Vaccine 36 (2018) 3794–3801

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety and immunogenicity of a Vi-DT typhoid conjugate vaccine: Phase I trial in Healthy Filipino adults and children

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ARTICLE INFO

Article history:
Received 12 March 2018
Received in revised form 3 May 2018
Accepted 7 May 2018

Keywords:
Typhoid
Conjugate vaccine
Vi-DT
Safety
Immunogenicity
The Philippines

ABSTRACT

Background: Typhoid fever remains a major public health problem in low- and middle-income countries where children aged 2–14 years bear the greatest burden. Vi polysaccharide is poorly immunogenic in children <2 years of age, and protection in adults is modest. The limitations of Vi polysaccharide vaccines can be overcome by conjugation of the Vi to a carrier protein. A typhoid conjugate vaccine composed of Vi polysaccharide conjugated to diphtheria toxoid (Vi-DT) has been developed. The Phase I study results are presented here.

Methods: This was a randomized, observer-blinded Phase I study to assess the safety and immunogenicity of Vi-DT compared to Vi polysaccharide vaccine, conducted in Manila, Philippines. Participants enrolled in an age de-escalation manner (18–45, 6–17 and 2–5 years) were randomized between Test (Vi-DT, 25 μg) administered at 0 and 4 weeks and Comparator (Vi polysaccharide, Typhim Vi® and Vaxigrip®, Sanofi Pasteur) vaccines.

Results: A total of 144 participants were enrolled (48 by age strata, 24 in Test and Comparator groups each). No serious adverse event was reported in either group. Solicited and unsolicited adverse events were mild or moderate in both groups with the exception of a 4-year old girl in Test group with grade 3 fever which resolved without sequelae. All participants in Test group seroconverted after first and second doses of Vi-DT while the proportions in the Comparator group were 97.1% and 97.2%, after first dose of Typhim Vi® and second dose of Vaxigrip®, respectively. Vi-DT showed 4-fold higher Geometric Mean Titers (GMT) compared to Typhim Vi® (adjusted for age strata, $p < 0.001$). No further increase of GMT was detected after the second dose of Vi-DT. Anti-DT IgG seroresponse rates were 81.2% and 84.5% post first and second Vi-DT doses, respectively.

Conclusions: Vi-DT vaccine was safe, well-tolerated and immunogenic in participants aged 2–45 years. ClinicalTrials.gov registration number: NCT02645032.

1. Introduction

Typhoid fever is one of the most common causes of bacteremia in several low- and middle-income countries (LMIC) and has been estimated to cause 11–21 million cases and 145,000–161,000 deaths per year [1]. Symptoms include fever, abdominal pain, and nausea, which last between one to four weeks, and 1–2% of hospitalized cases result in death [2,3]. Improved sanitation contributed to the sharp decline of typhoid fever in industrialized countries during the early 20th century [4,5] but such infrastructure is slow to materialize in places where the disease remains endemic [4,6]. Vaccination may provide a short-to-medium term measure to abate the typhoid burden of disease [2]. It is therefore essential to consider a comprehensive approach that combines targeted vaccination of at-risk populations as a short- to medium-term prevention measure, along with longer term solutions of improvements of water and sanitation and living standards [7].

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https://doi.org/10.1016/j.vaccine.2018.05.038
0264-410X/

Nomenclature

Abbreviations

AE	adverse event
DT	diphtheria toxoid
GCP	good clinical practice
GMT	geometric mean titers
GMF	geometric mean fold
IRB	institutional review board
IVI	International Vaccine Institute
LMIC	low- and middle-income countries
PFDA	Philippines Food and Drug Administration
PP	per protocol
RITM	Research Institute for Tropical Medicine
SAE	serious adverse event
SBA	serum bactericidal assay
SMC	Safety Monitoring Committee
Vi	*Salmonella* typhi capsular polysaccharide
Vi-DT	diphtheria toxoid conjugated Vi-polysaccharide vaccine
Vi-PS	*Salmonella* typhi capsular polysaccharide vaccine

Several safe and effective typhoid vaccines that could help reduce disease burden are licensed and available. Three or four doses of orally administered live-attenuated Ty21a provide about 50–70% protection for at least 7 years and is licensed in capsule form from 5 years of age or as a liquid formulation from 2 years of age, although the liquid formulation is not commercially available [8-10]. The single-dose injectable Vi polysaccharide vaccine provides similar levels of protection for at least 3 years and is licensed from 2 years of age [11,12]. Although Vi polysaccharide vaccination has been shown to protect individuals from typhoid fever, it has several limitations due to T cell-independent properties. Immune responses to bacterial capsular polysaccharides are characterized by T-cell independence, lack of affinity maturation, poor antibody subclass switching and inability to generate memory. This limits their use in children less than two years of age [13,14]. These limitations can be overcome by conjugation of the Vi polysaccharide to a carrier protein. Conjugation of the polysaccharide to a carrier protein converts the immune response to T-cell dependent characterized by affinity maturation, subclass switching and induction of memory [15]. Two Vi polysaccharide vaccines conjugated to tetanus toxoid as carrier protein are licensed in India for use from 3 to 6 months of age [16]. The immunogenicity of typhoid conjugate vaccines in children under 2 years of age is an important advance, [17] given the significant burden of disease in young children and infants [18,19].

