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Safety and immunogenicity of a candidate bioconjugate vaccine against *Shigella dysenteriae* type 1 administered to healthy adults: A single blind, partially randomized Phase I study

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ABSTRACT

Background: Shigellae cause severe disease in endemic countries, especially in children. Several efficacy trials have been conducted with candidate vaccines against *Shigellae*, but the lack of protection, the safety concerns, or manufacturing challenges hindered successful market approval. Conjugated vaccines have been shown to be safe and effective for different pathogens (*i.e.*, *Neisseria meningitidis*, *Shigella pneumonia*, *Haemophilus influenzae*). The bio-conjugation technology, exploited here for the *Shigella dysenteriae* candidate vaccine, offers a novel and potentially simpler way to develop and produce vaccines against one of the major causes of morbidity and mortality in developing countries.
Methods: A novel *S. dysenteriae* bioconjugate vaccine (GVXN SD133) made of the polysaccharide component of the *Shigella* O1 lipopolysaccharide, conjugated to the exotoxin protein A of *Pseudomonas aeruginosa* (EPA), was evaluated for immunogenicity and safety in healthy adults in a single blind, partially randomized Phase I study. Forty subjects (10 in each dose group; 2 μg or 10 μg with or without aluminium adjuvant) received two injections 60 days apart and were followed-up for 150 days.
Results: Both doses and formulations were well tolerated; the safety and reactogenicity profiles were consistent with that of other conjugated vaccines, adjuvanted or not, independent of the dose and the number of injections. The GVXN SD133 vaccine elicited statistically significant O1 specific humoral responses at all time points in all vaccination groups. Between-group comparisons did not show statistically significant differences in geometric mean titers of immunoglobulin G and A at any post-vaccination time point.
Conclusions: This study demonstrated that the GVXN SD133 vaccine has a satisfactory safety profile. It elicited a significant humoral response to *Shigella* O1 polysaccharides at all doses tested. The protein carrier also elicited functional antibodies, showing the technology's advantages in preserving both sugar and conjugated protein epitopes. This trial is registered at ClinicalTrials.gov (NCT01069471).
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1. Introduction

Q3 The World Health Organization (WHO) estimates *Shigellae* to cause at least 80 million cases of bloody diarrhea and 700,000 deaths each year [1]. Almost all *Shigella* infections occur in developing countries, and the majority of cases (~70%) and deaths (~60%) occur among children less than 5 years of age. Diarrheal disease associated with *Shigellae* also occurs among travelers and military forces.

There are four species of *Shigellae* classified on the basis of biochemical and serological differences: *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii* and *Shigella sonnei* [2].

S. flexneri serotypes have been associated with endemic shigellosis among children in developing countries, such as China, South and Southeast Asia, Egypt, Kenya, Peru and Israel, where up to 90% of cases are attributable to this *Shigella* group [4–6]. *S. sonnei* is

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the predominant serotype that causes shigellosis in industrialized countries, including the United States, and it is also an important agent of travelers' diarrhea [7]. The *S. dysenteriae* type 1 is rarely endemic, but can cause disease with severe complications and is historically associated with devastating pandemics with high case-fatality rates in all age groups, described for Central America, Central Africa and Southeast Asia [8–10].

Based on clinical severity, disease burden, and emergence of antimicrobial resistance, an urgent need for an effective vaccine to protect against infections due to *Shigella* is warranted [11–14]. In order to deliver the broadest protection against the most prevalent serotypes, a *Shigella* vaccine should contain at least the four antigens from *S. sonnei, S. flexneri* 2a, 3a and 6, in order to cover approximately 85% of currently circulating strains [3,11,15,16]. Inclusion of the *S. dysenteriae* type 1 would be an additional asset for this multivalent vaccine, as it would help to prevent pandemic outbreaks. Several attempts have been made so far toward the development of a functional vaccine against shigellosis and several strategies for vaccine production have been exploited. Live-attenuated whole-cell oral vaccines were shown to induce a robust immune response, but as well a high risk of reactogenicity and reversion [17]. The approach of using inactivated whole-cell vaccines has been shown to be safe and immunogenic, when administered orally in volunteers at repeated high doses [18]. However, the need for a high oral inoculum required, represents a continuous challenge for the further development of this category of vaccines [19]. In addition, a problem with oral live vaccines is their reduced immunogenicity when used in developing countries, probably due to the impact of factors such as malnutrition, aberrant intestinal microflora or concomitant infections [20]. Alternatively, several researchers have chemically conjugated purified *Shigella* lipopolysaccharides (LPS) to a protein carrier [21]. These conjugates were parentally administrated and were shown to be safe, immunogenic and efficacious against disease in vaccinated volunteers and in field trials in the Israeli Defence Forces, respectively [22,23]. Subsequent studies showed promising results of conjugate vaccines in adults and children, but not in infants [24–27]. These studies validated the O-specific polysaccharides of *Shigella* as the target antigen for a candidate vaccine and provided indications supporting that a parenteral vaccine administration could be efficacious against a mucosal infection (as already shown with commercial parenteral vaccines against mucosal pathogens like polio or HPV). However, the complex and expensive production of chemically synthesized conjugate vaccines makes the development of a multivalent conjugated *Shigella* vaccine challenging [28]. The GVXN SD133 candidate vaccine is a further step in the development of a *Shigella* vaccine, as it combines the advantages of the good safety profile and strong immune-response that conjugates do induce with the homogeneous and consistent manufacture process offered by the bioconjugation technology. This is a technology, directly synthesizing conjugates in vivo using appropriately engineered bacterial cells. Using the protein glycosylation machinery in *Escherichia coli*, different polysaccharides can be transferred to a variety of carrier proteins, allowing the production of bioconjugates that can be exploited as novel vaccines [29–31]. In the presented clinical trial a candidate vaccine was developed with this new technology and used for the first time.

