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BRIEF COMMUNICATION

Immunogenicity, reactogenicity, and safety of a human rotavirus vaccine, *Rotarix*, in Taiwanese infants who received a dose of hepatitis B immunoglobulin after birth

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This Phase-IV study evaluated the human rotavirus (RV) vaccine *Rotarix* (RIX4414) to provide additional local clinical data to the Taiwan Food and Drug Association (NCT01198769). Healthy infants aged 6–12 weeks who were given a hepatitis B immunoglobulin (HBIg) dose after birth, received two doses of RIX4414 (0, 2-month schedule). Anti-RV IgA antibody concentrations were measured using ELISA. A total of 15 infants were enrolled, and included in the according-to-protocol cohort. The anti-RV IgA antibody seroconversion rate 2 months post-Dose 2 was 100% (95% confidence interval = 78.2–100) and the geometric mean concentration was 254.7 U/ml (95% confidence interval = 145.0–447.7). Two episodes of gastroenteritis were reported, and one stool sample was tested for RV, which was negative. No fatal serious adverse events were reported during the study period between November 2010 and April 2011. The two-dose regimen of RIX4414 was highly immunogenic and safe when administered to healthy Taiwanese infants who received a HBIg dose after birth.

Trial registration number: NCT01198769.

Introduction

Worldwide, rotavirus (RV) is a major cause of severe dehydrating diarrhea in children aged <5 years.[1] Globally, RV-related diarrhea results in approximately 453,000

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deaths, accounting for 37% of diarrhea-related deaths and 5% of all deaths in children aged <5 years, each year.[2] RV diarrhea is widely prevalent throughout the Asia-Pacific region.[3,4] In Taiwan, RV is the leading cause of infectious gastroenteritis (GE), estimated to affect one child in every two to five children aged <5 years who will require medical care.[5] According to an epidemiology study conducted in 2007, 55.78% of children in Taiwan experienced acute diarrhea ranging from 15.5% among infants aged <6 months to 82.2% among children aged 4–5 years.[6]

Owing to the hyperendemicity and high hepatitis B surface antigen (HBsAg) carrier rate (15–20%) for pregnant women in Taiwan, it was strategically decided to administer a dose of hepatitis B immunoglobulin (HBIg) after birth to infants born to hepatitis B envelope antigen (HBeAg)-positive mothers.[7] This strategy was implemented in addition to the national hepatitis B (HB) vaccination program launched in 1984.[8] It has been observed that a combination of HBIg and HB vaccination significantly decreased the risk of perinatal transmission of hepatitis B virus (HBV).[9] The efficacy of protecting infants from hepatitis B virus infection due to the use of HBIg is >90%[10] and the HB vaccination coverage rate is >96%.[11]

An oral, live, attenuated human RV vaccine, *Rotarix* (RIX4414; GlaxoSmithKline, Belgium) is widely available.[12] It has been found to be immunogenic, efficacious, and safe, including when coadministered with other routine childhood vaccines, in studies conducted across the USA, Europe, Latin America, Asia, and Africa.[13–18]

Given that there is a theoretical concern with respect to the effect of immunoglobulin preparations on the response elicited by vaccines and upon the request of the Food and Drug Administration of Taiwan, the present postlicensure study was conducted to generate local clinical data on the immunogenicity and safety of RIX4414 when administered in healthy Taiwanese infants who had received a dose of HBIg after birth, to assess the potential impact of HBIg on the immune response to RIX4414.

Materials and methods

This Phase IV, open-labeled, single-center, single-group study (NCT01198769) was conducted at the National Taiwan University Hospital, Taipei, Taiwan between November 2010 and April 2011. Healthy infants aged 6–12 weeks, who had received a dose of HBIg after birth, received two oral doses of RIX4414 (0, 2-month schedule). RIX4414 was coadministered with other routine childhood vaccinations as recommended by the local immunization schedule.

Infants were excluded from participating in the study if they received any immunosuppressants/immunoglobulins (except for HBIg after birth), or investigational/non-registered or unforeseen vaccine/drug other than the study vaccine, or if they were previously vaccinated against RV, if they had confirmed cases of RV GE previously, or if they experienced GE 7 days before Dose 1 of the study vaccine. Other reasons for exclusion included infants' concurrent participation in another study, allergic reaction to any vaccine component, or serious chronic illness.

