) according to the nutritional status of subjects. In the pooled vaccine groups, severe RVGE was reported in 2.8% (6/211) of malnourished infants and in 2% (21/1181) of well-nourished infants; RVGE of any severity was reported in 6.6% (14/211) of malnourished infants.
Table 2. Percentage of subjects with severe rotavirus gastroenteritis (RVGE) and vaccine efficacy (VE) during the efficacy follow-up period (according to protocol cohort for efficacy analysis).

<table>
<thead>
<tr>
<th>Status at dose 1, group</th>
<th>Subjects in group, no.</th>
<th>Subjects reporting severe RVGE, no.</th>
<th>Total/severe RVGEa</th>
<th>VEa</th>
<th>Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well nourished</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10⁴.⁷ ffu</td>
<td>392</td>
<td>9</td>
<td>2.3 (1.1–4.3)</td>
<td>66.6 (26.5–86.2)</td>
<td>.003</td>
</tr>
<tr>
<td>10⁵.⁷ ffu</td>
<td>399</td>
<td>7</td>
<td>1.8 (0.7–3.6)</td>
<td>74.5 (39.7–90.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>10⁶.⁷ ffu</td>
<td>390</td>
<td>5</td>
<td>1.3 (0.4–3.0)</td>
<td>81.4 (50.7–94.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pooled vaccine groups</td>
<td>1181</td>
<td>21</td>
<td>1.8 (1.1–2.7)</td>
<td>74.1 (52.2–86.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>378</td>
<td>26</td>
<td>6.9 (4.5–9.9)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Malnourished</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10⁴.⁷ ffu</td>
<td>76</td>
<td>3</td>
<td>3.9 (0.8–11.1)</td>
<td>62.5 (96.2 to 93.6)</td>
<td>.209</td>
</tr>
<tr>
<td>10⁵.⁷ ffu</td>
<td>61</td>
<td>3</td>
<td>4.9 (1.0–13.7)</td>
<td>53.3 (94.7 to 92.0)</td>
<td>.345</td>
</tr>
<tr>
<td>10⁶.⁷ ffu</td>
<td>74</td>
<td>0</td>
<td>0.0 (0.0–4.9)</td>
<td>100.0 (39.8–100.0)</td>
<td>.006</td>
</tr>
<tr>
<td>Pooled vaccine groups</td>
<td>211</td>
<td>6</td>
<td>2.8 (1.1–6.1)</td>
<td>73.0 (11.2–82.3)</td>
<td>.013</td>
</tr>
<tr>
<td>Placebo</td>
<td>76</td>
<td>8</td>
<td>10.5 (4.7–19.7)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

a Data are % of subjects reporting any RVGE (95% confidence interval). 

b Two-sided; determined using Fisher’s exact test (significance level, α = .05).

Table 2. Percentage of subjects with severe rotavirus gastroenteritis (RVGE) and vaccine efficacy (VE) during the efficacy follow-up period (according to protocol cohort for efficacy analysis).

and in 3.7% (44/1181) of well-nourished infants. In the placebo group, severe RVGE was reported in 10.5% (8/76) of malnourished and in 6.9% (26/378) of well-nourished infants. Among the placebo and vaccine recipients, the incidence of RVGE was higher in malnourished infants but was not statistically significant (P > .05). The majority of RVGE episodes in both well-nourished and malnourished infants were caused by G1P[8] strain, and G9P[8] was the second most prevalent RV strain. In well-nourished placebo recipients, G1 wild-type rotavirus was identified in 51% and G9 type in 35% of observed RVGE episodes. Seventy-nine percent of severe RVGE episodes reported in malnourished infants receiving placebo were caused by G1 wild-type rotavirus and 14% by G9 type. VE against severe or all RVGE was similar in well-nourished and malnourished infants: 74% and 73% against severe RVGE and 61% for both against RVGE of any severity. These results were very similar to the protection rates against severe RVGE and RVGE of any severity for pooled vaccine groups reported for the complete original study cohort: 74% (95% CI, 56%–85%) and 61% (95% CI, 42%–74%), respectively [4]. It is also relevant to note that the VE was the highest in all infants vaccinated with the highest concentration (actually commercially available formulation) of RIX4414 strain in all cases, particularly in malnourished infants (92%–100%) (tables 1 and 2).

