Safety and Immunogenicity of the HPV-16/18 AS04-Adjuvanted Vaccine: A Randomized, Controlled Trial in Adolescent Girls

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Abstract

Purpose: Immunization of girls against oncogenic human papillomavirus (HPV) types before sexual debut is important for cervical cancer prevention. This phase III blinded, randomized, controlled trial in adolescent girls assessed safety of the HPV-16/18 AS04-adjuvanted vaccine.

Methods: Girls (mean age 12 years) in 12 countries received the HPV-16/18 L1 virus-like particle AS04-adjuvanted vaccine (N = 1,035) or hepatitis A virus vaccine as control (N = 1,032) at 0, 1, and 6 months. The primary objective was to compare the occurrence of serious adverse events (SAEs) between groups. HPV-16 and HPV-18 antibody titers were assessed by enzyme-linked immunosorbent assay post-vaccination.

Results: Up to study month 7, 11 girls in the HPV-16/18 vaccine group reported 14 SAEs and 13 girls in the control group reported 15 SAEs. The difference in SAE incidence between groups was .20% (95% CI, -.78, 1.20). No SAE in the HPV-16/18 vaccine group was considered related to vaccination or led to withdrawal. The incidence of solicited local and general symptoms up to 7 days post-vaccination was moderately higher with the HPV-16/18 vaccine than with control. The incidence of unsolicited symptoms, new onset of chronic diseases, and medically significant conditions was similar between groups. All girls seroconverted for both antigens after three doses of the HPV-16/18 vaccine; geometric mean titers were 19,882.0 and 8,262.0 EU/mL for anti-HPV-16 and -18 antibodies, respectively, in initially seronegative girls.

Conclusions: The HPV-16/18 AS04-adjuvanted vaccine was generally well tolerated and immunogenic when administered to young adolescent females, the primary target of organized vaccination programs. © 2010 Society for Adolescent Medicine. All rights reserved.

Keywords: Human papillomavirus; Vaccine; Cervical cancer; Adolescent; Girls; Safety; Immunogenicity

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Human papillomavirus (HPV) infection has been well established as the necessary cause of cervical cancer [1], the second most common cancer in women worldwide [2]. Fifteen oncogenic HPV types have been identified [3]; infection with types HPV-16 and HPV-18 is associated with approximately 70% of cervical cancer cases [4].

Many countries are currently implementing vaccination programs aimed mainly at young adolescent girls. Infection with HPV is frequently detected in sexually active adolescent girls [5, 6], and often occurs shortly after sexual debut [7]. Sexual debut at a very young age is a risk factor for cervical cancer development, suggesting that adolescents may be more vulnerable to establishment of persistent HPV infections than adult women [6]. These findings underline the importance of vaccinating prior to first intercourse.

An extensive clinical program of the HPV-16/18 AS04-adjuvanted vaccine has shown that it offers sustained protection against HPV-16/18 infection and associated cytohistological lesions in women aged 15–25 years [8–12]. Higher antibody levels have been obtained in adolescent girls than in young women [13]. A pooled analysis of 11 studies in more than 16,000 girls and women who received the HPV-16/18 vaccine demonstrated that the vaccine is well tolerated with a favorable safety profile in participants of all ages [14]. An integrated analysis evaluating safety in more than 68,000 participants demonstrated no evidence of an increase in the relative risk of autoimmune disorders associated with AS04-adjuvanted vaccines, including the HPV-16/18 vaccine [15].

Safety analyses from mass vaccination programs mainly conducted in young adolescent girls are becoming available, but do not benefit from inclusion of a control group. The present phase III, randomized, controlled study was conducted to evaluate the safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in a large group of adolescent girls.

Methods

Study participants and ethics

The study (NCT00196924) took place between June 2004 and August 2005 in 57 centers located in Australia, Colombia, the Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden, and Taiwan.

Prospective participants were healthy girls, aged 10–14 years. Girls were excluded if they had immunodeficiency, history of allergic disease likely to be exacerbated by a vaccine component, known acute or chronic clinically significant neurologic, hepatic, or renal functional abnormality, history of chronic conditions requiring treatment, or acute disease at enrollment. Girls were not excluded on the basis of HPV status, Pap smear history, or history of sexual activity.

The study was conducted in accordance with the Declaration of Helsinki (1996) and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol and informed consent and assent forms were approved by the Independent Ethics Committee or Institutional Review Board of each study center. Written informed assent and consent were obtained from each girl and her parent or guardian.

