Vaccine 35 (2017) 1675–1682

Contents lists available at ScienceDirect

Vaccine

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

Safety and immunogenicity of a modified vaccinia Ankara vaccine using three immunization schedules and two modes of delivery: A randomized clinical non-inferiority trial

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ARTICLE INFO

Article history:
Received 29 November 2016
Received in revised form 14 February 2017
Accepted 15 February 2017
Available online 27 February 2017

Keywords:
Smallpox
Vaccinia
Vaccine
Jet injector
PRNT
Hypersensitivity reaction

ABSTRACT

Introduction: To guide the use of modified vaccinia Ankara (MVA) vaccine in response to a release of smallpox virus, the immunogenicity and safety of shorter vaccination intervals, and administration by jet injector (JI), were compared to the standard schedule of administration on Days 1 and 29 by syringe and needle (S&N).

Methods: Healthy adults 18–40 years of age were randomly assigned to receive MVA vaccine subcutaneously by S&N on Days 1 and 29 (standard), Days 1 and 15, or Days 1 and 22, or to receive the vaccine subcutaneously by JI on Days 1 and 29. Blood was collected at four time points after the second vaccination for plaque reduction neutralization test (PRNT) (primary endpoint) and ELISA (secondary endpoint) antibody assays. For each subject, the peak PRNT (or ELISA) titer was defined by the highest PRNT (or ELISA) titer among all available measurements post second vaccination. Non-inferiority of a non-standard arm compared to the standard arm was met if the upper limit of the 98.33% confidence interval of the difference in the mean $\log_2$ peak titers between the standard and non-standard arm was less than 1.

Results: Non-inferiority of the PRNT antibody response was not established for any of the three non-standard study arms. Non-inferiority of the ELISA antibody response was established for the Day 1 and 22 compressed schedule and for administration by JI. Solicited local reactions, such as redness and swelling, tended to be more commonly reported with JI administration. Four post-vaccination hypersensitivity reactions were observed.

Conclusions: Evaluations of the primary endpoint of PRNT antibody responses do not support alternative strategies of administering MVA vaccine by S&N on compressed schedules or administration by JI on the standard schedule.

Trial Registration: clinicaltrials.gov Identifier: NCT01827371.

1. Introduction

Naturally occurring smallpox no longer exists but the threat of smallpox remains because of concerns that variola virus could be

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http://dx.doi.org/10.1016/j.vaccine.2017.02.032
0264-410X/

intentionally released [1,2]. To prepare for such an event the U.S. government has stockpiled three smallpox vaccines, one of which is a modified vaccinia Ankara (MVA) vaccine (IMVAMUNE® [Bavarian Nordic]), a third generation, replication-deficient vaccinia vaccine [3,4]. This MVA vaccine has been safely administered to persons with relative contraindications to receipt of replication-competent smallpox vaccines [5–8] and could potentially be given to such persons in the event of an emergency.

MVA vaccine is administered by subcutaneous (SC) injection in a two dose regimen on Days 1 and 29. In a postevent scenario, a compressed dosing regimen would be desirable if it more rapidly induces comparable protection. A previous study that evaluated a highly compressed schedule of administration on Days 1 and 8 found generally lower plaque reduction neutralization test (PRNT) antibody responses compared with the standard schedule [9]. It is possible that other less compressed schedules may achieve PRNT antibody responses comparable to the standard schedule. This study was designed to evaluate MVA vaccine administration by syringe and needle (S&N) on Days 1 and 15 and Days 1 and 22, to determine if the immune response to those schedules is non-inferior to the standard schedule.

In a mass vaccination situation the option of administration by needle-free jet injector (JI) could be beneficial. This study also assessed the safety and immunogenicity of MVA vaccine given SC on the standard schedule by JI compared to S&N.

2. Methods

2.1. Vaccine and administration

The MVA vaccine was provided as a lyophilized product to be reconstituted with water for injection for a dose of 1×10^8 $TCID_{50}$ per 0.5 mL. A volume of 0.5 mL was injected SC in the deltoid area by S&N or by disposable-syringe JI (the Stratis™ Needle-free Injection System, PharmaJet).

