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Prophylaxis Against Human Papillomavirus Infections with Gardasil® Vaccine

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Introduction

The recent development of two vaccines targeting the prevention of human papillomavirus (HPV) infection has created both anticipation and controversy in the public and medical communities. Gardasil® (Merck and Co., Inc.), approved by the Food and Drug Administration (FDA) on June 8, 2006, is a quadrivalent vaccine consisting of recombinant HPV Types 6, 11, 16, and 18.[1] A second bivalent vaccine containing recombinant HPV types 16 and 18, Cervarix® (GlaxoSmithKline), is currently under investigation.[2]

In the United States, the estimated prevalence of HPV infection is 20 to 40% in sexually active 20-year-old women; the estimated lifetime risk for one or more genital HPV infections for all women is at least 75%.[3] Approximately 70% of these infections are cleared within 1 year, while 91% are cleared within 2 years. It is not well understood or known whether this suggests the amount of viral matter present has dropped below detectable levels or if the virus is completely eliminated.[4]

Human papillomaviruses infect the stratified squamous epithelia of skin and mucous membranes, where they form benign lesions that have the potential of progressing to invasive cancers. Virtually all cases of cervical cancer result from sexual transmission of HPV. Worldwide, the incidence of cervical cancer is estimated to be 10% of cancers in women and is the second most common cause of death from cancer in women after breast cancer. Approximately 80% of cervical cancers occur in less-developed countries, where access to screening and treatment for HPV and cervical cancer are limited.[3]

There are more than 100 types of HPV that have been identified, of which approximately 18 have been determined to be oncogenic.[4] Of the oncogenic HPV types, HPV16 and HPV18 account for about 50% and 20% of cervical cancers, respectively.[3] It is believed that microtrauma or erosion of the overlying epithelial layers is a contributing factor allowing viral particles to establish infection in the basal epithelial cells.[3] The histologic precursor to squamous cell cervical cancer is cervical intraepithelial neoplasia (CIN), which has levels of progression from Stage 1 (low-grade dysplasia) to Stage 2/3 (moderate to high-grade dysplasia). The histologic precursor for cervical adenocarcinoma is adenocarcinoma *in situ* (AIS).[5] The disease course from HPV infection to development of malignancy usually takes at least 10 years, with the risk of cervical cancer being highest in women over

40 years of age.[3] A likely result of physiological proximity, HPV also causes an estimated 35 to 50% of vulvar and vaginal cancers. Additionally, HPV is the cause of genital warts (condyloma acuminata) which can be located in the cervico-vaginal, vulvar, and external genitalia areas but rarely progresses to cancer.[5] The inclusion of recombinant HPV6 and HPV11 in Gardasil® is targeted to protect against genital warts, as these two types of HPV account for approximately 90% of cases.[6]

Pharmacology

Gardasil® consists of highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccaromyces cerevisiae* and then self-assembled into VLPs. These VLPs are released from the *S. cerevisiae* cells by cell disruption and are further purified. The vaccine is then finalized by adsorbing the VLPs to an aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate).[5,6]

Clinical Studies of Gardasil®

The approval of Gardasil® was guided largely by the overwhelming evidence for efficacy determined in four separate Phase II and III trials.[1] The Phase II trials were termed Protocol 005, which only evaluated a vaccine for HPV type 16, and Protocol 007, which evaluated the quadrivalent vaccine for HPV types 6, 11, 16, and 18.[5,7,8] The FUTURE I (Females United to Unilaterally Reduce Ecto/Endocervical Disease) and FUTURE II trials were Phase III studies which also evaluated the quadrivalent vaccine.[6,9] In all four trials, the primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population, which consisted of those individuals who had received the complete series of three vaccinations within 1 year of study enrollment, did not deviate from the study protocol, and who were polymerase-chain reaction (PCR) negative for the relevant HPV types prior to the first dose and through 1 month following the third dose.[5]