Study objectives

The primary objective was to compare the occurrence of serious adverse events (SAEs) between the HPV-16/18 vaccine group and the control group up to month 7. Secondary objectives included evaluation of solicited local and general adverse events (AEs), unsolicited AEs, new onset of chronic diseases (NOCD), and medically significant conditions (MSC). Antibody responses and geometric mean titers (GMT) against HPV-16 and HPV-18 were evaluated in the vaccine group and compared with responses from young women enrolled in a separate study which has demonstrated protection against cytohistological lesions associated with HPV infection [8, 9, 12].

Study design and vaccines

This was a phase III, observer-blind, multicenter, randomized, parallel group, controlled study. There were five study visits at months 0, 1, 2, 6, and 7 (active phase of the study), with a follow-up telephone call at month 12. Girls were randomized 1:1 to receive either HPV-16/18 vaccine (GlaxoSmithKline Biologicals) or control vaccine (hepatitis A virus [HAV] vaccine; GlaxoSmithKline Biologicals) in a 0-, 1-, 6-month schedule. The randomization algorithm accounted for center and age strata (10–11 years and 12–13 years). Because of differences in vaccines appearance, study staff who administered them were not otherwise involved in study conduct; subjects and staff involved in assessment remained blinded.

Each dose of the HPV-16/18 vaccine consisted of 20 μg each of HPV-16 and HPV-18 L1 proteins, self-assembled as virus-like particles (VLP), adjuvanted with the Adjuvant System AS04 (comprising 500 μg of aluminum hydroxide and 50 μg of the immunostimulatory molecule, 3-O-desacyl-4’-monophosphoryl lipid A). Each dose of HAV control vaccine contained 360 enzyme-linked immunosorbent assay (ELISA) units (EU) inactivated HAV antigen and 250 μg aluminum as aluminum hydroxide. Both vaccines were supplied in individual 0.5 mL prefilled syringes to be administered intramuscularly into the deltoid muscle of the non-dominant arm.

Study endpoints and procedures

Safety. Participants reported solicited local and general symptoms (pain, redness, swelling, fever, headache, fatigue, gastrointestinal symptoms, arthralgia, myalgia, rash, and urticaria) for 7 days and unsolicited symptoms for 30 days. Urticaria or rash occurring within 30 minutes of each vaccine dose was documented. The intensity of solicited and unsolicited symptoms was graded on a scale of 0-3.

SAEs, NOCDs, MSCs, and pregnancies and their outcomes were reported up to month 12. NOCDs were
identified in blinded manner before analysis as described previously [14]. MSCs were defined as events prompting an emergency room or physician visit not related to a common disease. All solicited local AEs were considered related to vaccination. Investigators assessed the likely causality of all other AEs (solicited general and unsolicited).

Safety and reactogenicity were analyzed overall and according to ethnic group: White/Caucasian (including Arabic and North African), Black, Hispanic, Asian, and other.

Immunogenicity. Blood samples were collected at months 0, 2, and 7 from a subset of participants in 35 pre-defined centers in Colombia, Germany, Honduras, Korea, Panama, and Taiwan. Antibody titers to HPV-16 and HPV-18 were measured by ELISA. Anti-HPV-16 and anti-HPV-18 GMTs were compared with those from a reference study (NCT00689741) [8]. The ELISA assay used was identical in the present study and the reference study.

Statistics

It was estimated that 950 evaluable participants were needed in each group to achieve adequate power for the primary endpoint, the occurrence of SAEs up to month 7. On the basis of a 1.5% SAE incidence in the control group, the study had 70% power to rule out a 1.5% increase in the SAE incidence in the HPV-16/18 vaccine group compared with control and 91% power to rule out a 2% increase. If the control group had a 1% SAE incidence, the study had 84% power to rule out a 1.5% increase and 97% power to rule out a 2% increase. Moreover, the study had 80% power to detect a statistically significant difference between the two groups if the SAE incidence in the HPV-16/18 vaccine group was approximately twice that of the control group (3.9% vs. 2%). Assuming that 5% of the participants may be nonevaluable, 1,000 participants in each group needed to be enrolled.

Safety analyses up to month 7 were based on the total vaccinated cohort, which included all participants for whom data were available and who received at least one vaccine dose. Safety analyses from month 7 to month 12 were performed in the extended safety follow-up (ESFU) vaccinated cohort, which included all vaccinated girls who could be contacted by telephone at month 12. The 2-sided standardized asymptotic 95% confidence interval (CI) for the difference in SAE incidence between the study groups was calculated. Exact 95% CIs were calculated for all other safety endpoints. No other statistical comparisons were performed.

