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Stable emulsion (SE) alone is an effective adjuvant for a recombinant, baculovirus-expressed H5 influenza vaccine in healthy adults: A Phase 2 trial

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ABSTRACT

Background: Influenza A viruses of the H5 subtype have been identified as important targets for development of vaccines. Achievement of potentially protective antibody responses against pandemic strains has usually required the use of adjuvants.
Objectives: We evaluated a candidate A/Indonesia/05/2005 (H5) vaccine generated by baculovirus expression of recombinant hemagglutinin (HA) protein with or without stable emulsion (SE) as an adjuvant.
Methods: Healthy subjects 18–49 years old were randomized (1:1:1:1) to receive two doses of rHA at 7.5 ug per dose (no adjuvant), or 3.8 ug, 7.5 ug, or 15 ug per dose formulated with 2% SE separated by 21 days, and serum from day 0, 21, 42, and 201 assessed by hemagglutination-inhibition.
Results: 341 subjects were enrolled in the study and 321 received two doses of vaccine. Vaccination was well tolerated in all groups. After two doses, seroconversion was noted in only 9% (95% confidence interval 4%, 17%) of recipients of unadjuvanted vaccine at 7.5 ug, but in 70% (59%, 80%), 76% (65%, 85%), and 83% (73%, 91%) of those receiving adjuvanted vaccine at 3.8 ug, 7.5 ug, or 15 ug respectively.
Conclusions: Stable emulsion alone is an effective adjuvant for rH5 vaccine in healthy adults. All three adjuvanted dose groups met the current criterion for seroconversion rate for pandemic vaccines. This dose-ranging study also identified a group (15 ug per dose formulated with 2% SE) that met the criteria for both seroconversion and percentage of subjects achieving an HI antibody titer $\geqslant$ 40. These Phase 2 data support the further clinical development of SE adjuvanted Panblok H5.
Clinical trial registration: NCT01612000.
The protocol was approved by the relevant Institutional Review Board for each study site, and the study was conducted in accordance with the Declaration of Helsinki, International Conference of Harmonisation – Good Clinical Practice, and all applicable laws and regulations. All participants provided written informed consent before study procedures.

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1. Introduction

Preparation for pandemic influenza is a high priority for all public health authorities. The most recent pandemic experience in 2009 demonstrated the potential for a newly emergent pandemic influenza virus to circulate globally within a matter of months. Influenza viruses with a wide variety of hemagglutinin (HA) subtypes currently circulate in waterfowl, swine, and other animals, and multiple episodes of transmission of avian influenza viruses of the H5, H7 and H9 subtypes to humans have been reported. H5 viruses are of particular concern because of continued

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transmission episodes with severe disease in humans [1,2]. The cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO from 2003 to June 16, 2016 was 851 cases with 450 deaths (a ~53% mortality rate). It has also been documented that a relatively small number of mutations in the HA of H5 viruses can result in transmissibility in mammalian models [3,4]. In response to this continued threat, there has been considerable interest in the development of effective vaccines to prevent H5 infection in humans.

Baculovirus expression of recombinant hemagglutinin protein (rHA) is an attractive approach to pandemic vaccine development because of the speed of production and absence of infectious influenza virus in the production method, substantially reducing biosafety concerns. Production can be rapidly scaled up without concerns about the supply of embryonated eggs, and fermentation systems may be less vulnerable to contamination. Previous studies of candidate pandemic rHA vaccines in humans have demonstrated them to be approximately as immunogenic as traditional egg-derived vaccines [5], and to induce long-lasting immune memory [6].

The experience to date with multiple candidate pandemic vaccines, including rHA, has suggested that adjuvants will be required to induce vigorous responses to avian HA subtypes in naïve hosts. In a previous study, we evaluated the immunogenicity, reactogenicity and long-term safety of a recombinant H5 HA (Panblok H5) adjuvanted with a TLR4 agonist, glucopyranosyl-lipid A (GLA), formulated in a 2% stable emulsion (SE). The addition of GLA-SE to the rH5 was well tolerated and substantially improved the serum antibody response [7]. Because the stable emulsion is itself a squalene-based oil-in-water emulsion similar to other oil-in-water emulsions with significant adjuvant activities, we performed the current study to evaluate the ability of 2% SE without GLA to serve as an adjuvant for an rHA H5 vaccine candidate in healthy adults.