Protocol 005, a double-blind, randomized, placebo-controlled, multi-center Phase II trial conducted in women 16 to 23 years old evaluated a vaccine for HPV type 16. Participants received 40 mcg (0.5 mL) intramuscular doses of the vaccine (n=768) or placebo (n=765) at day 0, month 2, and month 6. Included were non-pregnant women who had no prior abnormal Papanicolaou (Pap) smears and had ≤5 male sex partners. Follow-up occurred at months 7 and 12, and every 6 months thereafter until month 48. The primary outcome was persistent HPV type 16 infection, defined as having a cervical biopsy positive for CIN or cervical cancer with DNA probes yielding HPV type 16, or being negative for HPV type 16 on day 0 and month 7 with subsequent HPV type 16 DNA detected at two or more consecutive visits 4 or more months apart, or HPV type 16 DNA detected only in a sample collected at the last visit prior to being lost to follow-up. Any adverse events occurring within 14 days of being vaccinated or body temperatures ≥37.7°C (100°F) within 5 days of being vaccinated were also analyzed. Median follow-up was 17.4 months. Forty-one cases of HPV type 16 infections occurred in the placebo group of which 31 were persistent HPV type 16 infections without CIN, 9 were HPV type 16-related CIN (5=grade 1, 4=grade 2), and 1 was an HPV type 16 positive patient lost to follow-up. In the placebo group, the incidence of persistent HPV type 16 infections was 3.8 per 100 woman-years at risk, whereas the incidence in the vaccine group was 0 per 100 woman-years at risk (95% CI 90-100; P<0.001). There were no significant differences between the groups for adversities with injection site pain being the most frequently reported adverse event. The authors concluded that administration of a monovalent HPV type 16 vaccine reduced the incidence of HPV type 16 infections and related CIN; however, a larger study was warranted to determine if the vaccine prevents clinical disease. Also, a multivalent vaccine including other types of HPV would be more beneficial.[7]

Protocol 007, a double-blind, randomized, placebo-controlled, multi-center Phase II trial conducted in women 16 to 23 years

Table 1: Combined Analyses of Efficacy of Gardasil® in the Per-Protocol Efficacy Population[5]

Population	Gardasil®		Placebo		% Efficacy (95% Confidence Interval)
	N	Number of Cases	N	Number of Cases	
HPV type 16- or HPV18-Related CIN Stage 2/3 or AIS					
Combined Protocols	8487	0	8460	53	100 (92.89-100)
HPV type 6-, 11-, 16-, or 18-Related CIN (stages 1, 2/3) or AIS					
Combined Protocols	7858	4	7861	83	95.2 (87.2-98.7)
HPV type 6-, 11-, 16-, or 18-Related Genital Warts					
Combined Protocols	7897	1	7899	91	98.9 (93.7-100)

