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Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and 4vHPV vaccine administered according to two- or three-dose schedules in girls aged 9–14 years: Results to month 36 from a randomized trial

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ABSTRACT

This observer-blind study (clinicaltrials.gov NCT01462357) compared the immunogenicity and safety of two doses (2D) of the HPV-16/18 AS04-adjuvanted vaccine (2D of AS04-HPV-16/18) vs. two or three doses of the 4vHPV vaccine [2D or 3D of 4vHPV] in 1075 healthy girls aged 9–14 years. Girls were randomized (1:1:1) to receive 2D of AS04-HPV-16/18 at months (M) 0, 6 (N = 359), 2D of 4vHPV at M0, 6 (N = 358) or 3D of 4vHPV at M0, 2, 6 (N = 358). 351, 339 and 346 girls, respectively, returned for the concluding visit at M36. Superiority was demonstrated at M7 and M12; comparison of the immune response to both vaccine antigens was made between 2D of AS04-HPV-16/18 and 2D or 3D of 4vHPV at subsequent time points in the according-to-protocol immunogenicity cohort (ATP-I; N = 958 at M36) and the total vaccinated cohort (TVC: N = 1036 at M36). HPV-16/18-specific T-cell- and B-cell-mediated immune responses and safety were also investigated. At M36, anti-HPV-16/18 ELISA responses in the 2D AS04-HPV-16/18 group remained superior to those of the 2D and 3D 4vHPV groups. In the M36 TVC, geometric mean titers were 2.78-fold (HPV-16) and 6.84-fold (HPV-18) higher for 2D of AS04-HPV-16/18 vs. 2D of 4vHPV and 2.3-fold (HPV-16) and 4.14-fold (HPV-18) higher vs. 3D of 4vHPV. Results were confirmed by vaccine pseudovirion-based neutralisation assay. Numbers of circulating $CD4^+$ T cells and B cells appeared similar across groups. Safety was in line with the known safety profiles of both vaccines. In con-

Abbreviations: 2D, 2-dose; 3D, 3-dose; AAHS, aluminum hydroxyphosphate sulphate; AE, adverse event; ANOVA, analysis of variance; AS04, Adjuvant System containing 50 μg 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL) adsorbed on aluminum salt (500 μg Al^{3+}); ATP, according-to-protocol; CI, confidence interval; CMI, cell-mediated immunity; ED_{50}, effective dose producing 50% response; ELISA, enzyme-linked immunosorbent assay; EU, ELISA unit; GMR, geometric mean titer ratio; GMT, geometric mean antibody titer; HPV, human papillomavirus; AS04-HPV-16/18, HPV-16/18 AS04-adjuvanted vaccine; 4vHPV, HPV6/11/16/18 vaccine; IFNγ, interferon-gamma; IL, Interleukin; M, month(s); IgG, immunoglobulin G; PBMC, peripheral blood mononuclear cells; PBNA, pseudovirion-based neutralisation assay; pIMD, potential immune-mediated disease; SAE, serious adverse event; TNFα, tumor necrosis factor alpha; TVC, total vaccinated cohort; VLP, virus-like particle; y, year(s).

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clusion, superior HPV-16/18 antibody responses were elicited by 2D of the AS04-HPV-16/18 compared with 2D or 3D of the 4vHPV vaccine in girls aged 9–14 years.

Clinical Trial Registration: NCT0146235.

1. Introduction

Today's estimates suggest that over 500,000 women are diagnosed with cervical cancer every year(y) and more than 260,000 die from the disease [1]. Cervical cancer is one of the most frequent cancers in women throughout the World [1,2]. Human papillomavirus (HPV)-16 and HPV-18 are responsible for approximately 70% of cervical cancer cases [3–7].

HPV vaccination began in 2006/2007 [8–10] when the first two HPV vaccines, the HPV-16/18 AS04-adjuvanted (AS04-HPV-16/18) vaccine (*Cervarix*, GSK) and the HPV6/11/16/18 (4vHPV) vaccine (*Gardasil*, Merck & Co., Inc.) were licensed for the prevention of cervical cancer and high-grade precursor lesions. Both vaccines contain L1 virus-like particles (VLPs) from the two oncogenic HPV types most prevalent in cervical cancer, i.e. HPV-16 and HPV-18 [1]. The main differences in the composition of both vaccines are the inclusion of HPV-6 and -11 L1 VLPs in the 4vHPV vaccine and the AS04 adjuvantation in the HPV-16/18 vaccine. In addition, the VLPs are manufactured by different methods [1]. More recently, a nonvalent vaccine was licensed using the same HPV-6, -11, -16 and -18 antigens as the four-valent vaccine and VLPs for 5 additional oncogenic HPV types (*Gardasil 9*, Merck & Co. Inc).

