A short report on highlights of world-wide development of RIX4414: A Latin American experience

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Abstract

An oral, human-derived monovalent (G1P1A) rotavirus vaccine, strain RIX4414, has been developed by GlaxoSmithKline, Rixensart, Belgium. The safety, immunogenicity and efficacy of this vaccine were evaluated in a randomized, double-blind, placebo-controlled, phase IIb trial conducted in Brazil, Mexico and Venezuela. Healthy infants were given two doses of vaccine (104.7, 105.2 or 105.8 ffu) or placebo at age 2 and 4 months, with routine DTPw-HBV and Hib vaccines. OPV was given separately, at least 2 weeks before or after administration of the study vaccine. A total of 2155 infants were enrolled, of whom 1618 received one of the three vaccine viral concentrations and 537 were given placebo. Analysis of efficacy included diarrheal episodes occurring from 2 weeks after second dose until one year of age. Efficacy rates against any rotavirus gastroenteritis, severe rotavirus gastroenteritis and hospitalizations for rotavirus disease were as high as 70% (46–84%; 95%CI), 86% (63–96%; 95%CI), and 93% (54–100%; 95%CI), respectively. For non-G1 (mainly G9) serotypes, RIX4414 vaccine conferred protection as high as 83% (40–97%; 95%CI) against severe gastroenteritis. A decrease was noted in the incidence of severe rotavirus-related gastroenteritis after first dose. It is demonstrated that two doses of RIX4414 are highly efficacious against severe rotavirus gastroenteritis and hospitalization, including disease caused by non-G1 strains, namely G9 serotypes.

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Rotavirus gastroenteritis still remains a major cause of morbidity and mortality among infants and young children in both developed and developing countries. In light of recent estimates of the global illness and deaths caused by rotavirus disease, there are each year approximately 25 million clinic visits, 2 million hospitalizations and between 352,000 and 592,000 deaths among children aged less than 5 years [1]. Several studies conducted in both inpatient and outpatient settings in Latin America have shown that 11.4–60% of children with acute diarrhoea were found to have rotavirus [2]. In a recent 2-year prospective surveillance for acute gastroenteritis in three South American countries, rotavirus-associated hospitalizations occurred at rates that ranged from 38% to 71% [3]. Of note, several studies carried out in Brazil have shown the complexity of circulating rotavirus strains across the country, with G1 type being predominant and G9 recently emerging as a common serotype [4]. It is currently recognized that an effective vaccine is required for the control of rotavirus disease, mainly for use in developing regions [5]. In addition, a vaccine for use in these settings should prove efficacious against possible multiple co-circulating rotavirus strains. GlaxoSmithKline Biologicals, Rixensart, Belgium has developed a live attenuated monovalent G1P1A [8] human-
derived rotavirus vaccine, strain RIX4414 (Rotarix™). Results from a pilot study in infants in Finland demonstrated that RIX4414 vaccine was well tolerated, immunogenic and highly efficacious over two epidemic seasons [6]. In order to assess the safety, immunogenicity and efficacy of this vaccine in less-developed regions, a randomized, double-blind, placebo-controlled, phase IIB, multi-centre trial was conducted in Brazil, Mexico and Venezuela. Two oral doses of RIX4414 at $10^{5.7}$, $10^{5.2}$, or $10^{5.8}$ foci forming units (ffu) or placebo were administered to healthy infants at age 2 and 4 months, concurrently with routine childhood vaccines (Tritanrix™, GlaxoSmithKline Biologics) against diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b (Hib) disease. Oral poliovirus vaccine (Polio Sabin™, GlaxoSmithKline Biologics) was administered at least 14 days before or after administration of the study vaccine. Overall 2155 infants were enrolled to participate in this study, of whom 1618 received one of the three vaccine concentrations and 537 received placebo. A stool sample was obtained from all cases of diarrhoea and tested for the presence of rotavirus by ELISA and positive samples were subsequently genotyped by RT-PCR. Diarrhoeal episodes reported from 2 weeks after the second dose until one year of age were included in the efficacy analysis and clinical severity of each episode was determined using a widely accepted 20-point scoring system [7]. Severe gastroenteritis was defined by a score ≥11.

Approximately 50% of rotavirus gastroenteritis episodes detected during the first efficacy follow-up period were serotyped as G1, the dominant serotype worldwide, and the remainder were caused by non-G1 strains (predominantly the emerging G9 serotype). Higher vaccine efficacy for severe disease and hospitalization was associated with viral titres above $10^{5.7}$ ffu. The efficacy rate against hospitalization after two doses of RIX4414 was as high as 93% (54–100%; 95%CI). Protective efficacy against severe rotavirus gastroenteritis was as high as 86% (63–96%; 95%CI), and 70% (46–84%; 95%CI) against any rotavirus gastroenteritis as measured from 2 weeks post-dose 2. Post-dose 1, a reduction in rotavirus gastroenteritis episodes, and decrease in the incidence of severe rotavirus gastroenteritis disease was already observed in vaccinees compared to placebo recipients. For non-G1 serotypes, the protection against severe rotavirus gastroenteritis was as high as 83% (40–97%; 95%CI), providing proof of concept that the monovalent G1P[8] vaccine elicits cross-protection against heterotypic strains.

In conclusion, results from this phase IIB trial demonstrate that two doses of RIX4414 (Rotarix™) are highly efficacious in Latin American infants living in Brazil, Mexico and Venezuela, providing broad and early protection, particularly against severe rotavirus gastroenteritis and related hospitalizations. Of particular importance is the fact that the monovalent RIX4414 vaccine can afford clinical cross-protection in settings where multiple circulating rotavirus strains can be identified, including the globally emerging G9 serotype. Phase III trials with RIX4414 are currently under way in Latin America involving over 63,000 infants in 11 countries. These larger studies are necessary in order to fully assess the safety of RIX4414 (Rotarix™) with regards to intussusception [8].

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References