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Evaluation of a primary course of H9N2 vaccine with or without AS03 adjuvant in adults: A phase I/II randomized trial

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ABSTRACT

Background: Avian influenza A H9N2 strains have pandemic potential.
Methods: In this randomized, observer-blind study (ClinicalTrials.gov: NCT01659086), 420 healthy adults, 18–64 years of age, received 1 of 10 H9N2 inactivated split-virus vaccination regimens (30 participants per group), or saline placebo (120 participants). H9N2 groups received 2 doses (days 0, 21) of 15 μg hemagglutinin (HA) without adjuvant, or 1.9 μg HA + $AS03_A$, 1.9 μg HA + $AS03_B$, 3.75 μg HA + $AS03_A$, or 3.75 μg HA + $AS03_B$; followed by the same H9N2 formulation or placebo (day 182). AS03 is an adjuvant system containing α-tocopherol ($AS03_A$: 11.86 mg; $AS03_B$: 5.93 mg) and squalene in an oil-in-water emulsion. Immunogenicity (hemagglutination inhibition [HI] and microneutralization assays) and safety were assessed up to day 546.
Results: All adjuvanted formulations exceeded regulatory immunogenicity criteria at days 21 and 42 (HI assay), with seroprotection and seroconversion rates of ≥94.9% and ≥89.8% at day 21, and 100% and ≥98.1% at day 42. Immunogenicity criteria were also met for unadjuvanted vaccine, with lower geometric mean titers. In groups administered a third vaccine dose (day 182), an anamnestic immune response was elicited with robust increases in HI and microneutralization titers. Injection site pain was reported more frequently with adjuvanted vaccines. No vaccine-related serious adverse events were observed.
Conclusions: All H9N2 vaccine formulations were immunogenic with a clinically acceptable safety profile; adjuvanted formulations were 4–8 times dose-sparing (3.75–1.9 vs 15 μg HA).
Trial registration: Registered on ClinicalTrials.gov: NCT01659086.

1. Introduction

Influenza pandemics occur when a novel influenza virus emerges and the majority of the human population has no immunity. While H9N2 viruses have been mildly pathogenic avian influenza viruses with limited incidence and severity in humans [1]. For example, there was one human H9N2 influenza case reported in 2016, in a 7-month-old girl in China, who developed mild disease after visiting a live poultry market and recovered without the need for hospitalization [2]. However, H9N2 viruses have the potential to evolve into highly pathogenic pandemic viruses [3].

Abbreviations: AE, adverse event; AESI, adverse event of specific interest; AS, adjuvant system; CBER, Center for Biologics Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; EMA, European Medicines Agency; GMT, geometric mean titer; HA, hemagglutinin; HI, hemagglutination inhibition; LL, lower limit; MAE, medically-attended adverse event; MGI, mean geometric increase; MN, microneutralization; pIMD, potential immune-mediated disease; PP, per-protocol; SAE, serious adverse event; SCR, seroconversion rate; SPR, seroprotection rate; UL, upper limit; US, United States; VRR, vaccine response rate; VVP, groups receiving 2 vaccine doses + placebo; VVV, groups receiving 3 vaccine doses.

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Vaccine development against potential pandemic subtypes is a key strategy for pandemic preparedness. Multiple clades of H9N2 viruses have been identified, most of which belong to either the G1-like lineage (e.g. A/quail/Hong Kong/G1/1997) or the Y280-like lineage (e.g. A/chicken/Hong Kong/G9/1997) [4]. Several H9N2 candidate vaccines have been developed [5–11]. However, as manufacturing facilities may be overwhelmed by demand during a pandemic, antigen-sparing through adjuvantation becomes an important strategy for faster and broader pandemic vaccination response [12].

We evaluated different regimens of monovalent split-virus Y280-like influenza A/chicken/Hong Kong/G9/1997 (H9N2) vaccine with or without adjuvant system AS03 in adults 18–64 years of age. We also assessed the quality of 2-dose priming by evaluating the immune response elicited by a third dose administered at day 182.

2. Methodology

2.1. Study design and participants

This phase I/II, observer-blind, randomized, placebo-controlled study was conducted in 3 centers in the United States (US) and 1 in Canada, between August 2012 and March 2014. The study was conducted in accordance with Good Clinical Practice guidelines, Declaration of Helsinki and local regulations. All study-related documents were approved by an independent ethics committee or institutional review board. Written informed consent was obtained from each participant before study participation. The study has been registered at www.clinicaltrials.gov (NCT01659086). A study protocol summary is available at www.gsk-clinicalstudyregister.com (Study ID 116358). Periodic reviews of clinical safety data were performed by an internal Safety Review Committee.