Immunogenicity analyses were based on the according-to-protocol immunogenicity cohort, which included participants who met all eligibility criteria, complied with study procedures, and had data available for antibodies against at least one antigen component of the HPV-16/18 vaccine. GMTs and the 95% CIs were calculated at each time point when a blood sample result was available, along with seroconversion rates. For the reference study, GMTs with their 95% CI before vaccination and at month 7 were calculated.

Comparison of the immune response between girls in the present study and young women in the reference study was descriptive. All analyses were performed using SAS® 8.2 and Proc StatXact-5® (Cytel Inc, Cambridge, MA).

Results

A total of 2,067 girls were enrolled (Figure 1). Compliance with the 3-dose schedule was high (98.2%) in both groups. Mean age at first vaccination was 12.1 years, and ethnicity for both groups was comparable (Table 1). Three girls from the control group withdrew for safety reasons, two because of nonserious AEs (pain at the injection site and joint swelling) and one because of a SAE (details later in the text). The ESFU vaccinated cohort included 2023 girls (Figure 1).

The according-to-protocol immunogenicity cohort included 1,341 girls (Figure 1). Because all Latin American centers were included in the immunogenicity subset, but only German centers from Europe and Korean and Taiwanese centers from the Asia-Pacific region, the ethnic origin distribution of the population was somewhat different compared with the total vaccinated cohort (Hispanic 44.3%, white/Caucasian 34.3%, Chinese 16.1%). For the reference population, the mean age at first vaccination was 20.2 years, and the women were predominantly white/Caucasian (66.8%).

Safety

The occurrence of SAEs was similar in both groups, with 11 girls (1.1%) in the HPV-16/18 vaccine group reporting 14 SAEs and 13 girls (1.3%) in the control group reporting 15 SAEs up to month 7 (Table 2). The difference in SAE incidence between the two groups was .20% (95% CI, −.78, 1.20). SAEs reported during this period in the HPV-16/18 vaccine group were abdominal pain (2), enterobiasis (1), gastroenteritis (1), herpangina (1), pneumonia bacterial (1), pseudocroup (1), upper respiratory tract infection (1), drug toxicity (1), gun shot wound (1), injury (1), ulna fracture (1), dehydration (1), syncope (1). SAEs in the control group were lymphadenitis (1), constipation (1), gastritis (1), appendicitis (5), Ludwig angina (1), urinary tract infection (1), concussion (1), transaminases increased (1), headache (1), anorexia nervosa (1), and ovarian cyst ruptured (1). Only one SAE was reported as related to vaccination: a urinary tract infection in conjunction with elevated liver enzymes reported in the control group. The girl recovered and was not withdrawn. One girl from the control group withdrew because of an SAE (anorexia nervosa); the event was not considered related to vaccination by the investigator.

Between months 7 and 12, 13 girls (1.3%) and 10 girls (1.0%) reported SAEs in the HPV-16/18 vaccine and control groups, respectively (Table 2). SAEs reported during this
period in the HPV-16/18 vaccine group were tympanic membrane perforation (1), abdominal pain (2), bronchitis acute (1), cellulitis (1), mastoiditis (1), concussion (1), convulsion (1), migraine with aura (1), intentional self-injury (1), dysmenorrhea (1), ovarian cyst (2). SAEs in the control group were autoimmune thyroiditis (1), pyrexia (1), gastroenteritis viral (1), pneumonia (1), ganglion (1), acute psychosis (1), anorexia nervosa (1), suicide attempt (1), dysmenorrhea (1), ovarian cyst (1), and dyspnea (1). None were reported as related to vaccination or led to withdrawal.

Pain was reported after 70.1% of doses of the HPV-16/18 vaccine and after 41.3% of doses of the control vaccine (Table 3). Redness and swelling were also reported more frequently following the HPV-16/18 vaccine. Grade 3 solicited local symptoms were reported rarely (≤5% of doses), although they were also more frequent in the HPV-16/18 vaccine group. The most frequently reported solicited general symptoms were headache, fatigue, and myalgia, occurring more often in the HPV-16/18 vaccine group than in the control group, as did arthralgia (Table 3). Rash and urticaria occurred rarely, although rash was more common in the HPV-16/18 vaccine group. There was no report of rash or urticaria in the immediate postvaccination period (30 minutes). Grade 3 solicited general symptoms occurred rarely. The pattern of symptoms was very similar in both groups with respect to incidence, severity, duration, and reported relationship to vaccination. The incidence of local and solicited symptoms did not increase with the second and third vaccine doses.

