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Safety, tolerability and immunogenicity of intramuscular administration of PRP-CRM_{197} Hib vaccine to healthy Japanese children: An open-label trial

Takehiro Togashi [a], Nodoka Mitsuya [b,*], Shuji Sumino [b], Yohei Takanami [b]

[a] Hokkaido Anti-Tuberculosis Association, Kita 8, Nishi 3-28, Kita-ku, Sapporo 060-0808, Japan
[b] Takeda Pharmaceutical Company Limited, 1-1, Doshomachi 4-chome, Chuo-ku, Osaka 540-8645, Japan

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ABSTRACT

Background: Japan licensed the conjugate *Haemophilus influenzae* type b vaccine, Vaxem™ Hib, based on clinical studies using subcutaneous injection. The present study was performed to ensure this vaccine is suitable for intramuscular injection in Japanese children.
Methods: Thirty-one healthy 2–6-month-old infants received three doses of Vaxem™ Hib by intramuscular injection at 4-week intervals and a booster dose 1 year later, concomitant with routine infant (DTaP-IPV and pneumococcal) and toddler (measles–rubella) vaccines. Immunogenicity was assessed before and after the primary series and booster dose by enzyme-linked immunosorbent assay for anti-polyribosyl-ribitol-phosphate (PRP) antibodies. Safety was assessed by medical examination and diary cards completed by the subjects' parents/legal guardians.
Results: There were no vaccine-related serious adverse events or withdrawals; all children completed the study. Four weeks after the primary series, the geometric mean anti-PRP titer (GMT) was 19.68 μg/mL, and all children had seroprotective titers (≥0.15 μg/mL) that persisted until the booster dose. Proportions of titers indicative of long-term protection (≥1.0 μg/mL) were 100% after the primary series and 77.4% before the booster. Anamnestic responses to the booster had a GMT of 51.33 μg/mL, and 100% had titers ≥1.0 μg/mL. All but one subject reported injection site reactions as resolved within 3 days of vaccination; systemic reactions due to Hib and routine vaccines were also resolved within this period.
Conclusions: Vaxem™ Hib was generally well tolerated and immunogenic in Japanese children when administered by intramuscular injection in a three-dose primary series and as a booster with concomitant routine vaccines.
Clinical trial registry: Registered on Clinical Trials.gov: NCT02074345.

1. Introduction

The Gram-negative bacterium, *Haemophilus influenzae* type b (Hib), can cause serious infection that can be fatal. Invasive Hib disease can lead to meningitis, pneumonia, epiglottitis and sepsis in young children, especially infants [1]. Original Hib vaccines based on the major capsular polysaccharide, polyribosyl-ribitol-phosphate (PRP), were not effective in infants owing to poor immunogenicity and the failure to induce immune memory [2]. This led to the development of PRP protein conjugate vaccines, where the conjugate protein recruits T cells to stimulate PRP responses, and induces immune memory to enhance their efficacy in infants. Different conjugate proteins used in licensed Hib vaccines include diphtheria toxoid (PRP-D), tetanus toxoid (PRP-T), a mutated non-toxic diphtheria toxin, CRM_{197} (PRP-CRM_{197}), and *Neisseria meningitidis* outer membrane protein complex (PRP-OMP), which have different characteristics in infants [3]. However, all licensed monovalent Hib conjugate vaccines induce high levels of anti-PRP antibodies after a primary series and a booster, and are considered interchangeable for the primary as well as the booster dose [4,5].

Abbreviations: AE, adverse event; CI, confidence interval; GMT, geometric mean anti-PRP titer; Hib, *Haemophilus influenzae* type b; MedDRA, Medical Dictionary for Regulatory Activities; PRP, polyribosyl-ribitol-phosphate; PRP-D, PRP-diphtheria toxoid; PRP-T, PRP-tetanus toxoid; PRP-CRM_{197}, PRP-mutated nontoxic diphtheria toxin; PRP-OMP, PRP-*Neisseria meningitidis* outer membrane protein complex; SAE, serious AE; SD, standard deviation.

* Corresponding author.
E-mail address: nodoka.mitsuya@takeda.com (N. Mitsuya).

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Following a World Health Organization recommendation that Hib vaccines be included in routine infant immunization programs [6], 192 countries had included Hib-conjugate vaccines in their national programs by the end of 2014 [7]. Data from countries that introduced Hib-conjugate vaccines into their routine infant immunization schedules reported a significant decrease in the incidence of pediatric Hib meningitis [8], to the point of eradication in some countries, such as the UK [9]. In Japan, a PRP-T vaccine (Act-HIB®, Sanofi Pasteur S.A., Lyon, France) has been available since 2008, and has been included in routine immunizations since 2013, where use of this vaccine has resulted in a decrease in Hib meningitis in Japanese children under 5 years of age from 7.7 per 100,000 between 2008 and 2010 to 0 per 100,000 in 2014 [10].

