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Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life

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ABSTRACT

A phase III, randomized, double-blind study evaluated the efficacy, reactogenicity, safety and immunogenicity of a human rotavirus vaccine, RIX4414 in Japanese infants aged 6–14 weeks when administered as two doses (0, 1-month schedule). Efficacy against any and severe rotavirus gastroenteritis leading to medical intervention caused by circulating wild-type rotavirus from two weeks post-Dose 2 until two years of age was 79.3% (95% CI: 60.5–89.8%) and 91.6% (95% CI: 62.4–99.1%), respectively. Solicited, unsolicited symptoms and serious adverse events were reported at a similar frequency in both groups. Serum anti-rotavirus antibody seroconversion rate one-month post-Dose 2 was 85.3% (95% CI: 68.9–95%) in RIXX4414 group. RIX4414 was efficacious, well-tolerated and immunogenic in Japanese infants and introduction of vaccination could help in reducing the disease burden.

1. Introduction

Rotavirus is the single main cause of severe acute gastroenteritis in children less than five years of age, resulting in over 527,000 deaths worldwide annually [1]. The majority of rotavirus-related deaths are seen in developing countries; nevertheless, the disease is not restricted to poor settings. Although rotavirus deaths are seldom observed in developed countries, rotavirus continues to be the main cause of gastroenteritis-related hospitalizations and doctor visits [2,3].

In a prospective surveillance in Japan, rotavirus was detected in approximately 58% of gastroenteritis hospitalizations in children less than five years of age [4]. Further, in a retrospective surveillance in Japan, 39–44% of year-round hospitalization in children aged <5 years with gastroenteritis was due to rotavirus, indicating rotavirus as the most important etiological agent of acute gastroenteritis [5]. A ten-year rotavirus hospitalization survey in Japan (between 1987 and 1996) reported the highest rate of rotavirus hospitalization incidence of 42.2 per 1000 person years in the 6–11 months age group in the overall time period studied [6]. Rotavirus gastroenteritis was also estimated to result in approximately 800,000 doctor visits every year leading to medical intervention among children aged 0–5 years in Japan [7]. At present, the treatment of rotavirus gastroenteritis is limited to symptomatic measures and no antiviral therapy is available.

A live-attenuated human rotavirus vaccine RIX4414 (*Rotarix*™, GlaxoSmithKline Biologicals) contains the most common G1P[8] strain which was derived from the parent 89-12 strain [8,9]. Clinical trials conducted across Europe, Latin America, Asia with the human rotavirus vaccine have demonstrated high efficacy against severe rotavirus gastroenteritis caused by circulating wild-type rotavirus [10–12]. Further, rotavirus vaccination also significantly reduced the incidence of severe rotavirus gastroenteritis among African

Abbreviations: AE, adverse event; ATP, according-to-protocol; CCID, Cell Culture Infective Dose; CI, confidence interval; DTPa, diphtheria-tetanus-acellular pertussis; ELISA, Enzyme-Linked Immunosorbent Assay; GMC, geometric mean concentration; GSK, GlaxoSmithKline; HBV, hepatitis B vaccine; MedDRA, Medical Dictionary for Regulatory Activities; RT-PCR, reverse transcriptase-polymerase chain reaction; SAE, serious adverse event; TVC, total vaccinated cohort; WT, wild-type.

