Drugs of the Future 2006, 31(2): 97-100

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.02.967420

Gardasil™

Anti-Papilloma Virus Vaccine

Quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine formulated with aluminum hydroxyphosphate sulfate adjuvant

EN: 313946

Abstract

Persistent infection with human papillomavirus (HPV) has been established as a cause of cervical cancer, and HPV types with a low oncological risk are also responsible for the majority of cases of genital wart infections. Sexually active adolescents are at high risk for acquiring the infection, and vaccination to prevent HPV infection could significantly reduce the considerable mortality and morbidity associated with the virus. Gardasil™ is a quadrivalent vaccine composed of virus-like particles (VLPs) of the L1 major capsid proteins of HPV types 6, 11, 16 and 18. Studies in chimpanzees indicated the presence of neutralizing antibodies to low- and high-risk HPVs that persisted for at least 30 weeks after the final immunization on a 0-, 8- and 24-week schedule. Clinical studies with either single HPV components of the vaccine or with Gardasil™ consistently demonstrated seroconversion, and geometric mean titers higher than would be observed in women with a natural history of HPV infection. In large phase III studies, vaccination with Gardasil™ on a 3-dose schedule resulted in 100% protection against cervical intraepithelial neoplasia, cervical cancer and external genital lesions over a 2-year follow-up period.

Introduction

Infections caused by the human papillomavirus (HPV) are the most common sexually transmitted infections. Up to 70% of sexually active women will become infected during their life time and sexually active adolescents are at particularly high risk of acquiring the infection. HPV results in significant morbidity and mortality throughout the world (1-3). More than 40 genotypes of HPV infect the epithelial lining of the genital tract, and epidemiological evidence has demonstrated strong and specific associations relating HPV infections to cervical cancer. Indeed, HPV DNA is detected in adequate specimens of cervical cancer in 95-100% of cases (1, 3-5). The high-oncogenic-risk genotypes HPV-16 and HPV-18 cause approximately 70% of cervical cancers and high-grade cervical intraepithelial neoplasias (2, 3).

Cervical cancer is the second most common cancer among women worldwide. In 2002, there were an estimated 493,000 new cases and 274,000 deaths. However, the incidence is highest in developing countries, where screening programs are not well developed (6). Low-oncogenic-risk HPV types 6 and 11 are responsible for approximately 90% of genital wart infections. These are present in around 1% of sexually active adults in the United States and it has been estimated that at least 15% have subclinical infection as detected by HPV DNA assays (1, 2, 7). Genital wart infections are frequently associated with considerable morbidity, recurrent infections and psychological distress (8).

Prophylactic vaccination has been investigated as a strategy to prevent the considerable morbidity and mortality associated with HPV-related clinical diseases, reduce the burden of healthcare costs and potentially reduce the need for screening programs (1, 2, 5, 9). A vaccine targeting HPV types 6, 11, 16 and 18 would target the majority of HPV-related clinical diseases. Gardasil™ is one such quadrivalent vaccine in clinical development. It is composed of virus-like particles (VLPs) of the L1 major capsid proteins formulated on Merck Aluminum Adjuvant (MAA). The Biologics License Application (BLA) for the investigational vaccine was recently granted priority review by the U.S. FDA and it has also been submitted for review in the E.U., Australia and several other markets worldwide (10).

Preclinical Pharmacology

The antibody, cytokine and cytotoxic T-lymphocyte (CTL) responses to monovalent or quadrivalent L1 VLP vaccines were evaluated in chimpanzees immunized at weeks 0, 8 and 24. Radioimmunoassay indicated the presence of neutralizing antibodies to low-risk (HPV-11) and high-risk (HPV-16) HPV 4 weeks after the second and third immunizations with the quadrivalent vaccine, which persisted for at least 30 weeks after the final immunization. HPV type-specific cytokine responses (interferon gamma, IL-5 and TNF-α) frequently occurred 1 month after the second or third immunizations and at weeks 44-

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52. Induction of HPV-specific CTL responses was rarely detected (11).

The quantitative and qualitative effects of the aluminum adjuvant employed in Gardasil™ were evaluated in rhesus monkeys immunized at weeks 0, 8 and 24. An HPV-specific antibody isotyping assay and a competitive immunoassay demonstrated that immunization with the quadrivalent vaccine formulated with MAA elicited a significantly stronger immune response against all four HPV types compared to the vaccine without adjuvant. Peak antibody titers were significantly higher 4 weeks after immunization and at week 52. The MAA-formulated vaccine also elicited a predominantly T helper type 2 (Th2) response and high levels of serum IgA that were maintained through 1 year. The study demonstrated that the quadrivalent vaccine formulated with MAA elicited a robust and durable immune response (12).