Discussion. Malnutrition is an underlying cause of childhood deaths [6, 7]. In trying to achieve a breakthrough for the control of infectious disease mortality, the synergy that exists between malnutrition and infectious disease should be reduced. This synergy has been most clearly demonstrated for diarrheal illness [7, 12]; diarrhea precipitates and accelerates the progression of malnutrition, which increases the duration of diarrhea and lessens resistance. Because rotavirus has been described as the most common cause of diarrheal disease worldwide and given the availability of rotavirus vaccines with good efficacy and safety profiles [1, 2], a positive impact to reduce this synergy is now a possibility. However, given the fact that malnutrition is common, it is important to evaluate whether malnutrition affects the efficacy of rotavirus vaccine, given that it has previously been reported that malnutrition may interfere with the efficacy of another rotavirus (RRV-TV) vaccine candidate [10].

To evaluate the effect of nutritional status on protective efficacy of a live attenuated human rotavirus vaccine (RIX4414), a secondary analysis of data from the efficacy study conducted in Brazil, Mexico, and Venezuela was completed. In this study, VE against RVGE was similar among well-nourished and malnourished infants: 74% and 73% against severe RVGE and 61% for both against RVGE of any severity. These results were very similar to the protection rates against severe RVGE and RVGE of any severity for pooled vaccine groups reported for the complete original study cohort: 74% (95% CI, 56%–85%) and 61% (95% CI, 42%–74%), respectively [4]. It is also relevant to note that the VE was the highest in all infants vaccinated with the highest concentration (10⁶.⁷ ffu), which is the viral titer contained in the commercially available vaccine, and that the VE was particularly high in malnourished infants (92%–100%). These findings are in contrast to the results of the RRV-TV rotavirus vaccine study [10]. This may be due to the low number of malnourished infants evaluated in that study.

At the same time, this RIX4414 study reminds us that malnutrition increases the severity of diarrheal disease [12]. The attack rate of severe RVGE was higher, although not statistically significant, in malnourished than in well-nourished children (10.5% vs. 6.9% in the respective placebo groups). The worldwide introduction of a rotavirus vaccine may therefore be par-
ticularly beneficial to children with malnutrition. Although it is likely that such a difference may have occurred by chance, one could argue that a trend toward higher efficacy among malnourished children may be related to the fact that they usually have more severe diarrhea and it is largely recognized that rotavirus vaccines induce a greater protection against severe than against mild/moderate diseases. Our data for the placebo group, however, showed that there was not significant difference in proportions of severe RVGE (vesikari scale score \( \geq 11 \)) between malnourished and well-nourished children.

Our results show that malnutrition did not seem to influence efficacy of the rotavirus vaccine (RIX4414), which confirms the lack of a firm association between malnutrition and the overall response to immunization \([13, 14]\). Moreover, malnourished children, who are more vulnerable to die of diarrhea, should be a prime focus for immunization programs to reduce the burden of severe rotavirus diarrheal disease. It should be noted that the present findings are limited to only the mild cases of malnutrition observed in our study.

More data to validate these results in areas with more severe malnourished children are needed. The planned development of clinical trials in the populations of Asia and Africa may present an opportunity to further evaluate the question of malnutrition and efficacy of RIX4414 (Rotarix; GlaxoSmithKline) vaccine.

Acknowledgments

We thank Dr. R. L. Ward, Children’s Hospital Medical Center (Cincinnati, OH), for performing the ELISAs. We thank the infants and their families for participating in the study. We also thank the pediatricians and microbiologists for their contributions: in Venezuela, María Peiró, Merly Villarroel, and Miguel González (pediatricians) and Germán González, Angela Ferrero, Giconda Clemente, and Rosabel González (microbiologists); in Brazil, Consuelo S. Oliveira, Eliete Araújo, Rosa Helena P. Gusmão, and Maria Cleonice A. Justino (pediatricians) and Edvaldo C. Brito Loureiro, Vânia N. Cavalcante, Yvone Gabbay Mendes, and Joana D’Arc P. Mascarinhos (microbiologists); in Mexico, Aurora Bautista-Marquez, María Edilia Luna-Cruz, Juan del Monte-Toledo, and Juan Pablo Jorba-Aliacar (pediatricians) and Fernando Tuz-Dzib and Letícia Reyes Gonzalez (microbiologists). We thank Silvia Damaso and Brigitte Cheuvart for statistical analyses; Slávka Baróniková for article coordination and editorial assistance; and Fernando Aguirre, Pascale Dieryck, Silvina Santucho, and the local clinical research assistants of GlaxoSmithKline Biologicals for study coordination.

References