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An update of prophylactic human papillomavirus L1 virus-like particle vaccine clinical trial results

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ABSTRACT

This review focuses on recent publications of clinical trials of two prophylactic human papillomavirus (HPV) vaccines: Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ USA), a quadrivalent vaccine containing L1 virus-like particles (VLPs) of types -6, 11, 16, and 18, and Cervarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium), a bivalent vaccine containing VLPs of types -16 and 18. In efficacy trials involving young women, both vaccines produced outstanding efficacy against primary and secondary endpoints associated with the vaccine type HPVs and were highly and consistently immunogenic. Both had excellent safety records and, as expected, the most frequent vaccine-related adverse were mild to moderate injection site sequelae. No evidence of waning protection was observed after four years for endpoints examined ranging from incident infection to cervical intraepithelial neoplasia grade 3 associated with the vaccine type HPVs. Gardasil® was also highly efficacious at preventing vaginal/vulvar lesions and genital warts. However, neither vaccine demonstrated therapeutic efficacy against prevalent infections or lesions, regardless of the associated HPV type. Cervarix™ has shown limited cross-protection against infection with specific closely related types while preliminary results of limited cross-protection have been presented for Gardasil®. As expected, more limited efficacy was noted for both vaccines when women with prevalent infection were included or endpoints associated with any HPV type were evaluated. Immunological bridging trials involving adolescent girls and boys were also recently published. For both vaccines, serum VLP antibody levels in girls were non-inferior to those generated in young women and antibody response to Gardasil® was also non-inferior in boys. The results of these studies have led to the approval of Gardasil® and Cervarix™ by national regulatory agencies in a number of countries.

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1. Introduction

This article reviews the results of human papillomavirus (HPV) virus-like particle (VLP) vaccine clinical trials published in 2006 and 2007. An impressive number of important studies were published in this short time frame. Information on earlier clinical trials is provided in the previous monograph [1]. The trials to be discussed fall into two categories, efficacy studies involving virologic and disease endpoints and immunologic bridging studies where the endpoints were limited to safety and VLP serum antibody titers. While the clinical trials of Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ, USA) and Cervarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium) are presented together, caution must be taken when directly comparing the results with the two vaccines due to differences in trial design, statistical analyses and methodologies used to generate the published analyses.

2. Vaccine formulations

Gardasil® and Cervarix™ are both composed of HPV L1 proteins that spontaneously self assemble into VLPs. However, they have different valencies, adjuvants, and are produced in different types of cells (Table 1) [2]. Cervarix™ was designed to prevent infection by HPV-16 and 18, the two types that cause 70% of cervical cancer. Gardasil® targets the same two cancer causing types and, in addition, is intended to prevent infection by HPV-6 and 11, which cause 75–90% of external genital warts. Both vaccines must be refrigerated and are administered by intramuscular injection in the deltoid area, but differ slightly in the timing of the second dose.

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Table 1
Characteristics of HPV VLP vaccines

	Gardasil®	Cervarix™
Manufacturer	Merck & Co., Inc.	GlaxoSmithKline
VLP types	-6/11/16/18	-16/18
Dose of L1 protein	20/40/40/20 μg	20/20 μg
Producer cells	*Saccharomyces cerevisiae* (bread yeast) expressing L1	*Trichoplusia ni* (Hi-5) insect cell line infected with L1 recombinant baculovirus
Adjuvant	225 μg aluminum hydroxyphosphate sulfate	500 μg aluminum hydroxide, 50 μg 3-O-deacylated-4′-monophosphoryl lipid A
Injection schedule	0, 2, 6 months	0, 1, 6 months

VLP: virus-like particle.
Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ USA); Cervarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium) [2].