2. Methods

Here we describe the evaluation of the safety and immunogenicity of a novel *S. dysenteriae* O1 bioconjugate vaccine (GVXN SD133) administered with or without aluminium hydroxide adjuvant in a Phase I single blind, partially randomized study conducted in Switzerland.

2.1. Participants

Healthy subjects of either gender aged 18 to 50 years were eligible if they had normal serum laboratory data and negative blood test results for human immunodeficiency, hepatitis B and C viruses. Exclusion criteria included a known history of previous *Shigella* infection or previous prolonged residence in a *Shigella* endemic region, or an agglutination *in-vitro* assay. Subjects with a compromised immune system, a family history of congenital or hereditary immunodeficiency, chronic (more than 14 days) administration of systemic immunosuppressant or other immune-modifying drugs within 6 months prior to the first vaccine dose were also excluded. A total of 40 subjects entered the study, 20 male and 20 female. The average age of the subjects was 22.9 years.

2.2. Ethics

The study was conducted at a single study center at the EBPI, Zurich, Switzerland, in accordance with the Declaration of Helsinki, ICH guidelines for good clinical practice and all applicable local and national regulations and directives. The Cantonal Ethics Committee of Zurich approved the study. All subjects provided informed consent after the nature and possible consequences of the study had been fully explained to them.

2.3. Vaccine

Four final products were administered as doses of 2 μg (Batch 130/GMP1/FC001D) or 10 μg (Batch G130/GMP1/FC001B) of *Shigella* O1 polysaccharide, formulated with or without 0.06% aluminium hydroxide (AL) (Batch G130/GMP1/FC001C and Batch G130/GMP1/FC001A, respectively) in saline buffer. The adsorption of the vaccine to the adjuvant was around 90%. A volume of 0.5 mL was administrated by intramuscular injection into the deltoid with 1 mL syringes (Terumo BS-01 T) and 23G needles (Terumo SG2 2325). The antigenic polysaccharide of *S. dysenteriae* O1 was expressed in *E. coli* and conjugated to genetically detoxified exotoxin protein A (EPA) of *Pseudomonas aeruginosa* (manuscript under preparation).

2.4. Study design

The Phase I single blind, partially randomized study assessed the safety, reactogenicity and humoral immune response of GVXN SD133 administered on Day 0 and Day 60. The study was conducted in a single-blind manner, *i.e.*, subjects were unaware of which treatment they were administered. All vaccine formulations looked like transparent solutions and subjects had no access to the room where syringes for injection were prepared. For safety reasons, the first 8 subjects were not randomized and enrolment was staggered and started with a group of four subjects with the 2 μg dose (with or without adjuvant), followed by another four subjects with the 10 μg dose (with or without adjuvant). Subsequently 32 subjects were randomly allocated to the four vaccination groups in a 1:1:1:1 ratio and a 1:1 gender ratio through sealed randomization envelopes. Visits occurred at screening, D0, D7, D30, D60, D67, D90 and D150. In addition, there were phone calls to the subjects on the day after each vaccination (D1, D61).

2.5. Objectives

2.5.1. Primary objective

The primary objective of this study was to demonstrate the safety and reactogenicity of the *S. dysenteriae* O1 bioconjugate vaccine (GVXN SD133) alone or in combination with an adjuvant (aluminium hydroxide, AL) at two different concentrations of O1

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