CIN = Cervical Intraepithelial Neoplasia
AIS = Adenocarcinoma *in situ*

old evaluated the efficacy and safety of a quadrivalent HPV vaccine against HPV types 6, 11, 16, and 18. Inclusion criteria were the same as in Protocol 005, except participants were required to have had ≤4 male sex partners. After receiving 0.5 mL doses of vaccine (type 6=20 mcg, type 11=40 mcg, type 16=40 mcg, and type 18=20 mcg; n=276) or placebo (n=275) at day 1, month 2, and month 6, patients were followed-up at months 7 and 12, and then every 6 months thereafter until month 36. Primary outcome was the composite of persistent infection associated with HPV types 6, 11, 16, or 18 or cervical or external genital HPV-associated disease. Persistent HPV infection was defined as HPV types 6, 11, 16, or 18 DNA in cervicovaginal samples 7 months after vaccination with subsequent HPV type DNA detected at two or more consecutive visits 4 or more months apart, or HPV types 6, 11, 16, or 18 DNA detected only in a sample collected at the last visit prior to being lost to follow-up. Human papillomavirus-associated disease was defined as CIN 7 months after vaccination, vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VaIN), external genital warts, or cervical, vulval, or vaginal cancer with vaccine-HPV type DNA detected. Safety outcomes were also evaluated. At 36 months, the combined incidence of persistent infection or disease with HPV types 6, 11, 16, or 18 fell by 90% in those subjects receiving the vaccine series compared to placebo (95% CI 71-97; P<0.0001). In those who received at least one dose of the vaccine, four patients developed infection associated with HPV (type 16-associated=3 and type 18-associated=1) compared to 36 subjects in the placebo group who developed HPV infection or disease (type 6-associated=13, type 11-associated=3, type 16-associated=21, and type 18-associated=9). This resulted in a statistically significant difference of incidence per 100 women-years at risk with infection or disease of HPV associated with types 6, 11, 16, or 18 to be 0.7% versus 6.7% with the quadrivalent vaccine or placebo, respectively. There was a higher incidence of injection site adverse effects in the vaccine-treated group compared to the placebo-treated group (86% vs. 77%, respectively). The authors concluded that the quadrivalent HPV vaccine against types 6, 11, 16, and 18 was efficacious in preventing HPV infections and associated diseases. Longer studies assessing the vaccine's duration of efficacy and the need for booster doses are necessary.[9]

To date, Phase III results of the FUTURE I and FUTURE II trials have been published only in abstract form and presented at previous meetings of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and Infectious Diseases Society of America (IDSA), respectively.[8]

The FUTURE I study was a double-blind, randomized, placebo-controlled trial evaluating the effect of a quadrivalent HPV vaccine for types 6, 11, 16, and 18 on the composite endpoint of rates of HPV-related CIN, AIS, cervical cancer, genital warts, VIN, VaIN, or vulvar/vaginal cancer. The study was conducted in women 16 to 23 years old. The vaccine or placebo was administered at day 1, month 2, and month 6. Follow-up occurred at months 3 and 7, and then every 6 months (total follow-up period not specified). After an average of 17 months of follow-up the vaccine prevented 100% of HPV 6-, 11-, 16-, and 18-related CIN grades 1-3, genital warts, and VIN/VaIN of any grade (95% CI 88-100). No cases of the composite endpoint occurred in the vaccine group compared to 40 cases in the placebo group. The authors concluded that the prophylactic administration of a quadrivalent HPV vaccine prevented the development of HPV-related infections and disease.[10]

The FUTURE II study was a randomized, placebo-controlled, multi-center trial conducted in women 16 to 23 years old to assess the effect of a quadrivalent HPV vaccine for types 6, 11, 16, and 18 on CIN 2/3 and cervical cancer rates. Patients received vaccine (n=5301) or placebo (n=5258) at day 1, month 2, and month 6. Follow-up occurred at months 7 and 12, and then every 12 months thereafter until month 48. The primary endpoint was the combined incidence of HPV type 16- or 18-associated CIN2/3, AIS, or cancer. There were 21 cases of the primary endpoint in the placebo group compared to 0 cases in the vaccine group. The rate of the composite endpoint was 0.3 per 100 woman-years at risk (95% CI 76-100; P<0.001). In addition, the vaccine was well-tolerated with injection site pain being the most frequently occurring adverse event. The authors concluded that prophylactic quadrivalent HPV vaccination prevented HPV 16- and 18-associated CIN 2/3, AIS, and cancer through 2 years of follow-up.[11]

The use of Gardasil® in these four trials suggests prophylactic vaccination against certain HPV types has substantial efficacy in preventing HPV-related diseases such as CIN and genital warts. Although the absolute number of HPV-related events in either group was relatively small, the differences among subjects receiving Gardasil® versus placebo shows that a benefit favoring Gardasil® does exist. This benefit becomes more apparent in the combined analyses of all four trials as seen in Table 1. The impact on incidence rates of cervical cancer and genital warts with implementation of widespread Gardasil® vaccination should be anticipated in years to come.