2. Materials and methods

2.1. Vaccine

The HA gene of the influenza virus represented in the vaccine, A/Indonesia/05/2005 (H5N1, Clade 2.1.3), was cloned independently into the plasmid baculovirus expression vector pPSC12. The PSC12 plasmid contained the *Autographica californica* Nuclear Polyhedrosis Virus (AcNPV) baculovirus polyhedrin promoter, the baculovirus 61K signal peptide and flanking baculovirus DNA derived from the EcoR1I-I fragment of AcNPV. After confirmation of the correct sequence, the DNA sequence was inserted into AcNPV by homologous recombination. Recombinant viruses containing the hemagglutinin gene were then used to express the HA in the high-yield insect cell line *expres*SF + ® using serum-free cell culture media. The rH5 influenza vaccine was provided by Protein Sciences Corporation (Meriden, CT) in bulk-dose vials containing 300 μg/mL rHA antigen; additional dilution with normal saline and mixture with adjuvant was conducted on site prior to dosing.

Stable oil-in-water emulsion (SE) adjuvant was provided by Infectious Disease Research Institute (Seattle, WA). SE is a stable oil-in water emulsion, where the oil concentration is 2% (v/v) composed of the excipients squalene (oil), glycerol, egg phosphatidylcholine, surfactant (poloxamer) and buffer (ammonium phosphate). Squalene is sourced from sharks, and the phosphatidylcholine is obtained from eggs; the other components are chemically synthesized. The SE emulsion is formulated in a high-pressure homogenizer and filter-sterilized.

Individual doses of vaccine were prepared by mixing vaccine and SE at the time of administration by an unblinded pharmacist or other qualified personnel and provided to an unblinded health care practitioner for administration to the subjects. Subsequent evaluations of reactogenicity and adverse events were performed by personnel blinded to study assignment.

2.2. Study design

The study was conducted as a randomized, observer-blind, multi-center clinical trial in 341 healthy subjects, ages 18–49 who had not previously been immunized against H5 and did not have occupational exposure to poultry. Eligible subjects were randomized (1:1:1:1) into one of 4 groups to receive two doses of either Panblok (H5 rHA) at a dose of 7.5 ug unadjuvanted, or Panblok H5 at doses of 3.8 ug, 7.5 ug, or 15 ug mixed with 2.0% stable emulsion (SE), by intramuscular injection.

Study vaccine was administered on Days 0 and 21 and subjects were observed for immediate adverse events and/or reactogenicity for 30 min following administration of each dose. Subjects recorded specifically solicited systemic and local symptoms as well as any additional adverse events in a diary during the 7 days following each vaccine dose. Other adverse events and medicinal interventions were recorded through Day 42 following vaccination. After Day 42, study subjects were followed on a quarterly (every 3 months) basis by telephone and visit for reports of SAEs, suspected adverse reactions (SARs) (serious or not), New Onset of Chronic Illnesses (NOCIs) or Adverse Events of Special Interest (AESI), and prescription medications used for the treatment of these events during the period extending to one year following the final dose. Adverse Events of Special Interest (AESI) included a list of inflammatory and autoimmune conditions that had been pre-specified for evaluation.

2.3. Serology

Serum samples were obtained for hemagglutination-inhibition (HAI) titers at baseline on Day 0 prior to first vaccine dose administration, on Day 21 (prior to dose 2), on Day 42 (21 days after dose 2) and on the final clinic visit Day 201 (6 months post dose 2).

Serum HAI antibody titers to A/Indonesia/05/2005 were determined in serum samples assayed from Days 0, 21 and 42 for the 313 subjects for whom data were available and who had no major protocol deviations (Modified Per Protocol Population). HAI antibody testing was carried out by Southern Research Institute (Birmingham, AL) using an assay that employed a whole virus antigen derived from influenza A/Indonesia/05/05 on the PR8 background (generously supplied by the Centers for Disease Control and Prevention) and horse red blood cells (Lampire Biologicals, Pipersville, PA). Serum samples were treated with receptor-destroying enzyme (Denka Seiken, Tokyo, Japan) to remove non-specific inhibitors of hemagglutination. Sera were tested at an initial dilution of 1:10, with subsequent two-fold serial dilutions. The assays were performed as described by Noah et al. [8].

2.4. Statistical analysis

The primary endpoint of the study was the seroconversion rate on Day 42. Seroconversion was defined according to Food and Drug Administration Center for Biologics Evaluation and Research (CBER) criteria as either a pre-immunization HAI titer <10 and a post immunization HAI titer $\geqslant$40 or a pre-immunization HAI titer $\geqslant$10 and a minimum four-fold rise in post-immunization HAI antibody titer [9]. The seroconversion rate in the Panblok 7.5 μg + SE treatment group was compared first to that in the unadjuvanted Panblok 7.5 μg treatment group using Fisher's Exact Test at a two-sided p-level of 0.05. In addition, 95% confidence limits on the difference of the percentages were calculated using exact procedures. Using a step-down procedure to avoid adjustment for

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