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Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine

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Abstract

Background: The duration of protection afforded by vaccines represents a critical test of their utility as public health interventions. Some vaccines induce long-term immunity, while others require booster doses. Vaccines that induce long-term protection are usually characterized by the generation of immune memory. Recent trials of a quadrivalent (types 6, 11, 16, 18) human papillomavirus (HPV) vaccine have demonstrated high efficacy through 5 years of follow-up. We evaluated the extent to which the vaccine is able to generate HPV type-specific immune memory.

Methods: A total of 552, 16–23-year-old women were enrolled in a double-blind, placebo-controlled study. At enrollment, subjects were randomized in a 1:1 ratio to receive three-dose regimens of quadrivalent HPV vaccine or placebo with 3 years' follow-up. A subset of 241 subjects ($n = 114$ in the quadrivalent HPV vaccine group and $n = 127$ in the placebo group) underwent 2 further years of follow-up. All extension subjects received quadrivalent HPV vaccine at month 60 to examine the extent of immune memory in response to the primary vaccination series.

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Results: Serum anti-HPV levels declined post-vaccination, but reached a plateau at month 24 that remained stable through month 60. Administration of a challenge dose of vaccine induced a classic anamnestic response, with anti-HPV levels 1 week post-challenge reaching levels observed 1 month following the completion of the three-dose primary series. At 1 month post-challenge, anti-HPV responses were higher than those observed 1-month post-dose 3.
Discussion: A three-dose regimen of quadrivalent HPV vaccine induces high efficacy and stable anti-HPV levels for at least 5 years. Vaccination also induces robust immune memory. These findings suggest that the efficacy of this vaccine will be long lasting.

Keywords: Human papillomavirus; Prophylactic vaccine; Virus-like particles; Cervical intraepithelial neoplasia (CIN); Genital warts; Cervical cancer; Clinical trial

1. Introduction

Human papillomavirus (HPV) infection is associated with cancers of the cervix, vulva, vagina, anus, penis, and the oropharynx [1–5], as well as genital warts [6]. Data suggest that within 3 years after initiation of sexual activity, up to 48% of women will have evidence of cervical HPV infection [7]. Infection with HPV is considered to be a requisite step in the development of cervical cancer [8]. Thus, HPV DNA is found in the cervices of over 99% of all women with cervical cancer [8].

Prophylactic HPV vaccination represents a promising strategy to prevent the occurrence of cervical cancer and other HPV-related diseases. Administration of quadrivalent HPV (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine (GARDASIL®, Merck & Co., Inc.) to 16–26-year-olds induces potent anti-HPV 6, 11, 16 and 18 responses. Anti-HPV levels in response to immunization with quadrivalent HPV vaccine have been shown to persist in vaccinated subjects through 4.5 years post-vaccination [9]. The vaccine was highly effective through 5 years post-enrollment, with no breakthroughs due to waning immunity [10]. What has not yet been determined, however, is how long protective antibodies generated in response to immunization with quadrivalent HPV vaccine will last. This is an important question, as women (and men) remain at risk for HPV infection as long as they are sexually active.

The duration of protection afforded by vaccines can vary. A three-dose regimen of Hepatitis B (Hep B) vaccine has been shown to provide immunity for a period of at least 20 years. On the other hand, a three-dose regimen of Diphtheria–Tetanus–Pertussis (DTaP) requires boosting at 5–10-year intervals through late adolescence.

One of the hallmarks of vaccines that confer long-term immune protection is the development of immune memory, which is defined as vaccine-induced generation of long-lived memory immune cells that, upon re-exposure to the relevant antigen, generate a vigorous immune response that prevents or aborts infection. An example of vaccine-induced immune memory can be seen with Hep B vaccine. Like the HPV vaccine, the Hep B vaccine is composed of a viral surface antigen (Hepatitis BsAg) arranged into virus-like particles, formulated with aluminum-containing adjuvant. This vaccine has been shown to induce an immune response that results in detectable antibody levels for at least 10 years [11,12]. Data from a recent long-term follow-up of over 1600 subjects immunized against HBV showed that protective antibody concentrations were still present in 64% of children and 89% of adults over 10 years after vaccination [13]. While substantial proportions of subjects in this and other trials do not show protective or detectable levels of anti-HBV antibodies years after immunization, it is hypothesized that booster vaccination is not necessary [13–15]. Data indicate that HBV antigen challenge of subjects with non-protective anti-HBV antibody levels who were previously immunized against HBV results in an anamnestic response, and rapid seroconversion for anti-HBV antibodies [15].

In this report, we present data from a Phase IIb clinical trial designed to evaluate whether quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine induces long-lived immune responses that can mediate an anamnestic response. Because it was not ethically feasible to expose subjects to actual infection, the antigen challenge was given as a dose of quadrivalent HPV vaccine. Although the minimum anti-HPV levels that confer protective efficacy have not been defined, a demonstration of immune memory provides important preliminary evidence that the quadrivalent HPV vaccine may confer long-term protective efficacy.

2. Materials and methods

2.1. Study design

The trial (Merck protocol V501-007) was a randomized, multi-center, double-blind, placebo-controlled study of a quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine. A total of 1106 women aged 16–23 years were enrolled in Brazil, Finland, Sweden, Norway, and the U.S. The study enrolled women who had no prior abnormal Pap smears, and reported a lifetime history of four or fewer male sex partners. Women were not enrolled if pregnant, and all subjects were asked to use effective contraception during the trial. Among virgins, enrollment was limited to those women who were ≥18 years of age and seeking contraception. Subjects with documented prior HPV infection were not excluded from the study. All subjects or parents/legal guardians signed informed consents following review of the protocol procedures. The study was conducted in conformance with applicable country or local requirements regarding ethical committee review,