FDA-Approved Indications, Dosage, and Administration

Gardasil® is indicated for females 9 to 26 years of age for the prevention of cervical cancer and/or genital warts caused by HPV types 6, 11, 16, and 18. This indication also includes the prevention of precancerous or dysplastic lesions such as:[5]

1) Cervical adenocarcinoma *in situ* (AIS)
2) Cervical intraepithelial neoplasia (CIN) grade 1, grade 2, and grade 3
3) Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
4) Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

Gardasil® should be administered as three separate intramuscular (IM) injections of 0.5 mL in either the deltoid region of the upper arm or high anterolateral area of the thigh. Each 0.5 mL dose

Table 2: Administration Schedule of Gardasil®[5,12]

First Dose	*Second Dose*	*Third Dose*
When indicated	2 months after first dose	6 months after first dose

contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein. The schedule for administration is provided in Table 2.[5,12]

The Advisory Committee on Immunization Practices (ACIP) Provisional Recommendations for Gardasil® include routine vaccination in females 11 to 12 years of age, but it can be initiated in females as young as 9 years of age. For females ages 13 to 26 years old who have not received the series, catch-up vaccination is recommended. Vaccination with Gardasil® outside this age group has not been clearly studied and guidelines have not yet been developed for these individuals. If a dose of Gardasil® is missed or delayed beyond the recommended schedule, it is not yet known how this will affect overall protection against HPV and how management of this situation should proceed. If a female has an equivocal or abnormal Pap smear or genital warts, administration of the Gardasil® regimen can still be given; however, the vaccine would only provide protection against HPV types not already acquired.[12] Since the prophylactic vaccines for HPV are still in the beginning stages of implementation, it has not been determined whether booster vaccinations will be required and when they should be administered, if indicated. Gardasil® can be administered at the same visit with other vaccines such as Tdap (tetanus-diphtheria and pertussis), Td (tetanus-diphtheria), and MCV4 (measles-containing vaccine).[11] As HPV is a sexually transmitted disease, prophylactic vaccination against HPV in men is currently being studied in multiple trials with Cervarix®.[13]

Contraindications and Precautions

The use of Gardasil® is contraindicated in those individuals who have known hypersensitivity to any active component or excipient of the vaccine, including yeast. Individuals who develop hypersensitivity reactions after receiving a dose of Gardasil® should not receive any further doses of the vaccine.[5] As with other intramuscular vaccines, Gardasil® should not be administered to individuals with bleeding disorders (e.g., hemophilia or thrombocytopenia) or patients on anticoagulant therapy unless the benefits outweigh the risk for hematoma.

It should be stressed that completing the dosing schedule of Gardasil® may not confer total immunity in some vaccine recipients and will not provide protection for diseases caused by HPV types other than 6, 11, 16, and 18. Individuals who have reduced immune function (e.g., genetic disorder or HIV) or are on immunosuppressive therapy may not sufficiently mount an immune response to the vaccine.[5]

Pregnancy and Lactation

Gardasil® is currently classified as Pregnancy Category B, but there have been no adequate and well-controlled studies conducted in pregnant women to date. Animal studies have shown no fetal harm when Gardasil® doses up to 300 times the human dose (mg/kg basis) were administered; however, it is not known if Gardasil® can cause fetal harm or effects on reproduction in human subjects. Due to the limited data available, the use of Gardasil® in pregnancy is not recommended at this time.[11] During clinical trials, 2266 women reported pregnancy, of which 15 cases of congenital anomaly were in women who received Gardasil® and 16 cases of congenital anomaly were in those who received placebo. Further analysis of these results showed that when the estimated conception date was within 30 days of receiving either Gardasil® or placebo, there were five cases of congenital anomalies in Gardasil® subjects and no cases of congenital anomalies in placebo subjects. The anomalies included pyloric stenosis, congenital megacolon, congenital hydronephrosis, hip dysplasia, and club foot; all are considered to be consistent with what may be seen in pregnancies of women ages 16 to 26 years old.[5] Merck and Co., Inc. is maintaining a Pregnancy Registry that monitors fetal outcomes; patients and healthcare providers are encouraged to report any exposure to Gardasil® during pregnancy by calling (800) 986-8999.[5,12]