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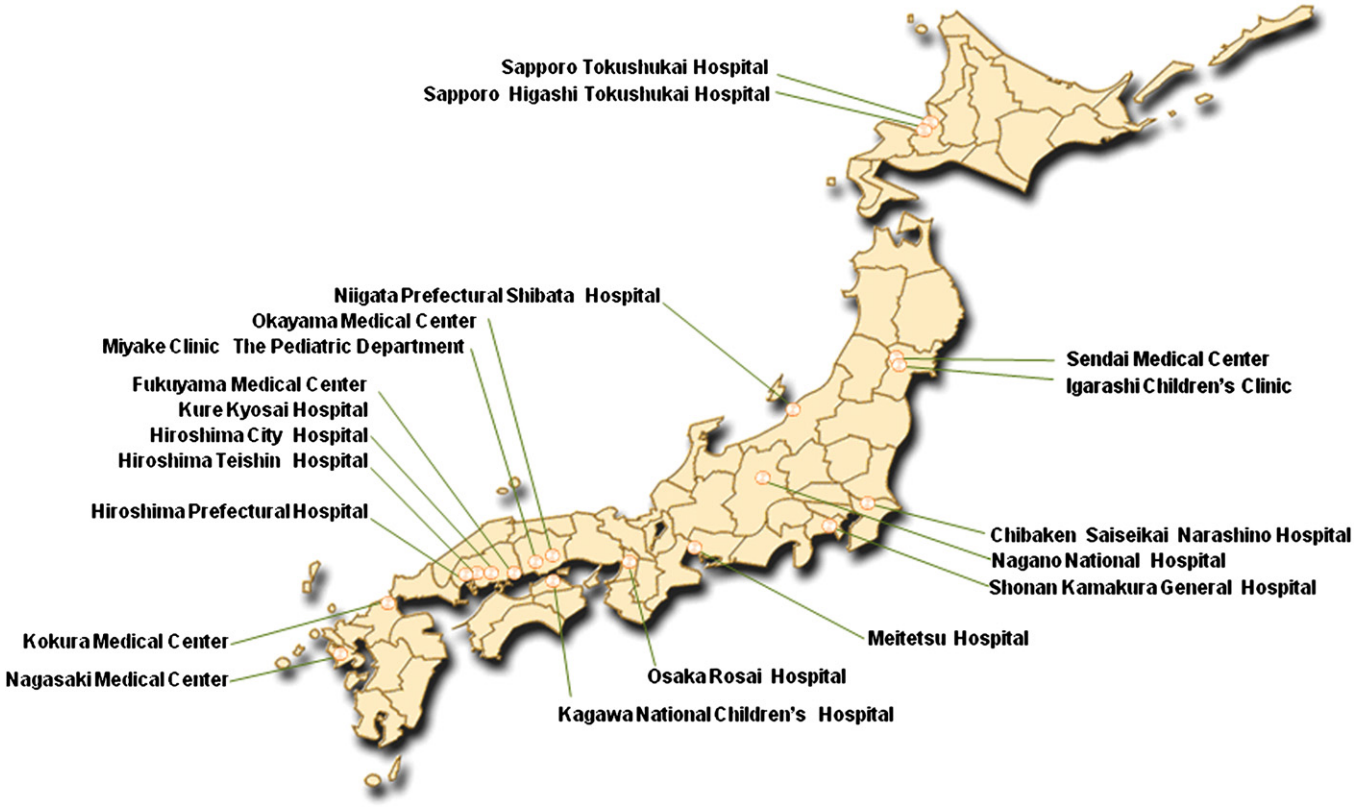

Fig. 1. Study site map.

infants [13]. The safety of the RIX4414 vaccine has also been proved in a large trial with over 63,000 infants [14].

This study, conducted in Japan assessed the efficacy, immunogenicity and safety of RIX4414 vaccine when administered to Japanese infants aged 6–14 weeks.

2. Materials and methods

2.1. Study design and population

This phase III, randomized (vaccine: placebo = 2:1 ratio), double-blind, placebo-controlled study was conducted across 20 study centers (two primary emergency care and 18 secondary emergency care centers) essentially covering the whole of Japan, with Hokkaido in the North, mainland, Kyoshu and Shikoku in the South (107625/NCT00480324) between June 2007 and November 2009 (Fig. 1). Of the 20 centers, 12 were public hospitals and eight were private hospitals. Parents/guardians of children who received care at the participating centers were approached to seek their willingness to let their child/ward participate in the study. Parents/guardians of eligible study participants signed the written informed consent before performance of any study-related procedures. The study protocol, amendment and informed consent were reviewed and approved by the ethics committee prior to study initiation. The study was conducted following Good Clinical Practice, including the Declaration of Helsinki. Ethical approval was sought from the Institutional Review Board of each study centers.

Two oral doses of RIX4414 vaccine/placebo were administered to healthy infants 6–14 weeks of age at Dose 1 according to 0, 1 month vaccination schedule. The routine childhood vaccines (diphtheria-tetanus-acellular pertussis [DTPa] and hepatitis B vaccine [HBV]) recommended in Japan was allowed to be administered concomitantly with the study vaccines according to local immunization practice. Infants were excluded if they had received any investigational drug or vaccine 30 days preceding the first dose of study vaccine/placebo, received other rotavirus vaccine, were administered immunosuppressive drugs, had a history of chronic gastrointestinal disease, suspected immunosuppression or immunodeficiency or had gastroenteritis seven days preceding the administration of first vaccine dose. Vaccination was postponed in case of an acute febrile illness, vomiting or diarrhea at the time of scheduled vaccination. Allergy to the study vaccine or any other component of the study vaccine and the presence of uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract established absolute contraindication to vaccination.

2.2. Study vaccines

Each dose (1 ml) of the lyophilized RIX4414 vaccine (*Rotarix*™) contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of live attenuated human rotavirus RIX4414 strain. The composition of placebo was similar to that of the RIX4414 vaccine but without the vaccine strain and was identical in appearance to the vaccine. The lyophilized vaccine and placebo were reconstituted with the supplied buffer before oral administration.

2.3. Assessment of efficacy

Occurrence of gastroenteritis (diarrhea [≥3 looser than normal stools per day] with or without vomiting) that led to medical intervention was actively followed-up from Dose 1 until two years of age. Starting from Day seven after Dose 1, the parents/guardians of children were contacted at least once every two weeks to check for the occurrence of gastroenteritis episodes. They were contacted either through telephone, short messaging services of the mobile