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Effect of reduced dose schedules and intramuscular injection of anthrax vaccine adsorbed on immunological response and safety profile: A randomized trial[☆,☆☆]

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ABSTRACT

Objective: We evaluated an alternative administration route, reduced schedule priming series, and increased intervals between booster doses for anthrax vaccine adsorbed (AVA). AVA's originally licensed schedule was 6 subcutaneous (SQ) priming injections administered at months (m) 0, 0.5, 1, 6, 12 and 18 with annual boosters; a simpler schedule is desired.
Methods: Through a multicenter randomized, double blind, non-inferiority Phase IV human clinical trial, the originally licensed schedule was compared to four alternative and two placebo schedules. 8-SQ group participants received 6 SQ injections with m30 and m42 "annual" boosters; participants in the 8-IM group received intramuscular (IM) injections according to the same schedule. Reduced schedule groups (7-IM, 5-IM, 4-IM) received IM injections at m0, m1, m6; at least one of the m0.5, m12, m18, m30 vaccine doses were replaced with saline. All reduced schedule groups received a m42 booster. Post-injection blood draws were taken two to four weeks following injection. Non-inferiority of the alternative schedules was compared to the 8-SQ group at m2, m7, and m43. Reactogenicity outcomes were proportions of injection site and systemic adverse events (AEs).
Results: The 8-IM group's m2 response was non-inferior to the 8-SQ group for the three primary endpoints of anti-protective antigen IgG geometric mean concentration (GMC), geometric mean titer, and proportion of responders with a 4-fold rise in titer. At m7 anti-PA IgG GMCs for the three reduced dosage groups were non-inferior to the 8-SQ group GMCs. At m43, 8-IM, 5-IM, and 4-IM group GMCs were superior to the 8-SQ group. Solicited injection site AEs occurred at lower proportions in the IM group compared to SQ. Route of administration did not influence the occurrence of systemic AEs. A 3 dose IM priming

Abbreviations: IM, intramuscularly; SQ, subcutaneous; AVA, anthrax vaccine adsorbed; PA, protective antigen; DoD, Department of Defense; CDC, Centers for Disease Control and Prevention; AVRP, Anthrax Vaccine Research Program; FDA, Food and Drug Administration; IND, Investigational New Drug; GCP, Good Clinical Practices; USAMMA, United States Army Medical Materiel Agency; LTx, lethal toxin; AE, adverse event.

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the U.S. Army or the Department of Defense.

☆☆ This trial is registered at www.clinicaltrials.gov under the registry number NCT00119067.

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schedule with doses administered at m0, m1, and m6 elicited long term immunological responses and robust immunological memory that was efficiently stimulated by a single booster vaccination at 42 months.

Conclusions: A priming series of 3 intramuscular doses administered at m0, m1, and m6 with a triennial booster was non-inferior to more complex schedules for achieving antibody response.

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1. Introduction

The U.S. licensed vaccine, anthrax vaccine adsorbed (AVA) (BioThrax®, Emergent BioSolutions Inc., Lansing, MI), is prepared from a cell-free culture filtrate which contains a mixture of proteins, including the principal immunogen protective antigen (PA), adsorbed to aluminum hydroxide (Alhydrogel, Brenntag Group, Denmark) as an adjuvant. AVA was originally licensed in 1970 [1,2] as a series of 0.5 mL injections administered subcutaneously in the upper outer arm, over the deltoid muscle, at months 0, 0.5, 1, 6, 12, and 18, followed by annual boosters. Evidence for the efficacy of AVA comes from several studies in animals, a controlled vaccine trial in humans using a similar product, observational data in humans, and immunogenicity data for humans and other mammals [3–14].

Due in part to increased vaccination of military personnel beginning in 1997 [15], the US Congress tasked the Centers for Disease Control and Prevention (CDC) to expand upon the Department of Defense (DoD) pilot studies of dose and schedule optimization [16,17] by undertaking the largest ever prospective study of AVA safety and immunogenicity in a diverse study population. The primary focus of the CDC Anthrax Vaccine Research Program (AVRP) was a 43-month prospective, randomized, double-blind, phase IV, placebo controlled clinical trial. The objectives of the AVRP were to document and ensure the safety and immunogenicity of AVA, and subsequently to minimize the priming dose series and optimize the booster schedule [18]. An interim analysis of safety and immunogenicity data generated on 1005 study participants through the first 7 months of their participation [19] provided the basis in 2008 for FDA to support a change to IM administration and elimination of the week 2 (m0.5) dose in the priming series [20]. We present a final study analysis of data collected from 1563 participants through all 43 months of participation.