Clinical Studies

The HPV-18 component of the quadrivalent VLP vaccine was evaluated in a randomized phase I immunogenicity and tolerability study. Forty women aged 16-23 years received a dose of 80 μg of the monovalent vaccine formulated with aluminum adjuvant or placebo according to a 2:1 random allocation, at day 0, 2 and 6 months. In the per-protocol cohort of 22 women who received the vaccine, 100% achieved anti-HPV-18 levels of at least 200 milliMerck units (mMU)/ml at month 7, the primary immunogenicity endpoint. Anti-HPV-18 responses increased after each dose of vaccine. According to vaccination report cards completed by subjects after each vaccination, significantly more women in the vaccine group than in the placebo group reported erythema at the injection site (41% *versus* 8%). Other injection-site reactions also tended to be reported more frequently in the vaccine group, but the differences between the groups were not statistically significant. Pain was the most common adverse event at the injection site, but none of these reactions was considered to be severe. Headache was the most frequently reported systemic adverse event, but these were comparable between the groups (13). The results of this study and some that follow are summarized in Table I.

A randomized, double-blind, proof-of-concept study was performed in 2,392 women aged 16-23 years of age to determine whether the HPV-16 component of the vaccine could prevent HPV-16 infection. Women were randomized to receive HPV-16 L1 VLP vaccine (40 μg) or placebo in a 1:1 ratio, at day 0, 2 and 6 months. The primary endpoint was persistent HPV-16 infection, and the primary analysis was limited to women who were negative for HPV-16 DNA and HPV-16 antibodies at study entry, and for HPV-16 DNA at month 7. A total of 1,533 women (64% of the study cohort) were included in the primary analysis and were followed for a median of 17.4 months after completion of the vaccination schedule. The incidence of persistent HPV-16 infection was 3.8 per 100 woman-years at risk in the placebo group and 0 per 100 woman-years at risk in the vaccine group (100% efficacy). At month 7 after the third dose of vaccine, the geometric mean titer of HPV-16 antibodies was 1510 mMU/ml among women who received the vaccine. This level was almost 60 times higher than the geometric mean titer of women who had detectable HPV-16 antibodies on day 0. The incidence of adverse events was similar between the two groups; the most frequently reported adverse event was pain at the injection site (14).

The immunogenicity, reactogenicity and tolerability of the HPV-16 component vaccine was also evaluated in a 2-year, randomized, double-blind, dose-ranging study. A total of 480 young women received doses of the monovalent vaccine (10, 20, 40 or 80 μg) or placebo according to the 3-dose schedule (day 0, 2 and 6 months). All vaccine doses produced a statistically significant antibody response compared with placebo. At month 7, geometric mean titers were 36-78-fold higher in subjects seronegative at baseline compared with the geometric mean titer at baseline in women with serological evidence of natural HPV-16 infection. Women seropositive at baseline achieved geometric mean titers 1.1-2.4-fold higher than those seronegative at baseline. Serum geometric mean titers remained high in all subjects throughout the 1.5-year postvaccination period. The vaccine was generally well tolerated. The most frequently reported injection-site reactions were pain, tenderness and soreness, and the most common systemic adverse event was headache. The incidence of adverse events was comparable across the groups (15).

The efficacy of Gardasil™ was evaluated in a randomized, double-blind, placebo-controlled phase II study in 552 young women conducted in Brazil, Europe and the U.S. Of these, 431 were included in the per-protocol analysis of the combined incidence of persistent infection with the HPV types or cervical or external genital disease in women vaccinated with Gardasil™ compared with those who received placebo. Women were vaccinated at day 1, 2 and 6 months, and swabs were taken for analysis of HPV on 7 occasions to month 36. The incidence of infection or disease associated with HPV-6, -11, -16 or -18 was 0.7 per 100 women-years at risk in the vaccine group compared with an incidence of 6.7 per 100 women-years at risk in the placebo group. These results equated to a vaccine efficacy of 90%. All women assigned the vaccine in the per-protocol population developed detectable antibody responses to all four HPV types at month 7. Gardasil™ was generally well tolerated, with the majority (94%) of adverse events described as mild or moderate in intensity (16).