The national Independent Ethics Committee reviewed and approved all study-related documents. The guidelines of Good Clinical Practice and the Declaration of Helsinki were abided by during the conduct of the study. Parents/guardians provided written informed consent before any study-related procedures were performed.

The lyophilized formulation of RIX4414 was developed and manufactured by GlaxoSmithKline, Belgium. Each dose (1 mL) of RIX4414 contained at least $10^{6.0}$ median cell culture infective dose of the active virus strain.

Blood samples were collected prevaccination and 2 months post-Dose 2 of RIX4414 to determine the anti-RV IgA antibody concentrations using an in-house enzyme linked immunosorbent assay (assay cut-off = 20 U/mL).

Following each dose of RIX4414, the percentage of infants reporting solicited general (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhea, and vomiting) and unsolicited symptoms during the 8-day and 31-day postvaccination follow-up periods, respectively, were recorded. Intensity of solicited general symptoms was assessed on a 0–3 scale with grade 3 symptoms considered as severe (Table 1). Serious adverse events were recorded from Dose 1 of the vaccine until the end of the study period.

Stool samples were collected for any GE episodes from Dose 1 of RIX4414 until 2 months post-Dose 2, and tested for the presence of RV using enzyme linked immunosorbent assay.

A sample size of 15 infants was predefined assuming an overall seroconversion rate of 90%.

Seroconversion rates (defined as the appearance of anti-RV IgA antibody concentration ≥20 U/mL in infants who were seronegative before Dose 1 of RIX4414) and geometric mean concentration (GMC) were calculated with 95% confidence interval (CI). The GMCs were calculated by taking the antilog of the mean of the log concentrations transformations.

The percentage of infants reporting all the symptoms were calculated with their exact 95% CIs.

All statistical analyses were performed using SAS 9.1 (SAS, Cary, NC, USA) and Proc StatXact-7 (Cytel Inc., Cambridge, MA, USA).

Results

A total of 15 infants were enrolled in the study. There were no withdrawals. None of the infants were eliminated from

Table 1 Definitions of Grade 3 solicited general symptoms.

Symptoms	Grade 3 intensity definition
Irritability/ Fussiness	Crying that could not be comforted/ prevented normal daily activities
Diarrhea	≥6 looser than normal stools/d
Vomiting	≥3 episodes of vomiting/d
Fever	Rectal temperature >39.5°C
Loss of appetite	No food intake
Cough/Runny nose	Prevented normal daily activities

the study. Therefore, the total vaccinated cohort and the according-to-protocol cohort were the same. The median age of infants was 9 weeks (range, 8—10 weeks) at the time of Dose 1 of RIX4414 and 18 weeks (range, 15—20 weeks) at Dose 2; 53.3% of infants were female and the majority of infants (93.3%) were of east Asian heritage.

Two months post-Dose 2 of RIX4414, 100% (95% CI = 78.2—100) of infants had anti-RV IgA antibody concentrations ≥20 U/mL. The overall GMC was 254.7 U/ml (95% CI = 145.0—447.7).

The overall incidence of symptoms (solicited and unsolicited) recorded during the 8-day follow-up period was 86.7% (95% CI = 59.5—98.3). Between both doses of RIX4414, there was no increase in incidence of solicited or unsolicited symptoms. During the 8-day follow-up period, irritability was the most frequently reported solicited general symptom (73.3%; 95% CI = 44.9—92.2) followed by loss of appetite (66.7%; 95% CI = 38.4—88.2]) (Fig. 1). During this period, the most common Grade 3 solicited general symptom was irritability (13.3%; 95% CI = 1.7—40.5) followed by vomiting (6.7%; 95% CI = 0.2—31.9) (Fig. 1). During the 31-day follow-up period, at least one unsolicited symptom was reported for 26.7% (95% CI = 7.8—55.1) of the infants. Eczema was the most frequently reported unsolicited general symptom (13.3%; 95% CI = 1.7—40.5) during the 31-day follow-up period. Grade 3 unsolicited general symptoms were not reported. One serious adverse event, bronchiolitis, was recorded 17 days post-Dose 2 of RIX4414 in one infant. It lasted for 25 days; however, it was considered unrelated to the vaccine by the investigator. No fatal cases were reported during the study period.