2.2. Eligibility criteria

Healthy persons 18–64 years of age (inclusive) at the time of first study vaccination, weighing ≥49.9 kg, were enrolled if the investigator determined that they would comply with the study protocol (detailed exclusion criteria: online supplement). Women of childbearing potential had to practice adequate contraception from 30 days pre-vaccination to 2 months post-dose 3, and have a negative pregnancy test on the days of vaccination.

2.3. Study vaccine

The inactivated split-virus vaccine formulations (GSK Vaccines, Quebec, Canada) contained 1.9 or 3.75 μg HA of A/chicken/Hong Kong/G9/1997 NIBRG-91 virus strain adjuvanted with $AS03_A$ or $AS03_B$, or 15 μg unadjuvanted HA. AS03 is an adjuvant system containing α-tocopherol ($AS03_A$: 11.86 mg; $AS03_B$: 5.93 mg) and squalene in an oil-in-water emulsion. Placebo control was saline. Vaccines or placebo were administered intramuscularly into the deltoid region. Volumes administered per dose differed among formulations (1.9 μg HA + $AS03_A$: 0.375 μL; 3.75 μg HA + $AS03_A$, 3.75 μg HA + $AS03_B$, and placebo: 0.5 mL; 1.9 μg HA + $AS03_B$: 0.25 mL; 15 μg HA: 1 mL).

2.4. Randomization and blinding

Participants were randomized to 1 of 10 vaccine groups or control group (Table 1). Vaccine groups received 2 doses (days 0, 21) of 1.9 μg HA + $AS03_A$, 1.9 μg HA + $AS03_B$, 3.75 μg HA + $AS03_A$, 3.75 μg HA + $AS03_B$, or 15 μg HA unadjuvanted antigen, followed by a third dose of the same formulation (VVV groups) or saline placebo (VVP groups) on day 182. The control group received 3 doses of saline.

Treatment allocation at investigator sites was performed using an internet-based randomization system that used a minimization procedure accounting for center, age groups (18–40; 41–64 years), and receipt of influenza vaccine (seasonal and/or H1N1 pandemic) in the previous 3 influenza seasons (yes/no).

The study was conducted in an observer-blind manner; vaccine and placebo preparation and administration were done by personnel not participating in any clinical evaluations. Participants, those responsible for evaluation of study endpoints and the sponsor were unaware of treatment assignments.

2.5. Objectives

Co-primary objectives were to assess whether the adjuvanted formulations induced an immune response to vaccine-homologous virus that met US Food and Drug Administration Center for Biologics Evaluation and Research (CBER) and European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guidance targets, 21 days after the first and second dose.

Secondary objectives included evaluation of AS03 adjuvant effect on immunogenicity; assessment of CBER/CHMP criteria for the unadjuvanted formulation; hemagglutination inhibition (HI) antibody response up to day 546; microneutralization (MN) titers; and reactogenicity and safety.

2.6. Immunogenicity assessment

Venous blood samples were collected on days 0, 7, 21, 28, 42, 182, 191, 385 and 546. Immunogenicity against A/chicken/Hong Kong/G9/1997 (H9N2)-like influenza virus was assessed for each of these time points using an HI assay and for days 0, 21, 42, 182 and 191 using a MN assay (further details can be found in the online supplement), performed by Viroclinics Biosciences B.V. Assay cut-offs were 10 for HI and 28 for MN (reciprocal of initial serum dilution).

The following parameters were derived from the HI assay: seropositivity rate, seroprotection rate (SPR), geometric mean titer (GMT), seroconversion rate (SCR), and mean geometric increase (MGI). Participants were considered seropositive if they had an antibody titer above or equal to the assay cut-off. SPR was defined as proportion of participants with reciprocal HI titers ≥ 40 post-vaccination. GMTs were calculated by taking the anti-log of the mean of the log (base 10) transformed reciprocal titers; titers below assay cut-off were given an arbitrary value of half the cut-off. SCR was defined as proportion of participants with either reciprocal HI titer <10 pre-vaccination and ≥40 post-vaccination, or pre-vaccination reciprocal titer ≥10 and ≥4-fold increase post-vaccination; 'pre-vaccination' was day 0 for dose 1 and 2 assessments, and day 182 for dose 3 assessments. MGI was defined as geometric mean of within-subject ratios of post-vaccination to pre-vaccination (day 0) reciprocal HI titer for dose 1 and 2, or post- to pre-dose 3 reciprocal HI titer.

For the MN assay, derived parameters were seropositivity rate, GMT, and vaccine response rate (VRR; proportion of vaccinees with post-vaccination reciprocal titer ≥4-fold higher than pre-vaccination, with 'pre-vaccination' being day 0 for dose 1 and 2 assessments, and day 182 for dose 3 assessments). For MN GMT and VRR calculations, seronegative participants were assigned reciprocal titers of 14 (half the minimal reciprocal titer detectable).

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