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A phase 3, randomized, double-blind, placebo-controlled study of the safety and efficacy of the live, oral adenovirus type 4 and type 7 vaccine, in U.S. military recruits

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ABSTRACT

Adenovirus (ADV) types 4 (ADV-4) and 7 (ADV-7) are presently the major cause of febrile acute respiratory disease (ARD) in U.S. military recruits. We conducted a multi-center, randomized, double-blind, placebo-controlled phase 3 study of the new vaccine to assess its safety and efficacy. Healthy adults at two basic training sites were randomly assigned to receive either vaccine (two enteric-coated tablets consisting of no less than 4.5 $\log_{10}$ $TCID_{50}$ of live ADV-4 or ADV-7) or placebo in a 3:1 ratio. Volunteers were observed throughout the approximate eight weeks of their basic training and also returned for four scheduled visits. The primary endpoints were prevention of febrile ARD due to ADV-4 and seroconversion of neutralizing serum antibodies to ADV-7, which was not expected to circulate in the study population during the course of the trial. A total of 4151 volunteers were enrolled and 4040 (97%) were randomized and included in the primary analysis (110 were removed prior to randomization and one was removed after randomization due to inability to swallow tablets). A total of 49 ADV-4 febrile ARD cases were identified with 48 in the placebo group and 1 in the vaccine group (attack rates of 4.76% and 0.03%, respectively). Vaccine efficacy was 99.3% (95% CI, 96.0–99.9; $P < 0.001$). Seroconversion rates for vaccine recipients for ADV-4 and ADV-7 were 94.5% (95% CI, 93.4–95.5%) and 93.8% (95% CI: 93.4–95.2%), respectively. The vaccine was well tolerated as compared to placebo. We conclude that the new live, oral ADV-4 and ADV-7 vaccine is safe and effective for use in groups represented by the study population.

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1. Introduction

Military recruits at basic training (BT) camps are particularly susceptible to respiratory infections due to the nature of their training, in which large numbers of individuals from different geographic locations live and train together in relatively confined spaces for extended periods. Despite the effectiveness of influenza vaccination, initiated during World War II, recurrent epidemics of acute respiratory disease (ARD) remain a significant problem in new recruits undergoing basic training (BT). Typical ARD in recruits is a febrile illness with cough, sore throat, nasal discharge, headache and fatigue that persists for 3 to 10 days. The illness is debilitating, a major cause of lost training time, complicated by pneumonia in about 10% of cases and can, although rarely, be fatal. Studies have

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[1] See Appendix A.

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determined that the majority of these ARD cases are caused by ADV, usually types 4 and 7 and less frequently types 3, 14 and 21 [1,2]. Historically, ADV has infected up to 80% of basic recruits, 20% of whom may be hospitalized; 90% of hospitalized cases of pneumonia have been attributed to ADV infections [3–5].

In the 1960s, it was discovered that live ADV-4 vaccine could be safely administered by the oral route, induce production of virus-neutralizing antibodies in serum, and protect against subsequent respiratory disease [6,7]. Though approximately 90% effective against ADV-4 ARD disease in military recruits, the vaccine failed to impact overall ARD rates due to the replacement of ADV-4 infections with ADV-7 [5]. Subsequently, a similar ADV-7 vaccine was developed and simultaneous administration of ADV-4 and ADV-7 vaccines was found to be safe, to effectively protect against ARD due to both types, and to dramatically decrease overall ARD rates [8,9]. These vaccines effectively controlled ADV ARD in recruit training camps from the 1970s until 1999 when remaining supplies were exhausted after the manufacturer (Wyeth Labs) ceased production in 1996. The Department of Defense (DoD) did not attempt to secure alternative means of vaccine production and, following the loss of the Wyeth vaccine, ADV ARD promptly returned to pre-vaccine levels, and there have been at least three vaccine-preventable ADV-associated recruit deaths [10,11].

In 2001, the U.S. Army contracted Barr Laboratories (now Teva Pharmaceuticals) to develop and manufacture a replacement ADV vaccine. The replacement vaccine tablets were designed to be virtually identical to their predecessors and were determined to have similar physical (disintegration time; virus quantity) and clinical (dosing; fecal shedding duration; seroconversion rates) properties. A successful initial study of the replacement ADV-4 and 7 vaccine was conducted in 2004, in which this new vaccine was demonstrated to be well tolerated and capable of inducing substantial rates of seroconversion [12]. We now report results of the pivotal phase 3 clinical study, required by the Food and Drug Administration (FDA) for licensure, to characterize the safety profile of the vaccine, the vaccine's efficacy against ADV-associated respiratory disease and its ability to induce adenovirus type-specific serum neutralizing antibodies in volunteers from two U.S. military basic training centers.