To ensure the supply of such an important component of childhood immunization schedules, Takeda Vaccines has recently licensed a PRP-CRM_{197} vaccine (Vaxem™ Hib) in Japan. However, this licensure was based on a clinical research program demonstrating the safety, tolerability and immunogenicity of Vaxem™ Hib when administered by subcutaneous injection in 278 Japanese children, because inactivated infant vaccines are routinely administered subcutaneously in Japan. In other countries, Hib conjugate vaccines are typically administered by intramuscular injection, and in 2011, the Japanese Pediatric Society requested the Ministry of Health, Labour and Welfare to also allow inactivated vaccines to be administered intramuscularly. Under these circumstances, the clinical study was planned to assess the safety, tolerability and immunogenicity of the intramuscular administration of Vaxem™ Hib to Japanese children in a three-dose infant primary series, with a subsequent booster dose 1 year later. This study was performed to support the application to change the labelling of Vaxem™ Hib to include intramuscular administration by assessing the safety, tolerability and immunogenicity of the intramuscular administration of Vaxem™ Hib.

2. Methods

This was a multi-center (four sites), open-label, phase 3 study conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and applicable local regulations. The Institutional Review Board of each site approved the protocol, and the study was performed according to the Declaration of Helsinki. Parents or legal guardians supplied written informed consent before the enrolment of their infants. The objective of this study was to assess the safety and immunogenicity of Vaxem™ Hib when administered as a three-dose primary and one-dose booster by intramuscular injection in Japanese children. This was a non-comparative study, and there was no control group.

2.1. Participants

Eligible participants were healthy infants who had not previously received a Hib vaccination, were 2–6 months of age and were available for the duration of the study. Children were excluded if they had evidence of any serious acute illness or chronic underlying medical condition (cardiovascular, renal, hepatic, or hematologic disease, or developmental disorder), any history of immunodeficiency or anaphylaxis to ingredients of the study vaccine, or had received or were scheduled to receive treatment with blood products. Participants were not to receive any live vaccine within 27 days, or any inactivated vaccine within 6 days, prior to the first dose of study vaccine.

2.2. Vaccine administration

Vaccine (lot No. H816-006) was supplied as 0.625 mL liquid per vial, each 0.5-mL dose containing 10 μg PRP oligosaccharide conjugated to CRM_{197} with 0.3 mg aluminum phosphate as adjuvant in phosphate buffered saline (the formulation licensed for subcutaneous use in Japan). For this study, vaccination was performed by intramuscular injection in the anterolateral thigh muscle using a 1-inch needle. Three doses were administered at 4-week intervals, and a fourth dose 1 year after the third primary dose.

In the primary series, the routine infant DTaP-IPV and pneumococcal infant vaccinations were permitted being given concomitantly at separate sites in other limbs if they were administered on the same day, or given 7 days before or 15 days after the study Hib vaccinations. Concomitant administration of oral rotavirus vaccine was also permitted. Concomitant administration of measles–rubella vaccine was permitted with the booster dose.

2.3. Immunogenicity

A 2-mL blood sample was drawn immediately before the first primary and fourth (booster) vaccinations, and 4 weeks after the third primary and fourth (booster) vaccinations. Sera were prepared immediately and stored at −40 °C to −20 °C. Immune responses were determined by enzyme-linked immunosorbent assay to measure anti-PRP antibodies, which were expressed as geometric mean titer (GMT, μg/mL), and as proportions with titers ≥0.15 μg/mL, indicative of short term seroprotection, and proportions with titers ≥1.0 μg/mL, indicative of long-term seroprotection [11].

2.4. Safety assessments

Safety was evaluated using System Organ Class and Preferred Terminology of the Medical Dictionary for Regulatory Activities (MedDRA) for all adverse events (AEs), and by examining the causal relationship (“adverse reactions” were those judged by the investigator to be related to vaccination), outcome, severity, time of onset (from time of last injection) and duration. AEs were monitored during the study period up to 4 weeks after the third vaccination, and from the booster vaccination to 4 weeks after the booster injection.

Solicited AEs were collected for 2 weeks after each vaccination, using diary cards completed by the subjects’ parents/legal guardians. These included local reactions (erythema, swelling, induration, tenderness) and systemic AEs (rash, irritability, abnormal crying, decreased appetite, vomiting, diarrhea, somnolence, and sleeplessness). Axillary temperature was also recorded daily on the diary cards. Safety was further assessed at each study visit by the physician.

Serious AEs (SAEs, defined as any untoward medical occurrence after any dose that resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or led to a congenital anomaly/birth defect) were monitored throughout the study, from the signing of informed consent until the last study visit 4 weeks after the booster.

2.5. Statistics

The statistical analysis was descriptive only, and there was no formal statistical hypothesis. Therefore, the number of participants (30) was not determined based on any formal statistical power calculations, but rather to show an adequate immune response and tolerable reactogenicity of intramuscular administration.