The use of Gardasil® in nursing mothers should be approached with caution, as it is unknown whether antibodies or vaccine antigen can be excreted into human breast milk;[5] however, the ACIP currently states that lactating women can receive the vaccine.[12]

Adverse Effects

Vaccine-related events that occurred at a frequency of 1% or more in subjects receiving Gardasil® or placebo are reported in Table 3.

As with all vaccines, reporting of adverse events following administration or events suspected to be related to Gardasil® can be reported to the Vaccine Adverse Event Reporting System (VAERS) at (800) 822-7967 or online at www.vaers.hhs.gov.

Cost

The average wholesale price (AWP) for Gardasil® is $116.48 per 0.5 mL syringe or vial.[14]

Cleveland Clinic Formulary

Cleveland Clinic has recently added Gardasil® to the Formulary, but its use is restricted to the outpatient setting only.

Conclusion

The development of a vaccine that can dramatically decrease the incidence of cervical cancer has the potential to profoundly affect current immunization standards. It should also be strongly emphasized that completion of the Gardasil® vaccination schedule does not substitute for cervical cancer screening and routine Pap smears should be performed as currently recommended for a patient's age. There is also controversy about how standard vaccination with Gardasil® may affect sexual behaviors, causing some parents or guardians to be reluctant in accepting the vaccine as an option for the prevention of cervical cancer or genital warts. Proper education prior to initiating the vaccination schedule may improve the understanding of the need for prophylaxis against HPV infections.

Table 3: Injection-Site and Systemic Adverse Events[5]

Adverse Event (1 - 5 Days Post–Vaccination)	Gardasil® (N=5088) %	Aluminum-Containing Placebo (N=3470) %	Saline Placebo (N=320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritis	3.1	2.8	0.6
Adverse Event (1 - 15 Days Post-Vaccination)	**Gardasil® (N = 5088) %**	**Placebo Combined (N = 3790) %**	
Systemic Event			
Fever	10.3	8.6	

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Medication Safety

Promethazine (Phenergan®), a commonly used intravenous (IV) and oral agent with antihistamine, sedative, and antiemetic effects, is also known to be a vesicant. There have been case reports of promethazine causing local injuries after inadvertent intra-arterial injection or infiltration, sometimes leading to amputation. The preferred route of administration is via deep intramuscular (IM) injection, however there are data to support the use of promethazine via slow IV push. Due to emerging case reports of patient harm with the use of promethazine, the Institute for Safe Medication Practices (ISMP) has recommended to the Food and Drug Administration (FDA) that the product labeling be reviewed to consider eliminating the IV route of administration. In addition to the FDA request, the ISMP has also made the following recommendations:

- Administer promethazine IM (deep IM)
- If IV Push administration of promethazine is required, it should be administered via a central line
- Consider using 6.25 to 12.5 mg of promethazine as the starting IV dose, especially for elderly patients
- Administer promethazine through a large-bore vein and check the patency of the access site prior to administration
- For intermittent infusion administration, promethazine should be diluted in a minimum of 10 to 20 ml of normal saline and administered over 10 to 15 minutes
- Administer promethazine through a running IV line at the port furthest from the patient's vein
- Advise patients to notify a health care provider if burning or pain occurs during or after the injection of promethazine

The above recommendations have been added to Cleveland Clinic Adult IV Guidelines. If additional information is needed, please see http://www.ismp.org/Newsletters/acutecare/articles/20060810.asp?ptr=y or contact the Drug Information Center at 216-444-6456, option #1.

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