The International Vaccine Institute (IVI, Seoul, Republic of Korea) developed a typhoid conjugate vaccine (Vi-DT) where the Vi polysaccharide (a clinical isolate from India (C6524)) is conjugated to diphtheria toxoid as carrier protein. In order to meet the global demand of typhoid conjugate vaccines, IVI has transferred this technology to SK Chemicals, Republic of Korea for future commercialization.

2. Materials and methods

The clinical study (Clinicaltrials.gov NCT02645032) was approved by the Philippines Food and Drug Administration (PFDA) and the Institutional Review Boards (IRB) of the Research Institute for Tropical Medicine (RITM) and IVI. The study was conducted in accordance with the ICH E8 Guidelines for Good Clinical Practice (GCP) and the ethical principles of the Declaration of Helsinki. Before any study intervention, a written informed consent was obtained from eligible adult participants and from the parents or legal guardians of participants aged 2–17 years. Assent was also obtained from 7 to 17 years old children according to the 2011 Philippines National Ethics Guidelines.

2.1. Study design and participants

This was a randomized, observer-blinded, Phase I study to assess the safety and immunogenicity of 25 μg Vi-DT typhoid conjugate vaccine (Test vaccine) compared with Vi polysaccharide typhoid vaccine (25 μg) (Typhim Vi®, Sanofi Pasteur) (Comparator vaccine). Since Test and Comparator vaccines differ in their presentation, the study was observer-blinded (safety evaluators and other trial staff remained blinded with the exception of the vaccine administrator) to ensure evaluator's blinding to prevent bias in assessment of adverse events. This study was conducted at RITM, Manila, the Philippines, from May 2016 to Feb 2017. Healthy Filipino participants aged 2–45 years were enrolled into 3 cohorts of 18–45, 6–17, and 2–5 years in an age de-escalation manner.

The primary objective of the study was to evaluate the safety of Vi-DT, while the secondary objectives were to assess the immunogenicity of Vi-DT comparatively to Typhim Vi®.

2.2. Vaccines

The Test vaccine (Vi-DT) used in this study is a purified Vi polysaccharide conjugated to diphtheria toxoid. The vaccine containing two active ingredients, 25 μg of purified Vi polysaccharide (*S.* Typhi C6524) and diphtheria toxoid (*Corynebacterium diphtheria* PW No.8) formulated with stabilizers was administered intramuscularly as 0.5 mL/vial. The Comparator vaccine Typhim Vi® (Sanofi Pasteur) contained 25 μg of purified Vi polysaccharide (*S.* Typhi Ty2). Since the Comparator vaccine is administered as a single dose, the second dose administered was a flu vaccine (Vaxigrip®, split viron, inactivated influenza vaccine, southern hemisphere, Sanofi Pasteur) to keep the blinding. Both Comparator vaccines were given intramuscularly in the deltoid muscle of the left upper arm for participants aged ≥3 years and in the anterolateral left thigh *vastus lateralis* muscle for children aged 2–3 years. Vaccines were stored at +2–8 °C. The first and second doses of Test and Comparator vaccines were administered 4 weeks apart.

2.3. Assessment of safety and reactogenicity

Participants were assessed for immediate reactions up to 60 min following vaccination. Participants/parents/guardians were provided with a thermometer and diary cards (DC) to record axillary temperature and any adverse event (AE) daily up to 7 days after each dose for solicited or up to 28 days for unsolicited adverse events. Local reactogenicity events (at the site of injection) included pain, tenderness, erythema/redness, swelling/induration and pruritus after study vaccine administration. Tenderness as a solicited reaction was not sought in children as it is difficult to assess in younger participants. Tenderness was sought in adults and adolescents only. Solicited systemic AEs included fever, headache, fatigue, arthralgia, myalgia, chills, nausea/vomiting and acute allergic reaction after study vaccine administration. Unsolicited Adverse Events were defined as, any other adverse event that occurred from the date of administration of the investigational product (IP) to 28 days following each dose (Days 0–28). Unsolicited AEs were classified into System Organ Class (SOC) and Preferred Term (PT) using MedDRA (version 18.1, 2015). Par-