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Defining the optimal formulation and schedule of a candidate toxoid vaccine against *Clostridium difficile* infection: A randomized Phase 2 clinical trial☆

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ABSTRACT

Background: Clostridium difficile, a major cause of nosocomial and antibiotic-associated diarrhea, carries a significant disease and cost burden. This study aimed to select an optimal formulation and schedule for a candidate toxoid vaccine against *C. difficile* toxins A and B.
Methods: Randomized, placebo-controlled, two-stage, Phase 2 study in a total of 661 adults aged 40–75 years. Stage I: low (50 μg antigen) or high (100 μg antigen) dose with or without aluminum hydroxide (AlOH) adjuvant, or placebo, administered on Days 0–7–30. Stage II: Days 0–7–30, 0–7–180, and 0–30–180, using the formulation selected in Stage I through a decision tree defined a priori and based principally on a bootstrap ranking approach. Administration was intramuscular. Blood samples were obtained on Days 0, 7, 14, 30, 60 (Stage I and II), 180, and 210 (Stage II); IgG to toxins A and B was measured by ELISA and in vitro functional activity was measured by toxin neutralizing assay (TNA). Safety data were collected using diary cards.
Results: In Stage I the composite immune response against toxins A and B (percentage of participants who seroconverted for both toxins) was highest in the high dose + adjuvant group (97% and 92% for Toxins A and B, respectively) and was chosen for Stage II. In Stage II the immune response profile for this formulation through Day 180 given on Days 0–7–30 ranked above the other two administration schedules. There were no safety issues.

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Conclusions: The high dose + adjuvant (100 μg antigen + AlOH) formulation administered at 0–7–30 days elicited the best immune response profile, including functional antibody responses, through Day 180 and was selected for use in subsequent clinical trials.

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1. Introduction

Clostridium difficile (*C. difficile*) is a gram-positive, spore-forming anaerobe, which causes colonic mucosal injury and inflammation by the release of toxins A (a 308 kDa enterotoxin) and B (a 270 kDa cytotoxin) [1]. While carriage of the organism may be asymptomatic, *C. difficile* is a major cause of nosocomial and antibiotic-associated diarrhea in Europe and North America, and severe cases can lead to pseudomembranous colitis and toxic megacolon [2,3]. *C. difficile* infection (CDI) imposes a significant burden of disease [4] and infection rates have increased substantially over recent years. In the US alone, recent data suggest almost 500,000 infections and approximately 29,000 deaths in 2011 [5]. As well as its importance as a nosocomial infection, *C. difficile* is also increasingly present in the community [6] and the financial burden is high, being estimated at over $7 billion annually in Europe [7] and the US [8,9] combined.

Given the limitations of current treatment options, the high rates of recurrence [8,10–12], and with *C. difficile* spores tolerating most disinfection procedures [13], combatting CDI by targeted disease prevention is ideal. Toxins A and B both damage colonic cells, and studies have suggested a relationship between the immune response to these toxins and protection against CDI [14–18]. No vaccine is available against CDI, however a bivalent, toxoid vaccine to stimulate immunity to toxins A and B and negate their harmful effects is currently being developed [19]. Phase 1 data have shown good tolerability and a strong immune response to both toxins in adults including the elderly [20]. Crucial to the continued clinical development of this candidate vaccine is a robust assessment of a range of formulations and dosing schedules. This study was conducted to identify the formulation and schedule to be used in later phase clinical studies. As such, Stage I of the study was designed to assess the safety and immunogenicity of four formulations (high or low dose of antigen, with or without adjuvant) administered in the same schedule and Stage II assessed two further schedules using the formulation selected in Stage I.

2. Methods

2.1. Study design and participants

This randomized, placebo controlled, Phase 2 study was conducted in two stages in 39 centers in the USA. In Stage I a range of doses (low [50 μg total antigen] or high [100 μg total antigen]) and formulations (with or without aluminum hydroxide adjuvant) were assessed for a candidate *C. difficile* vaccine using the same administration schedule. In Stage II two additional schedules of administration were assessed using the formulation selected after Stage I. In Stage I the investigators, participants, outcome assessors, and laboratory personnel were blinded to the formulation administered. Stage II was open-label (except for laboratory personnel). Local independent ethics committees approved the study protocol and amendments. The study was conducted according to the applicable local and national requirements, Good Clinical Practice and applicable International Conference on Harmonization guidelines, and conformed to the principles of the Declaration of Helsinki (Edinburgh revision, October 2000).

Each participant signed an informed consent form prior to enrolment. Vaccine administration took place between 27 October 2010–15 June 2011 (Stage I) and 15 November 2011–23 July 2012 (Stage II) (ClinicalTrials.gov NCT01230957).

To be eligible, participants were aged between 40 and 75 years (stratified into equal groups aged 40–64 years and 65–75 years in each stage) and considered to be at risk of *C. difficile* infection based on (i) impending hospitalization within 60 days of enrolment, or (ii) current or impending (within 60 days of enrolment) residence in a long-term care facility or rehabilitation facility. The main exclusion criteria were: pregnancy or lack of effective contraception, participation in another clinical study, non-study vaccination (other than influenza or pneumococcal vaccines) in the previous 4 weeks, previous vaccination against *C. difficile*, current or prior episode of CDI, receipt of blood products in the previous 3 months, congenital or acquired immunodeficiency or receipt of anti-cancer chemo- or radiotherapy in the previous 6 months, >2 weeks corticosteroid therapy in the previous 3 months, seropositivity for HIV/hepatitis B/hepatitis C, anticipated or current kidney dialysis, hypersensitivity to any vaccine component, bleeding disorder contraindicating intramuscular (IM) injection, chronic disease or addiction that could interfere with study procedures, history of diverticular intestinal bleeding, surgery for gastrointestinal malignancy in the previous 3 months.

In Stage I, participants were randomized to one of five groups and received three doses of vaccine (low or high dose with or without adjuvant) or placebo at Days 0–7–30 (see Table 1). One of these formulations was then selected for Stage II, based on immunogenicity. In Stage II, additional participants were randomized to receive the selected vaccine formulation according to two alternative vaccination schedules: Days 0–7–180, or 0–30–180. All injections were intramuscular (IM), ideally into alternate arms for sequential vaccinations.

2.2. Vaccines

The investigational *C. difficile* toxoid vaccine was a formalin-inactivated, highly purified preparation of toxoids A and B, and presented as a freeze-dried preparation that was reconstituted with diluent (either adjuvant or water for injection) prior to IM injection (0.5 mL). The adjuvant was 400 μg AlOH provided as 1600 μg/mL in water for injection. Placebo was 0.9% saline.

2.3. Serology

Blood samples were collected on Days 0, 7, 14, 30, 60 (all participants), 180, and 210 (all participants in Stage II and those in Stage I who received the formulation selected for Stage II), and analyzed for (i) serum anti-toxin IgG to *C. difficile* toxins A and B (enzyme-linked immunosorbent assay [ELISA]), and (ii) anti-toxin A and B neutralizing capacity (toxin neutralizing assay [TNA]). All analyses were conducted centrally at the Sponsor's Global Clinical Immunology laboratory.

For the ELISA, full-length *C. difficile* toxin A or toxin B was used to coat ELISA plates. All controls, reference, and samples were added to the microtiter plates, incubated at 37 °C followed by incubating with goat anti-human IgG conjugated to horseradish peroxidase.

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