2. Methods

2.1. Participants and recruitment

The study was sponsored by CDC under an Investigational New Drug (IND) application, was approved by the human investigations committees at participating clinical sites and at CDC, and was conducted according to the International Conference on Harmonization Good Clinical Practices (GCP). Study centers included Walter Reed Army Institute of Research, Silver Spring, MD; Baylor College of Medicine, Houston, TX; Emory University School of Medicine, Atlanta, GA; Mayo Clinic, Rochester, MN and University of Alabama at Birmingham, Birmingham, AL. Oversight was provided by a Data and Safety Monitoring Board (DSMB).

Volunteers had to be no less than 18 years and no greater than 61 years of age at the time of enrollment. Additional inclusion and exclusion criteria, methods for randomization and blinding, as well as sample size calculations, are presented as supplemental material. The number of enrollees required by sample size calculations was doubled to allow for attrition due to the length of the study.

2.2. Interventions

AVA was provided by the Military Vaccine (MilVax) Agency, DoD, through the United States Army Medical Materiel Agency (USAMMA). Over the study duration 6 lots of vaccine were used: FAV063, FAV074, FAV079, FAV087, FAV107, and FAV113. Placebo injections were saline (0.9% (w/v) NaCl, Abbott Laboratories, Chicago, IL).

Participants were randomized to one of 6 study groups. One group (8-SQ) received AVA as originally licensed, or 6 SQ injections of AVA administered at months 0, 0.5, 1, 6, 12, and 18, followed by 2 annual boosters administered at months 30 and 42. A second group (8-IM) received AVA administered intramuscularly (IM) on the same schedule as the 8-SQ group. Three groups received AVA on reduced dose schedules (7-IM, 5-IM, 4-IM). These reduced dose schedule groups all received AVA at m0, m1, and m6, with one or more of the doses at m0.5, m12, m18 and/or m30 replaced with saline injection. All reduced dosage group participants received a booster at m42 (Table 1). The final group was administered saline placebo at all 8 times points, with participants equally divided between SQ and IM route of administration (Fig. 1 and Table 1). All vaccine and placebo injections were administered as a 0.5 mL dose.

2.3. Serological evaluation

Participant immune response profiles were determined for 13 serial pre- and post-injection blood samples.[4] Samples were assayed for anti-PA IgG by ELISA and reported as titers and concentration in μg/ml [21–24]. Dilutional titers were calculated on a continuous scale and reported as the reciprocal of dilution [25]. The ELISA lower limit of quantification (LLOQ) was 3.7 μg/ml for concentrations of anti-PA IgG and 58 for titers. All reported values were from a minimum of two independent tests. The three primary endpoints based on the magnitude of anti-PA IgG antibody response were: (1) the proportion of participants achieving a ≥4-fold rise in anti-PA specific IgG titer compared to pre-injection titer (%4XR), (2) the geometric mean anti-PA specific IgG titer (GMT), and (3) the geometric mean concentration (GMC). To calculate geometric mean concentrations and titers, IgG concentrations and titers below the LLOQ [26] were set to ½ LLOQ, or 1.85 μg/ml and 1/29 respectively; 4-fold responses for participants < LLOQ were defined at 4 times the LLOQ. This is in contrast to the interim analysis in which ½ LLOQ was used [19].

Lethal toxin (LTx) neutralization activity (TNA) was determined for a subset of enrollees. A secondary endpoint, the TNA geometric mean titer (ED50 GMT), was calculated as the reciprocal of the serum dilution which neutralized 50% of in vitro LTx cytotoxicity [27–31]; TNA samples were run in triplicate. The LLOQ for the TNA assay was an ED50 titer of 36; TNA ED50 titers below the LLOQ were set to ½ LLOQ titer, or 18.

[4] Pre-injection samples were obtained during the injection visits (m0, m1, m6, m12, m18, m30, m42); m0 served as the baseline sample. Post-injection samples were obtained 4 weeks following injection (m1, m2, m7, m13, m19, m31, m43); m1 served as the post-injection sample for both the m0 and m0.5 injections.

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