2. Methods

2.1. Participants

Healthy men and women were recruited within three days of their arrival at Army and Navy basic training (BT) centers in Ft. Jackson, SC and Naval Station Great Lakes, IL, respectively. Recruitment and enrollment procedures were designed to provide individuals the opportunity to freely determine their willingness to participate or not: training officers or senior enlisted personnel were not present during any of the study enrollment or recruitment activities; at all times during the recruitment and enrollment process, an independent ombudsman who was not affiliated in any way with the research study or the military was present to ensure the voluntary nature of participation was adequately stressed and upheld; finally, vaccination occurred two or three days after enrollment, thereby providing volunteers with additional time to reconsider their decision to participate.

Volunteers provided written informed consent and were then screened to determine eligibility. Participants were eligible if they were emancipated 17-year olds or 18 years and older and agreed to avoid unprotected sexual intercourse for 90 days after vaccination. Exclusion criteria included: pregnancy (a urine pregnancy test was performed within 72 hours prior to vaccination); chronic medical conditions; known allergy to vaccine components; systemic corticosteroid use; and immunosuppression or any immunosuppressed individual or a child less than one year old living at the volunteer's home of record. Volunteers were compensated $50 for each blood draw performed at the four study visits.

2.2. Role of the sponsor and military

Barr Laboratories and military investigators designed the protocol and statistical analysis plan (SAP) following discussions with the U.S. Food and Drug Administration (FDA). The protocol and SAP were approved by institutional review boards of the U.S. Army and Navy and conducted under IND in accordance with the Declaration of Helsinki and guidelines for good clinical practices. An independent data safety monitoring committee monitored adverse events and conducted the interim analysis. Results were analyzed by Barr in accordance with the pre-specified SAP. Additional analyses were conducted by the military investigators. The trial was registered with the U.S. National Institutes of Health clinical trial registry (ClinicalTrials.gov, NCT00382408) prior to its initiation.

2.3. Vaccine and placebo

The vaccine was produced under Good Manufacturing Practice (GMP) guidelines by Barr Laboratories as enteric-coated tablets as previously described [12]. Each tablet was required to contain no less than 32,000 tissue-culture infective doses ($4.5 \log_{10}$ $TCID_{50}$) of lyophilized ADV-4 or 7 prepared from tissue cultures of human diploid fibroblast cells (WI-38). Three lots of ADV-4 ($4.9–5.5 \log_{10}$ $TCID_{50}$) and ADV-7 ($5.2–5.8 \log_{10}$ $TCID_{50}$) tablets were administered throughout the trial. Identical-appearing placebo tablets were prepared that contained sugar (lactose) in place of live adenovirus. Volunteers were directly observed swallowing two intact tablets together (within 15 min) with up to 30 mL of water.

2.4. Randomization

All subjects were randomly assigned in a 3:1 ratio in blocks of 8 to either vaccine or placebo in sequential order and stratified by study site. Study medication was packaged as 2 vaccine tablets (one ADV-4 and one ADV-7) or 2 placebo tablets per bottle. A Barr Pharmaceuticals statistician who was otherwise not associated with this study generated the randomization code for treatment assignments. The randomization code was stored in a secure location within the Barr Regulatory Document Center. Investigators, study personnel, and study participants were blinded to the investigational product assigned.

2.5. Study design

At both study sites, 23 enrollment sessions were held between September 30, 2006 and September 29, 2007 for new recruits who arrived within the three days prior to an enrollment session. Recruits who arrived to initiate training on other days were not eligible for the trial, and only a small percentage of the total recruits undergoing training were enrolled in the study at any time. First, a study staff member verbally described the protocol to potential volunteers. This briefing served as an introduction to the study, describing why and where it was being conducted, the informed consent process, risks and benefits, and other matters pertaining to the study process. Immediately following the briefing, potential volunteers viewed an institutional review board (IRB) approved video that further described details of the trial, the vaccine, and the informed consent process. Written informed consent was obtained from each participant before any study procedure was performed.

The study product (vaccine or placebo) was administered once to each volunteer two or three days after enrollment, concurrently