The initially licensed schedule for the HPV vaccines comprised 3 doses administered at months (M) 0, 1 or 2, and 6 [7–13]. However, high vaccine coverage and compliance rates proved to be difficult to achieve with a 3-dose (3D) regimen. The high immune response to the AS04-HPV-16/18 vaccine observed in the adolescent population 9-14y of age led to the investigation and eventually to registration of 2-dose schedules (2D) in this age group in most countries [14,15]. WHO started recommending a 2D in young girls from 2014 [16].

The mechanism of protection against mucosal infection is essentially thought to be antibody-mediated. Superiority in terms of neutralizing antibody titers after vaccination with Cervarix compared to Gardasil was previously demonstrated in adult women with the standard 3D schedule [17–21]. Higher anti-HPV antibody titers have the potential to elicit a longer duration of protection. The comparison of the immunogenicity elicited by the reduced schedule of Cervarix compared to both 2D and 3D of Gardasil vaccines was therefore warranted in the HPV naïve population targeted by mass vaccination programs where the duration of protection is of paramount importance.

This study was thus designed to assess immunogenicity and safety of a 2D schedule of the AS04-HPV-16/18 vaccine vs. 2D and 3D of the 4vHPV vaccine in girls aged 9-14y.

2. Material and methods

2.1. Study design and ethics

The study was observer-blind, randomized and age-stratified with three parallel groups (Fig. 1) conducted at 21 sites in France, Hong Kong, Singapore and Sweden (November 2011 to October 2015). The trial is registered with ClinicalTrials.gov (NCT01462357) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Protocol is summarized at www.gsk-clinicalstudyregister.com (GSK Study Identifier 115411).

The primary objective was to evaluate if immunogenicity to HPV-16 and -18, as measured by enzyme-linked immunosorbent assay (ELISA), of a 2D AS04-HPV-16/18 vaccine was non-inferior/superior to a 2D 4vHPV vaccine 1 M after the last vaccine dose (M7). Secondary objectives included evaluation of the non-inferiority/superiority of 2D AS04-HPV-16/18 vs. 2D and 3D 4vHPV at all subsequent time points until study conclusion (M36). Other secondary immunogenicity objectives included assessment of HPV-16/-18 neutralizing antibodies (by pseudovirion-based neutralisation assay (PBNA)) and frequencies of specific memory B and T cells. Safety was also evaluated.

2.2. Study participants

Healthy girls aged 9-14y were eligible to participate as per the protocol requirements. Informed consent was obtained from subjects and their parents or legal guardians.

2.3. Vaccines, randomization and masking

Enrolment was stratified by age (approximately 50% aged 9-11y and 50% aged 12-14y), and girls were randomized (1:1:1 ratio in each age stratum) to receive either 2D AS04-HPV-16/18 (at M0,6, 2D HPV-6/11/16/18 at M0,6 or 3D HPV-6/11/16/18 at M0,2,6, in the deltoid muscle of the non-dominant arm. Compositions of both vaccines have been described previously [1]. Batch numbers of vaccine lots were AHPVA144B, AHPVA133C, AHPVA133E, AHPVA151C, AHPVA133A and AHPVA184C for AS04-HPV-16/18; NP39130, and H006966 for 4vHPV; and PHPVA012A for placebo vaccine.

The study was observer-blind. Girls from the 2D groups received placebo [Al $(OH)_3$] at M2 to maintain the blinding. The randomization code was generated using *MATEX*, a program developed for use in *SAS* (Cary, NC, USA), by GSK, Belgium.

In pre-selected sites, the first 50 subjects from each age stratum in each group (300) were assigned to the cell-mediated immunity (CMI) sub-cohort for measurement of circulating HPV-specific B- and T-lymphocytes. The same subjects were included in the PBNA subset.

2.4. Immunogenicity assessments

Blood was sampled at M0 (pre-vaccination) and at M7, 12, 18, 24 and 36 for the measurement of HPV-16/-18 antibodies by ELISA and PBNA in a subset. An additional blood sample was taken from girls assigned to the subset.

Anti-HPV-16/-18 antibodies were determined by ELISA using the purified type-specific recombinant VLPs present in the AS04-HPV-16/18 vaccine as coating antigen [7,22]. Seronegativity corresponded to a titer lower than assay cut-off (19 ELISA units [EU]/mL for anti-HPV-16 and 18 EU/mL for anti-HPV-18). Neutralizing HPV-16/-18 antibodies were determined by PBNA [1,23]. Pseudovirions were produced independent of vaccine constructs as described previously [22]. In this procedure, assay cut-off is 40 ED_{50} (effective dose producing 50% response, for each antigen).

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