The immunogenicity and tolerability of Gardasil™ were also compared in adolescents (aged 10-15 years) and young adult women. A total of 510 boys, 506 girls and 513 young women were vaccinated at day 1, 2 and 6 months. Seroconversion rates at month 7 were 100% for anti-HPV-6, -11 and -16, and 99.6% for anti-HPV-18. Month 7 geometric mean titers were up to 2.7-fold higher in the adolescent cohort than in the young adult cohort. Adverse events were comparable among cohorts (17).

Table I: Clinical studies of Gardasil™ for the prevention of human papillomavirus infection (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Randomized Double-blind	Gardasil™, 80 μg x d 0 & mo 2 & 6 (n=27) Placebo (n=13)	40	High-titer anti-HPV-18 responses were seen in all women administered Gardasil™, which was generally well tolerated	13
Randomized Double-blind Multicenter	Gardasil™, 40 μg o.d. x 3 (n=1194) Placebo (n=1198)	2392	Administration of Gardasil™ was well tolerated, prevented persistent human papillomavirus infection and decreased the risk of human papillomavirus-related cervical intraepithelial neoplasia in healthy women	14
Randomized Double-blind Multicenter	Gardasil™, 10 μg on d 0 & mo 2 & 6 (n=112) Gardasil™, 20 μg on d 0 & mo 2 & 6 (n=104) Gardasil™, 40 μg on d 0 & mo 2 & 6 (n=107) Gardasil™, 80 μg on d 0 & mo 2 & 6 (n=52) Placebo (n=105)	480	Serum anti-HPV-16 L1 antibody responses were seen with all doses of Gardasil™ in healthy women, with responses lasting at least 1.5 years	15
Randomized Double-blind Multicenter	Gardasil™ i.m. on d 1, 2 & 6 (n=277) Placebo (n=275)	552	Intramuscular injections of Gardasil™ were generally well tolerated and effective in preventing infection by common human papillomavirus types and the development of associated clinical disease over 36 months in healthy volunteers	16
Open	Gardasil™ i.m. on d 1 & mo 2 & 6	1016	Gardasil™ produced higher anti-papillomavirus responses in sexually naïve subjects than in adult women	17
Randomized	Gardasil™ on d 1 & mo 2 & 6 Placebo	5455	Gardasil™ was effective as prophylaxis against human papillomavirus-related cervical dysplasia and external genital lesions	18
Randomized Multicenter	Gardasil™ i.m. on d 1 & mo 2 & 6 Placebo	12,167	Gardasil™ was generally well tolerated and reduced the incidence of papillomavirus-related cervical intraepithelial neoplasia, adenocarcinoma *in situ* and cancer in healthy young women	19

The impact of Gardasil™ on the incidence of cervical dysplasia and external genital lesions was evaluated in a phase II study (FUTURE I: Females United To Universally Reduce Endo-ectocervical disease). A total of 5,455 young women were randomized to Gardasil™ or placebo and were vaccinated at day 1, 2 and 6 months. Cervical samples for Papanicolaou (Pap) testing were taken at regular intervals over a 2-year follow-up period and colposcopy referral was algorithm-based. The per-protocol population included women who received 3 doses, had no major protocol violations, were seronegative at day 1 and DNA-negative to month 7 for the respective HPV type. In this population, there were no cases of cervical intraepithelial neoplasia (CIN) grades 1-3 or worse, or of external genital lesions, representing a 100% efficacy rate for the vaccine. In the modified intention-to-treat population including women who received at least 1 dose of vaccine and were negative for the respective HPV type at day 1, efficacy rates of 97% for CIN and 95% for external genital lesions were observed. The vaccine was generally well tolerated (18).

The impact of Gardasil™ on the rates of CIN 2/3 and cervical cancer was evaluated in FUTURE II, a prospective, randomized (1:1), double-blind phase III study in 12,167 young adult women from 13 countries. Women received either Gardasil™ or placebo at day 1, 2 and 6 months, with Pap tests and swabs for HPV taken at intervals to month 48. In the per-protocol population, vaccination prevented HPV-16/18-related CIN 2/3, adenocarcinoma *in situ* and cervical cancer with 100% efficacy through 2 years of postvaccination follow-up. In the modified intention-to-treat population, efficacy was 97%. Vaccination was generally well tolerated, with the most common adverse event being injection-site pain (19-21).

Several other phase III clinical trials are under way with the vaccine (22-27).

Gardasil™ has been granted priority review by the U.S. FDA following submission of the BLA in December 2005. The review goal date is June 8, 2006. License applications have also been submitted in a number of other countries, including the E.U. (10).

Source

Merck & Co., Inc. (US).

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