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Safety and immunogenicity of an AS03-adjuvanted A(H1N1)pmd09 vaccine administered simultaneously or sequentially with a seasonal trivalent vaccine in adults 61 years or older: Data from two multicentre randomised trials

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ABSTRACT

During the 2009–2010 Northern Hemisphere influenza season, both seasonal and pandemic influenza vaccines were expected to be administered to elderly people, which is an important target group for influenza vaccination. Two multicentre randomised clinical studies were conducted in participants aged ≥61 years to assess the immunogenicity and reactogenicity following vaccination with two doses of an AS03-adjuvanted A(H1N1)pmd09 vaccine when either sequentially administered (21 days before first dose [*N* = 73] or 21 days after second dose [*N* = 72]) or co-administered (first dose [*N* = 84] or second dose [*N* = 84]) with a licensed trivalent seasonal influenza vaccine (TIV). Overall, 313 participants from 2 centres in Sweden (ClinicalTrials.gov, NCT00968890) and 6 centres in Germany (NCT00971425) were randomised to one of the four treatment groups. The AS03-adjuvanted A(H1N1)pmd09 vaccine elicited a good immune response against A(H1N1)pmd09-like virus in all treatment groups after the first and second dose, meeting and exceeding the European licensing criteria for pandemic influenza vaccines. After one dose of the AS03-adjuvanted A(H1N1)pmd09 vaccine, haemagglutination inhibition seroconversion rates ranged from 85% (95% confidence interval: 74–93%) to 93% (85–97%), seroprotection rates from 87% (76–94%) to 96% (90–99%) and geometric mean fold rise from 15 (11–19) to 20 (16–25). The haemagglutination inhibition immune responses to the AS03-adjuvanted A(H1N1)pmd09 vaccine seemed lower when TIV was administered 3 weeks before, while immune responses to TIV seemed not affected by either vaccination schedule. Solicited symptoms were more frequently reported following administration of the AS03-adjuvanted A(H1N1)pmd09 vaccine compared to TIV, but these were mainly mild to moderate in intensity and transient in the four treatment groups. These results suggest that sequential or co-administration of the AS03-adjuvanted A(H1N1)pmd09 vaccine and TIV induced a good immune response to both vaccines and had a clinically acceptable safety profile in people aged ≥61 years.

1. Introduction

The identification of patients with human-to-human transmission of the swine-origin A(H1N1)pmd09 influenza virus resulted in the announcement of Pandemic Alert by the World Health Organization in 2009 [1–5]. The lack of similarity between the pandemic and seasonal circulating influenza viruses resulted in large-scale vaccination programmes. Compared to previous seasonal influenza seasons, risks of hospitalization and death were increased in children and young adults, while they were lower in elderly people. Underlying mechanisms explaining the relative protection of older people included pre-existing immunity following exposure to antigenically similar pre-1950s influenza A viruses and prior vaccination during the 1976 pandemic influenza for US citizens [6–8]. Although other groups were at increased risk during the

Abbreviations: AE, adverse event; AS03, oil-in-water emulsion based adjuvant system; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titre; GSK, GlaxoSmithKline; HA, haemagglutinin antigen; HI, haemagglutination inhibition; PPI, per-protocol cohort for immunogenicity; SAE, serious adverse event; SCR, seroconversion rate; SPR, seroprotection rate; TIV, trivalent seasonal influenza vaccine; TVC, total vaccinated cohort.

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pandemic, the highest mortality rate was in older people [9,10]. They were also an important target group for vaccination with both seasonal and pandemic vaccines for the 2009–2010 Northern Hemisphere influenza season.

GlaxoSmithKline (GSK) Vaccines' trivalent seasonal vaccine (TIV) and AS03-adjuvanted A(H1N1)pmd09 vaccine were shown to induce good immune responses in adults and elderly people [11–13]. Their concomitant administration could simplify immunization schedules assuming no negative interferences are found. Sequential administration was another alternative if the safety and immunogenicity profiles of either vaccine were shown not to be altered. In a previous study, priming with AS03-adjuvanted H5N1 influenza vaccines and unadjuvanted influenza vaccines were shown to respectively enhance and reduce immune responses to subsequent vaccination with an heterologous influenza vaccine [14]. The present study was designed to assess whether sequential or co-administration of the AS03-adjuvanted A(H1N1)pmd09 vaccine and TIV was immunogenic and safe in participants aged ≥61 years.

2. Materials and methods

2.1. Study design

Two randomised studies were conducted in 2 Swedish centres from September 2009 until September 2010 (Co-administration study: COA) and 6 German centres from September 2009 until October 2010 (Sequential administration study: SEQ). In COA (ClinicalTrials.gov: NCT00968890), participants were randomised to 2 parallel groups (1:1, co-administration groups 1 and 2: COA1 and COA2) (Fig. 1) using a central internet randomisation system. The study was partially blinded: AS03-adjuvanted A(H1N1)pmd09 vaccines were administered open-label, while TIV and placebo vaccines were blinded. In COA1, TIV was co-administered with the AS03-adjuvanted A(H1N1)pmd09 vaccine on Day 0 and the placebo vaccine on Day 21 (Fig. 2). In COA2, the placebo vaccine was co-administered with the AS03-adjuvanted A(H1N1)pmd09 vaccine on Day 0 and TIV on Day 21.

