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Safety and immunogenicity of a glycoprotein D genital herpes vaccine in healthy girls 10–17 years of age: Results from a randomised, controlled, double-blind trial

The HSV-040 Study Group*

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ABSTRACT

Objective: The investigational AS04-adjuvanted herpes simplex virus type 2 (HSV-2) glycoprotein D (gD2) subunit prophylactic vaccine ('HSV vaccine'; GlaxoSmithKline Vaccines) has been shown to be well tolerated in adults, but limited data exist for pre-teen and adolescent girls, a likely target population. The primary objective of this study was to compare the occurrence of serious adverse events (SAEs) over 12 months between HSV vaccine recipients and saline recipients (placebo control group) in pre-teen and adolescent girls. The immunogenicity of the HSV vaccine was also assessed.

Methods: Healthy girls aged 10–17 years, stratified by age (10–15 years; 16–17 years), were randomised 2:1:1 to receive the HSV vaccine, a hepatitis A vaccine (*Havrix*™; HAV control) or placebo (saline) according to a 0-, 1-, 6-month schedule. Participants and study personnel not involved in the preparation or administration of vaccines were blinded to treatment. Safety and immunogenicity analyses were performed overall and by age (10–15 years; 16–17 years) and HSV serostatus.

Results: No statistically significant difference in the percentage of subjects with SAEs was observed between the HSV and saline group, or between the HSV and pooled control (HAV and saline) groups. The HSV vaccine was well tolerated, although a higher incidence of solicited local symptoms was observed in the HSV group than in the control group. Neither age nor HSV serostatus at the time of study entry had an impact on the safety profile of this vaccine. The HSV vaccine was immunogenic regardless of pre-vaccination HSV serostatus. Higher anti-gD geometric mean concentrations were observed in HSV-1 seropositive participants than in HSV-1 seronegative participants.

Conclusion: The HSV vaccine had an acceptable safety profile, and was well tolerated and immunogenic when administered to girls aged 10–17 years regardless of age or HSV pre-vaccination serostatus.

1. Introduction

Genital herpes simplex disease is caused by herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and is one of the most common sexually transmitted infections [1]. Initial infection may produce mild to severe local symptoms or occur without recognised disease. Reactivation of latent virus may produce recurrent disease or manifest as asymptomatic viral shedding [2,3]. Neonatal herpes is an uncommon but serious consequence of HSV transmission from mother to infant [4,5]. Additionally, genital herpes is associated with increased susceptibility to sexual acquisition of the human immunodeficiency virus [6–8].

Current strategies for preventing sexual transmission of HSV infection include increasing awareness through education, the use of condoms and suppressive antiviral therapy for HSV-infected partners. Prophylactic vaccination against HSV is expected to reduce sexual transmission and would consequently help control the spread of genital herpes [3].

HSV-2 has historically been viewed as the predominant etiological agent of genital herpes. Therefore, the development of vaccine candidates has targeted HSV-2. However, recent epidemiological studies show an increase in both genital herpes disease, especially in young women, and in neonatal herpes caused by HSV-1 [1,9].

Abbreviations: Alum, aluminium hydroxide; AS04, aluminium hydroxide and 3-O-deacylated monophosphoryl lipid A adjuvant system; ATP, according to protocol; 95% CI, 95% confidence interval; ELISA, enzyme-linked immunosorbent assay; EU, ELISA units; gD2, herpes simplex virus type 2 glycoprotein D; GMC, geometric mean concentration; GSK, GlaxoSmithKline; HAV, hepatitis A vaccine; HSV, herpes simplex virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; IgG, immunoglobulin G; IU, international units; MPL, monophosphoryl lipid A; NOCD, new onset chronic diseases; OD, optical density; (S)AE, (serious) adverse event; TVC, total vaccinated cohort.

* Jan Hendrik Richardus, MD, PhD, Department of Infectious Disease Control, Municipal Public Health Service (GGD) Rotterdam-Rijnmond, Rotterdam, The Netherlands P. O. Box 70032, 3000 LP Rotterdam, The Netherlands.
Tel.: +31 104339438.
E-mail address: jh.richardus@rotterdam.nl

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An investigational HSV-2 glycoprotein D (gD2) subunit vaccine against genital herpes caused by HSV-1 or HSV-2, adjuvanted with AS04 (aluminium hydroxide and 3-O-deacylated monophosphoryl lipid A [MPL]), elicits gD2-binding antibodies and HSV neutralising antibodies [10,11] and is well tolerated in adults [10–12]. However, HSV-2 seroprevalence substantially increases after sexual debut, from 1.4% in 14–19 year-olds to 26.1% in 40–49 year-olds in the US [2005–2008] [13] and from 2.7–4.7% for children ≤15 years to 10.0–17.5% in adults in Germany [1999–2006] [14]. Thus, an important target group for vaccination is young women or girls before their sexual debut.

Since completion of the present study, a large efficacy study failed to show the efficacy of this vaccine against genital herpes disease overall (caused by HSV-1 or HSV-2) in HSV-1 and HSV-2 seronegative women (18–30 years), however, the vaccine was efficacious against HSV-1 infection and disease [11]. Here, we evaluate the safety and immunogenicity of this investigational vaccine in 10–17 year-old girls.