Overall, 386 girls in the HPV-16/18 vaccine group (37.3%) and 427 girls in the control vaccine group (41.4%)...
reported 685 and 698 unsolicited symptoms within the 30-day postvaccination period, respectively (Table 2). Considering different disease categories, the incidence of unsolicited symptoms was generally similar in both vaccine groups. The most frequently reported unsolicited symptoms were upper respiratory tract infection (5.8% and 6.7% of girls in the HPV-16/18 and control vaccine groups, respectively), nasopharyngitis (5.4% and 5.9%, respectively), pharyngolaryngeal pain (2.7% and 2.1%, respectively), headache (2.6% and 3.3%, respectively), tonsillitis (2.3% and 1.3%, respectively), and pharyngitis (2.1% and 2.2%, respectively). Few girls experienced grade 3 or possibly related symptoms (Table 2), and there was no difference between vaccine groups in their incidence or pattern.

A total of 25 (2.4%) and 21 (2.0%) girls in the HPV-16/18 and control vaccine groups, respectively, reported AEs classified as NOCD up to month 7 (Table 2). The most common NOCDs were allergic rhinitis, asthma, hypersensitivity, and chronic urticaria, reported at similar incidences in both groups. A total of 12.6% and 15.5% of girls in the HPV-16/18 vaccine and control groups, respectively, reported MSC during the 30-day postvaccination period. Corresponding values between months 7 and 12 were 3.6% and 3.5% (Table 2), respectively. Up to month 7, five girls in the HPV-16/18 vaccine group reported six cases of syncope. One case occurred on the day of vaccination and was considered causally related; another case occurred 1 day after vaccination and was not considered causally related. Other cases occurred 11–26 days after vaccination and were not considered related. One girl reported convulsion 33 days after vaccination and this was also not considered to be related. In the control group, two girls reported syncope vasovagal on the day of vaccination, and one case was considered related. Two other girls in the control group reported syncope 24 and 28 days after vaccination, neither of which was considered related. Between months 7 and 12, one girl in the HPV-16/18 vaccine group and one girl in the control group reported a convulsion, neither were considered related to vaccination.

Seven pregnancies were reported up to month 12 of the study, five in the HPV-16/18 vaccine group and two in the control group. Four girls gave birth to healthy babies, two girls (one in each group) had an elective termination, and the other pregnancy outcome was unknown at the time of the analysis. There was little difference in the frequencies of solicited local symptoms between the ethnic groups, except for grade 3 pain which was reported more frequently by Hispanic girls in both vaccine groups (after 9.5%, 3.5%, and 1.2% of HPV-16/18 vaccine doses by Hispanic, white/Caucasian, and Asian girls, respectively; corresponding values were 1.7%, .5%, and 0% in the control group). Hispanic girls also tended to report more solicited general symptoms than did white/Caucasian or Asian girls in both study groups. Unsolicited symptoms were reported more frequently by Hispanic and Asian girls than by white/Caucasian girls, although there was no difference between the vaccine groups. As only a few girls in the black or other ethnic groups were recruited, no conclusions could be drawn for these groups.

### Immunogenicity

Most girls (90.6%) receiving the HPV-16/18 vaccine were seronegative for both HPV-16 and HPV-18 antigens before...
vaccination. One month after the second dose of the HPV-16/18 vaccine, >99% of initially seronegative girls had seroconverted for both antigens, and all seroconverted by 1 month after the third dose.

Antibody levels in the present study in 10–14-year-old girls were considerably higher than those in the young women aged 15–25 years in the reference study: 4-fold and 2-fold higher for anti-HPV-16 and anti-HPV-18 antibodies, respectively (Figures 2A, B).

Geometric mean titers analyzed by country were comparable to the overall analysis, except in Honduras and Taiwan. The GMT levels for anti-HPV-16 antibodies were 14,778.0 (12,668.5; 17,238.7) and 22,954.0 (19,597.1; 26,049.3) EU/mL in initially seronegative girls from Honduras and Taiwan, respectively. Corresponding values for anti-HPV-18 antibodies were 6,149.1 (5,314.5; 7,114.7) and 10,843.1 (9,342.6; 12,584.6) EU/mL.