2.2. Study design

In this open-label, phase 2 study subjects were randomly assigned to receive MVA vaccine by S&N on Days 1 and 29 (Arm A), 1 and 22 (Arm B), or 1 and 15 (Arm C), or to receive MVA vaccine by JI on Days 1 and 29 (Arm D). Treatment randomization and statistical analysis was carried out by the Emmes Corporation which served as the statistical and data coordinating center for this study. The randomization sequence was generated based on a block randomization design with a block size of 4. Within a block, subjects were initially randomized to one of the four groups with equal probability. Upon enrollment, each subject was assigned a randomization number from the electronic data entry system that corresponded to a treatment on a randomization list available at the study site. Near the end of the enrollment period, the study was halted due to an immediate hypersensitivity serious adverse event (SAE). When the halt was lifted, 60 subjects who had received a first vaccination were out of the eligible window to receive their second vaccination, and additional subjects were enrolled to replace them per the protocol to ensure that at least 80 evaluable subjects per arm were included in the primary analyses. To maintain treatment balance, incomplete blocks were filled first using the existing treatment allocations followed by the addition of new allocations following the same randomization design. When the replacement subjects were enrolled, the randomization ratio was adjusted to match the number of subjects in each arm that needed to be replaced.

Eligible subjects were healthy, smallpox vaccine naïve adults 18–40 years of age. Complete eligibility criteria are listed on clinicaltrials.gov. Subjects were enrolled at six NIH-sponsored Vaccine and Treatment Evaluation Unit (VTEU) sites in the United States (Group Health, Saint Louis University School of Medicine, Baylor College of Medicine, Emory University, University of Iowa, and University of Maryland School of Medicine). The first subject was enrolled June 17, 2013 and the last follow-up visit occurred April 22, 2015.

After each vaccination subjects recorded oral temperature and solicited local and systemic reactogenicity information on a memory aid from the day of vaccination (Day 1) through Day 15. Safety laboratory assessments were performed on blood samples obtained on Day 15 after each vaccination. Unsolicited adverse events (AEs) were collected from the time of first vaccination through Day 29 after the last vaccination and SAEs were collected from the time of first vaccination until the end of follow-up (6 months after the second vaccination).

2.3. Immunogenicity assays

The PRNT and ELISA antibody assays were performed by Bavarian Nordic as previously described [7] except that the PRNT assay neutralization medium contained 0.1% human serum albumin instead of fetal bovine serum and used an optical density cut off of 0.35 instead of 0.3. The level of detection (LOD) for the PRNT assay was 2 and for the ELISA assay was 50. For each assay, values of ½ the LOD were imputed for results below the LOD. Blood specimens were collected for PRNT and ELISA assays prior to each vaccination and at Days 8, 15, 22, and 29 after the second vaccination.

2.4. Data analysis

2.4.1. Sample size

The sample size of 88 enrolled subjects per study arm was selected to yield 80 evaluable subjects per study arm, assuming a 10% drop out rate. This had at least 80% power to determine whether the geometric mean peak (GMP) PRNT titer for each of Arms B, C, and D was non-inferior to that for Arm A with a margin of 2-fold based on a one-sided test with a Bonferroni-corrected Type I error rate of 0.83%. The sample size calculations were based on immunogenicity data from the previous study of the schedule of MVA vaccine administration [9].

2.4.2. Statistical analysis

The primary safety objective was to compare the occurrence of solicited local reactions in subjects receiving MVA vaccine on the standard schedule by JI (Arm D) compared to S&N (Arm A). For each type of solicited local reactions, severity was defined as "none or mild" or "moderate or severe" based on the most severe response recorded after each vaccination and proportions were compared using a Fisher's Exact test. Secondary and tertiary safety objectives were to assess SAEs and AEs, respectively, in all study arms.

The primary and secondary immunogenicity objectives for the study were to determine if the vaccinia-specific individual peak PRNT (primary objectives) and ELISA (secondary objectives) antibody titers of each investigational arm (Arms B, C, or D) were non-inferior to the control arm (Arm A). For each subject, the peak PRNT (or ELISA) titer was defined by the highest PRNT (or ELISA) titer among all samples collected between Day 8 and Day 32 post-second vaccination. For each investigational arm (Arms B, C, or D), the difference in the mean $\log_2$ GMP titers for the control (A) and investigational arm, and the associated two-sided Bonferroni-corrected 98.33% confidence interval (CI) for that difference, was calculated. If the upper limit of the CI was <1, the tested investigational arm was considered non-inferior to Arm A. The tertiary immunogenicity objective was to characterize and