Throughout the study period, two GE episodes were reported in two infants. A GE stool sample was collected from only one infant, in which there was no RV identified.

Discussion

This postlicensure study evaluated the immunogenicity and safety of RIX4414 in Taiwanese infants born to HBeAg-positive mothers who had received a dose of HBIg after birth. The results of this study indicate that the use of HBIg did not negatively impact the immunogenicity and safety profile of two doses of RIX4414.

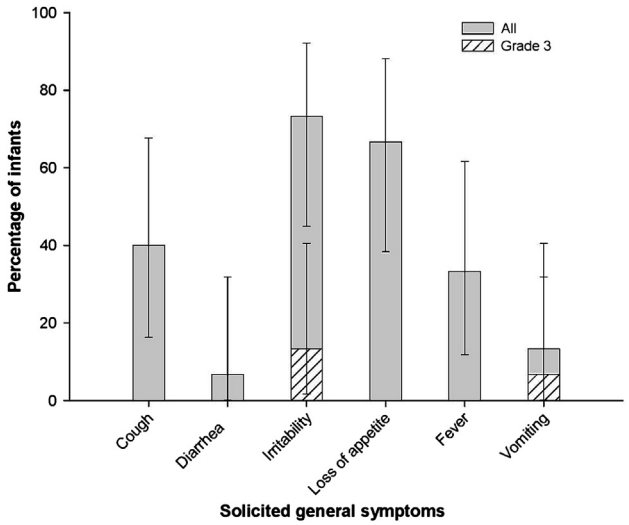

Figure 1 Percentage of infants reporting each solicited general symptom during the 8-day follow-up period post-vaccination. Error bars represent 95% confidence interval.

The immunogenicity results of this study are consistent with an earlier Phase III Asian clinical trial. The results of this previous study reported a seroconversion rate of 85.7% (95% CI = 69.7—95.2) and corresponding GMC of 105.8 (95% CI = 67.4—166.2) 1—2 months post-Dose 2 in healthy Taiwanese infants who did not receive HBIg after birth.[16] Although the previous study was a large trial, the immunogenicity cohort of Taiwanese infants was low (RIX4414 group = 35 infants).[16] Our results suggest that immunogenicity of RIX4414 was not compromised despite the use of HBIg.

The safety results of this study indicate that RIX4414 is well tolerated in vaccinated infants. No increase in the incidence of solicited or unsolicited symptoms between two doses of RIX4414 suggests safety of the two-dose regimen. While a recent Korean study reported irritability as the most common solicited general symptom, cough/runny nose was reported to be the second most common solicited general symptom, which is not the case in our study. Similarly, among unsolicited symptoms, the previously conducted study reported nasopharyngitis as the most common,[19] while the current study found eczema to be the most prevalent.

It has been suggested that immunoglobulins might interfere with immune responses to live virus vaccinations.[20] However, the present study suggested that HBIg does not alter the immune response elicited by RIX4414. Additionally, the United States Advisory Committee on Immunization Practices confirms the administration of RV vaccines before/concurrently/after administration of any immunoglobulin.[20]

The results of this study should be interpreted with caution given that the sample size was modest and the enrollment was from a single center. The success of the HBV immunization program and provision of HBIg in Taiwan has led to a decline in the HBsAg carrier population resulting in the limited sample size. In addition, *Rotarix* is commercially available in Taiwan. Therefore, enrolling a larger group of infants without previous exposure to RV vaccination was a challenge. Despite these limitations, the results from this study are similar to the results observed in a previous study conducted in Taiwan with the same vaccine.[16]

In conclusion, the data from this study support the administration of RV vaccination in infants who have been given HBIg within 24 hours after birth, as immunogenicity of *Rotarix* was not compromised despite the use of HBIg.

Trademarks

Rotarix is a registered trademark of GlaxoSmithKline group of companies.

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