**Discussion**

This study shows that the HPV-16/18 vaccine has a favorable safety profile and induces high levels of anti-HPV-16 and -18 antibodies in young adolescent girls, the primary target population for HPV vaccination.

There was no difference between study groups in the occurrence of SAEs at month 7, the primary endpoint. Few SAEs occurred, and no SAE in the HPV-16/18 vaccine group was considered related to vaccination or led to withdrawal. The occurrence of unsolicited symptoms was comparable between vaccine groups and few girls experienced grade 3 or causally related symptoms. The most frequently reported symptoms were upper respiratory tract infection and nasopharyngitis, as may be expected in this population. The occurrence of NOCD and MSC was low and similar in both vaccine groups; the types of conditions reported were as expected for this population. There was no difference between vaccine groups with respect to pregnancy outcomes.

The incidence of injection site reactions and some solicited general symptoms was higher in the HPV-16/18 vaccine group than in the control group. Grade 3 local and general symptoms were rare, although grade 3 local symptoms occurred more often in girls receiving the HPV-16/18 vaccine. This trend has been seen in previous studies and in a pooled analysis of 11 clinical trials of the HPV-16/18 vaccine [14]. It is probable that this reflects the stronger immunologic stimulation induced by AS04 adjuvantation, as studies of other vaccines adjuvanted with AS04 have also shown increased reactogenicity [16]. However, in the
present study, the increased occurrence of local reactions did not adversely affect compliance with the full vaccination schedule, which was more than 98%. High compliance (>90%) has also been seen in other studies of the HPV-16/18 vaccine [8, 10, 13].

In both the vaccine and control groups, Hispanic girls tended to report grade 3 pain more often than other girls, and both Hispanic and Asian girls reported unsolicited symptoms more often than white/Caucasian girls. For a given ethnic group, there are differences from one study to another in adverse event reporting behaviors (unpublished observations). Therefore, such differences are unlikely to reflect an intrinsic pre-disposition of a given ethnic group to report symptoms more often than white/Caucasian girls. For a given ethnic group, there are differences from one study to another in adverse event reporting behaviors (unpublished observations). Therefore, such differences are unlikely to reflect an intrinsic pre-disposition of a given ethnic group to report symptoms more often than white/Caucasian girls. For a given ethnic group, there are differences from one study to another in adverse event reporting behaviors (unpublished observations). Therefore, such differences are unlikely to reflect an intrinsic pre-disposition of a given ethnic group to report symptoms more often than white/Caucasian girls.

Although this was a relatively large study, it was not of sufficient size to thoroughly evaluate all safety aspects. In particular, the sample size was insufficient to reliably detect the occurrence of rare adverse events. However, a pooled analysis of HPV-16/18 vaccine trials and an integrated analysis of autoimmune disorders in trials of various AS04-adjuvanted vaccines showed no cause for concern in this regard [14, 15]. A further limitation is that the study did not explore the effect of vaccination on cytologic endpoints, such as investigations are not feasible in this age group (10–14 years). However, as already mentioned, antibody levels were higher in this study than in a previous study of young women in which 100% vaccine efficacy against cervical intraepithelial neoplasia 2+ lesions associated with HPV-16/18 has been demonstrated up to 6.4 years after first vaccination [12]. This suggests that the high and sustained efficacy against clinical endpoints observed in young women would likely translate to young adolescent girls, the target population for the HPV-16/18 vaccine in many vaccination programs.

The HPV-16/18 vaccine must produce high antibody levels in adolescents to provide protection at the time of peak exposure to the virus and must offer long-term protection. The AS04 Adjuvant System in the vaccine formulation is likely to be important in the vaccine’s strong immunogenicity, as it produces higher and more sustained antibody titers, together with a more vigorous memory B-cell response, than a formulation adjuvanted with aluminum salts alone [17]. Mathematical modeling based on data in young adult women indicates that antibody levels will remain several folds higher than those associated with natural infection for at least 20 years for both antigens [18]. Given that even higher antibody levels seem to be obtained when the vaccine is administered to young adolescent girls, this may suggest that vaccine efficacy is likely to be sustained for many years.

In conclusion, this study shows that the HPV-16/18 AS04-adjuvanted vaccine has a favorable safety profile and stimulates high anti-HPV-16 and -18 antibody levels in young adolescent girls. Antibody levels in this population are higher than those induced in young women, suggesting that the sustained efficacy of the vaccine seen in young women is likely to be translated to young adolescent girls, the key population for public health immunization programs.
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