Each VLP type is produced and purified separately and during final formulation the different types are mixed. In addition to valency, another difference between the two vaccines is the choice of adjuvants. Different aluminum salts are used in the two vaccines. The Gardasil® vaccine used only an aluminum adjuvant (aluminum hydroxyphosphate sulfate), whereas the Cervarix™ adjuvant system, called AS04, contains monophosphosphoryl lipid A (MPL), a detoxified form of lipopolysachharide (LPS) and aluminum hydroxide. Aluminum salt-based adjuvants typically induce a Th2 type of response and this was observed when Merck's aluminum adjuvant was combined with HPV VLPs. However, MPL activates innate immune responses via toll-like receptor molecules and so can induce a mixed Th1/Th2 differentiation pattern in human T cells [3,4]. Th1 responses are generally sought in therapeutic vaccines designed to generate cell mediated immune responses, in contrast to prophylactic vaccines designed to generate antibody responses. Th1 and Th2 responses induce antibody responses that typically have different ratios of specific immunoglobulin types and IgG subtypes, but at present there is no evidence that the various antibody species differ in HPV neutralizing potential. GlaxoSmithKline (GSK) has published that VLP antibody titers in women are about 2-fold higher when their VLPs are formulated in AS04 rather than simple aluminum hydroxide. A more complete review of adjuvants and immune responses is discussed in this monograph by Stanley M et al. [5]. There has been no direct comparison between VLPs adjuvanted with AS04 and the aluminum salts of Gardasil® to date.

3. Efficacy trial designs

Results from two small phase II and three relatively large phase III efficacy studies were reported in the last two years (Table 2) [6–10]. All of the trials were blinded, randomized, and placebo controlled trials of young women (mean age 20 years). Participants were recruited at multiple sites in Europe, North America, South America, Asia and Australia. A community-based efficacy trial of Cervarix™ is also underway in Costa Rica, but prophylactic efficacy data is not yet available [11].

In keeping with the primary goal of evaluating immunoprophylaxis, an exclusion criterion for number of lifetime sexual partners, less than five for the quadrivalent vaccine or six or less for the bivalent vaccine, was included in the efficacy trials to reduce the percentage of women with prior exposure to genital HPV infection. However, women with prevalent infection, as measured by the presence of genital tract HPV DNA, or evidence of past exposure, as measured by serum antibodies to VLPs, were not excluded from randomization or vaccination, with the exception of GSKs study 001/007. The phase II studies focused more on infection endpoints because of their smaller trial size, whereas the pivotal phase III trials are focused more on disease endpoints, particularly cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+). This endpoint has been recommended as a surrogate clinical endpoint for cervical cancer by the US Food and Drug Administration (FDA) and other national regulatory authorities. Specific primary and secondary endpoints used in the individual trials are indicated in Table 2.

All clinical trials were designed to follow-up women for up to at least four years. The phase III studies with CIN endpoints had defined interim analyses when a pre-determined number of disease events accumulated, and these analyses have been published [7,9]. Importantly, these interim analyses are the basis for regulatory approval in many countries.

The screening interval was six or twelve months. This interval is an important variable because more cases of infection and disease are detected with the shorter interval. However, the increase

Table 2
Outline of vaccine efficacy trials in young women

Characteristic	GSK 001/007	Merck 007	PATRICIA	FUTURE I	FUTURE II
Vaccine	Cervarix™	Gardasil®	Cervarix™	Gardasil®	Gardasil®
Study phase	II	II	III	III	III
Control	500 μg aluminum hydroxide	225 μg aluminum hydroxy-phosphate sulfate	Hepatitis A vaccine	225 μg aluminum hydroxy-phosphate sulfate	225 μg aluminum hydroxy-phosphate sulfate
# Participants	1,113	552	18,644	5,455	12,167
Mean age (years) (range)	20 (15–25)	20 (16–23)	20 (15–25)	20 (16–24)	20 (15–26)
Lifetime no. of sex partners	≤6	≤4	≤6	≤4	≤4
Screening frequency	6 months	6 months	12 months	6 months	12 months
Mean duration of follow up	48 months	60 months	15 months[a]	36 months[a]	36 months[a]
Primary efficacy endpoint	Incident -16/18 infection	-6/11/16/18 persistent infection and cervical or external genital disease	-16/18 CIN2+	-6/11/16/18 CIN1+ and external genital lesions	-16/18 CIN2+
Secondary endpoints	Persistent infection, CIN1+, adverse events	Adverse events	Persistent infection or CIN1+ by any type; Adverse events	Adverse events	Adverse events

CIN: cervical intraepithelial neoplasia; CIN1+: CIN grade 1 or worse; CIN2+: CIN grade 2 or worse; FUTURE: Females united to unilaterally reduce endo/ectocervical disease; GSK: GlaxoSmithKline; PATRICIA: Papilloma trial against cancer in young adults [6–10].
[a] Interim analysis of projected four year follow-up trial.