2. Methods

2.1. Study objectives

The primary objective of this study was to compare the occurrence of serious adverse events (SAEs) between the HSV and saline groups throughout the study period. Secondary objectives were to compare the occurrence of SAEs, new onset chronic diseases (NOCDs) and other medically significant conditions between the HSV and pooled control groups, and to evaluate reactogenicity in all groups following vaccination. We also assessed biochemical and haematological parameters, anti-gD2 antibody responses and humoral immune response to the lipid component of the adjuvant by measuring anti-MPL antibody concentrations in subsets of participants.

2.2. Study design and participants

This was a phase IIIa, double-blind, randomised, controlled study conducted in 146 centres from 18 countries in North America (United States and Canada), Europe (France, Greece, the Netherlands, Spain, Belgium, the United Kingdom, Estonia, Hungary, Romania, Iceland, Lithuania, Denmark, Sweden and Norway) and Australasia (Australia and New Zealand).

Healthy girls aged 10–17 years were enrolled between April 2004 and July 2007. Enrolment was age-stratified (10–15 and 16–17 years), with no more than 50% and no fewer than 25% of participants in the 16–17 years stratum. Participants were randomised, using a central randomisation system (2:1:1), to receive 3 doses of the HSV vaccine (GlaxoSmithKline Vaccines; the HSV group), a commercially available hepatitis A vaccine (HAV) (*Havrix*™, GlaxoSmithKline Vaccines; HAV group) or saline as placebo. All participants and study personnel who were not involved in the preparation or administration of study vaccines were blinded to the treatment administered. Each participant was followed for approximately 12 months after the first vaccine dose, with an additional follow-up telephone contact at 18 months.

2.2.1. Eligibility and ethics

All participants were to have a negative urine pregnancy test before each vaccination. Participants of childbearing potential had to be abstinent or using an effective birth control method 30 days before the first vaccine up to 2 months after final vaccination. Participants were excluded if they showed signs of any obvious health problem; if any investigational or non-registered drug or vaccine other than the study vaccines was received within 30 days before receiving the study vaccine, or was planned for use during the study period; or if they had previously been vaccinated against herpes or had received MPL adjuvant. A summary of the protocol is available on the clinical trials registry, http://www.clinicaltrials.gov (NCT00224484).

Written informed consent was obtained from the parents or legal guardian of each subject enrolled. Participants above the legal age of consent in their country additionally signed an informed consent form. This study was conducted according to Good Clinical Practice and the 1996 Declaration of Helsinki. The study protocol was approved by an ethics review committee at each study site according to local regulatory requirements. An independent data monitoring committee was responsible for overseeing the study, including review of safety data prior to unblinding.

2.3. Study vaccines and administration

The HSV vaccine (GlaxoSmithKline Vaccines) contained 20 μg of truncated gD2 and the AS04 adjuvant system, comprising 50 μg of MPL and 0.5 mg of aluminium hydroxide (alum) [11]. Each dose (0.5 ml) of the HAV (GlaxoSmithKline Vaccines) contained 360 enzyme-linked immunosorbent assay (ELISA) units of inactivated HAV with 0.25 mg of alum adjuvant. One dose of placebo contained 0.5 ml of commercially available 0.9% saline. Three doses of vaccine or saline were administered in the non-dominant deltoid at Day 0, Month 1 and 6.

2.4. Safety assessment

SAEs were monitored by the investigator up to Month 18. Unsolicited adverse events (AEs) were recorded for 30 days (Day 0–29) after each dose. Local and general solicited AEs were recorded for 7 days (Day 0–6) after each dose. Maximum severity was assessed on a scale of 1 (mild) to 3 (severe). Fever and injection site redness and swelling were scored by sponsor, from grade 0 (<37.5 °C/absent) to 3 (>39.0 °C/>30 mm and persisting more than 24 h).

NOCDs and other medically significant conditions (including autoimmune disorders, asthma and type I diabetes) were recorded up to Month 18. Conditions prompting emergency room or physician visits not related to common diseases were also reported. NOCDs were assessed by both the investigator and sponsor physician for causal relationship to the vaccine, with final decision taken by the investigator.

Haematological and biochemical parameters were evaluated for a subset of participants pre-vaccination (Day 0) and after 3 vaccine doses, at Months 7 and 12. The subset included all participants from pre-specified sites in each geographic region (Supplementary content).

Pregnancies occurring during Months 0–18 were recorded and followed for 6–8 weeks after the estimated delivery date. Any complication or elective termination was recorded as an AE or SAE. Participants who became pregnant during the study did not receive additional doses of study vaccine.

2.5. Immunogenicity assessment

HSV serostatus was determined before vaccination at the first study visit (Day 0), using the HSV non-type specific Enzygnost® anti-HSV IgG test kit (Behring; cut-off value, 0.1 OD) and the HSV-2 type-specific HerpeSelect™ 2 ELISA (Focus Technologies; cut-off, index value 1.1), validated by western blot [10,12,15], for all participants.

Antibody responses against HSV gD2 and MPL were quantitatively evaluated using in-house ELISAs [10,12,16] at Day 0 and Months 7 and 12 in subsets of participants assigned to undergo assessment of biochemical and haematological parameters