In SEQ (NCT00971425), participants were randomised to 2 parallel groups (1:1, sequential administration groups 1 and 2: SEQ1 and SEQ2) using a central internet randomisation system. In SEQ1, TIV was administered 21 days prior (Day-21) to the first AS03-adjuvanted A(H1N1)pmd09 vaccine dose (Day 0) and the placebo vaccine 21 days after (Day 42) the second AS03-adjuvanted A(H1N1)pmd09 vaccine dose (Day 21). In SEQ2, the placebo vaccine was administered on Day-21, the AS03-adjuvanted A(H1N1)pmd09 vaccine on Days 0 and 21, and TIV on Day 42 (Fig. 2).

Vaccines were administered intramuscularly in the deltoid region of the non-dominant (AS03-adjuvanted A(H1N1)pmd09 vaccine) or dominant (TIV/placebo) arm. The laboratory in charge of the immunogenicity testing was blinded to the treatment. The studies were conducted in accordance with the ICH principles of Good Clinical Practice and the Declaration of Helsinki. All study-related documents were approved by an independent/local ethics committee(s). A summary of each study protocol is available at www.gsk-clinicalstudyregister.com (GSK study ID: 113525/113572 COA/SEQ).

2.2. Study objectives

The primary objective of these studies was to assess in participants aged ≥61 years whether the HI (haemagglutination inhibition) immune responses to the AS03-adjuvanted A(H1N1)pmd09 vaccine met or exceeded all the CHMP (Committee for Medicinal Products for Human Use) guidance targets for pandemic influenza vaccines [15] in terms of SCR (seroconversion rate), SPR (seroprotection rate) and GMFR (geometric mean fold rise) at Day 42. In COA, a co-primary objective was to assess whether the HI immune responses to TIV met or exceeded at least one of the CHMP guidance targets for seasonal influenza vaccines [16] at 21 days post-vaccination.

Secondary objectives were to evaluate the HI immune responses to the AS03-adjuvanted A(H1N1)pmd09 vaccine up to Day 364 and to TIV up to 21 days post-vaccination and the safety and reactogenicity of both vaccines. In COA, a secondary objective was to evaluate the persistence of the HI immune response to TIV up to Day 364. In SEQ, an exploratory objective was to describe the immune response to the AS03-adjuvanted A(H1N1)pmd09 vaccine in terms of neutralising antibodies.

2.3. Study participants

Participants were male or female aged ≥61 years at the time of the first vaccination, who the investigator believed would comply with the protocol requirements. Written informed consent was obtained from each participant. Exclusion criteria included: previous administration of either of the study vaccines or administration of any vaccine within 30 days before first vaccination, use of an investigational or non-registered product, confirmed or suspected immunosuppression, receipt of immunoglobulins or blood products within 3 months preceding the study, and known or suspected allergy to any constituent of the vaccines.

2.4. Study vaccines

Both vaccines were developed and manufactured by GSK Vaccines. The AS03-adjuvanted A(H1N1)pmd09 vaccine (*Pandemrix*™) was a monovalent split-virus vaccine containing 3.75 μg of haemagglutinin antigen (HA) per dose of A/California/7/2009(H1N1) NYMC X-179A strain and $AS03_A$ adjuvant. $AS03_A$ is an oil-in-water emulsion based adjuvant system containing 11.86 mg tocopherol per dose. The antigen and the adjuvant were separate in multidose vials and mixed prior to administration. The trivalent inactivated split-virion influenza vaccine (*Fluarix*™) contained 45 μg of HA from three influenza strains (15 μg each): A/Brisbane/59/2007(H1N1) IVR-148, A/Uruguay/716/2007(H3N2) NYMCX-175C and B/Brisbane/60/2008(B).

2.5. Immunogenicity assessment

Serum antibody levels to vaccine antigens were assessed in a validated microtitre HI assay using chicken red blood cells. All HI assays were performed by GSK Vaccines laboratories using standardised, validated procedures with adequate controls as previously described [17]. The seropositivity-rate was defined as the percentage of participants with a titre ≥1:10; SCR as the percentage of vaccinees with a titre ≥1:40 for initially seronegative participants, or at least a four-fold increase in post-vaccination titre compared to pre-vaccination titre in initially seropositive participants; SPR as the percentage of vaccinees with a titre ≥1:40, a level accepted as indicating protection; and GMFR as the geometric mean of the within-subject ratios of post-vaccination reciprocal titre to pre-vaccination reciprocal titre. Assessment of HI immune response to the vaccines was based on the European Medicines Agency (CHMP) guidance targets for influenza vaccines [15,16]. The CHMP criteria for pandemic influenza vaccines in participants aged ≥60 years are fulfilled if the point estimate for SCR is >30%, SPR is >60% and GMFR is >2.0. The CHMP criteria for TIV are met if the point estimate for SCR is >30% or SPR >60% or GMFR >2.0.