PEDIATRIC PHARMACOTHERAPY

UNIVERSITY of VIRGINIA Children's Hospital

Volume 21 Number 3 March 2015

9-Valent Human Papillomavirus Virus (HPV) Vaccine

Marcia L. Buck, Pharm.D., FCCP, FPPAG

On December 10, 2014, the Food and Drug Administration (FDA) announced the approval of a new 9-valent human papillomavirus virus (HPV) vaccine.[1,2] This vaccine, Gardasil® 9, incorporates five new HPV types, 31, 33, 45, 52, and 58, not included in the original quadrivalent Gardasil® product. It is estimated that protection against the five additional strains will further reduce HPV-associated cancers in women by 14% and in men by 5%, improving the ability of vaccination to reduce cervical cancer rates from 70% to 90%.

At their February 27, 2015 meeting, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended that the 9-valent HPV vaccine be added to the options for HPV immunization in adolescents and young adults.[3,4] The committee continues to support the use of all three currently available products to allow for a gradual transition to the 9-valent vaccine. Either the new or previous vaccines can be used as part of routine vaccination in children at age 11 or 12 years. The HPV vaccine is also recommended in girls and women 13 to 16 years of age and in boys and men 13 to 21 years of age who have not yet been vaccinated. It is anticipated that guidance will be provided at the June ACIP meeting on the need for administration of one or more doses of the 9-valent vaccine in adolescents who were previously immunized with either the quadrivalent or bivalent vaccine.

The ACIP also changed their previous recommendation that the same HPV vaccine product be used for the entire three-dose series, allowing those patients currently in the process of being immunized to be switched to the 9-valent vaccine for completion of the series.[4] In addition, the committee altered the timing of the series to make return visits more flexible, stating that the second dose may be given one or two months after the first, with the third dose given 6 months after the first.

Vaccine Production

Human papillomaviruses (HPVs) are classified as types, assigned in order of discovery. All of HPVs have a circular genome within a capsid shell consisting of major (L1) and minor (L2) proteins. Purified L1 protein will form empty shells that resemble the virus, creating virus-like particles (VLPs). The HPV vaccine is a recombinant vaccine containing virus-like particles (VLPs) of the purified L1 protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Administration of the vaccine results in the development of a humoral immune response, although the mechanism for triggering this response is not well understood.

The L1 proteins are produced by fermentation of *Saccharomyces cerevisiae* and self-assemble into VLPs. The VLPs are released from the yeast cells by cell disruption and then adsorbed onto an aluminum-containing adjuvant. A 0.5 mL dose of the vaccine contains 20-60 mcg of each HPV type L1 protein, 500 mcg aluminum, 9.56 mg sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, and no more than 7 mcg of yeast protein.

Indications

The 9-valent HPV vaccine is indicated for the immunization of girls and women between 9 and 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer caused by the HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts caused by HPV types 6 and 11, as well as precancerous or dysplastic lesions caused by these HPV types.[2] It is also indicated for use in boys between 9 and 15 years of age for the prevention of anal cancer, genital warts, and precancerous or dysplastic lesions caused by these same HPV types.

Evaluation of Potential Impact

Two studies evaluated the potential benefit of the 9-valent HPV vaccine during its development.[5,6] In 2012, Serrano and colleagues used data on the distribution of HPV types gathered from an international study of 8,977 HPV-positive cases and a published meta-analysis of 115,789 HPV positive women to determine the relative contribution of the nine HPV types among all cases of HPV-related cervical disease.[5] The nine HPV types contained in the vaccine accounted for 89.4% of the cases of HPV-related disease, with 18.5% of those cases caused by the five strains not covered in the original quadrivalent vaccine. The authors estimated that adoption of the 9-valent vaccine as part of routine immunization practices could prevent almost 90% of HPV-related invasive cervical cancer worldwide.

The authors published a subsequent study in 2014 examining the potential impact of the 9-valent vaccine in preventing HPV-related cervical disease in Brazil, China, India, and Mexico.[6] Data on HPV type prevalence were gathered from an international study of 1,356 patients and a meta-analysis of 6,025 women from the four countries. The HPV types contained in the 9-valent vaccine accounted for 88.6% of the cases of invasive HPV-related cervical disease in Brazil, 97.3% in China, 92.2% in India, and 85.7% in Mexico. The addition of the five new HPV types increased the potential efficacy of the vaccine by 12-19% in the four countries studied.

Clinical Trials

The safety and efficacy of the 9-valent HPV vaccine were evaluated in five clinical trials prior to FDA approval. These studies, briefly described in the Gardasil® 9 prescribing information, include comparison studies with the quadrivalent HPV vaccine in women 16 to 26 years of age and studies in girls and boys 9-15 years of age to evaluate seroconversion and safety. Across all clinical trials, at least 99.5% of subjects became seropositive within one month of receiving their third dose. Maintenance of immune response has been established for up to 24 months after the initial dose of the vaccine, although more long-term antibody titer studies will be needed.

The results of a phase 2b-3 study evaluating the efficacy and immunogenicity of the 9-valent HPV vaccine were published in the February 19, 2015 issue of *The New England Journal of Medicine*.[7] Joura and colleagues enrolled 14,215 women 16 to 26 years of age in their international randomized, double-blind comparison study. The subjects received either the 9-valent or quadrivalent vaccine in three doses, at day 1, month 2, and month 6. Cytologic testing was performed at baseline and at regular intervals throughout the study, ending at month 54 post-vaccination. Antibody titers were also evaluated after vaccination, and the titers for HPV types 6, 11, 16, and 18 were compared to ensure non-inferiority of the 9-valent vaccine to the quadrivalent vaccine.

The rate of high-grade cervical, vulvar, or vaginal disease related to HPV 31, 33, 45, 52, and 58 was 0.1 per 1,000 person-years in the 9-valent vaccine group, compared to 1.6 per 1,000 person-years in the quadrivalent vaccine group, or 1 case versus 30 cases, resulting in an efficacy of the 9-valent vaccine of 96.7% (95% CI 80.9 to 99.8). Seroconversion was documented in nearly 100% of the patients in the 9-valent vaccine group within 1 month of their third dose. Antibody responses to HPV types 6, 11, 16, and 18 were not significantly different between the two groups. Injection site reactions (pain, swelling, erythema, or pruritus) were common in both groups, occurring in 90.7% of women given the 9-valent vaccine and 84.9% of those given the quadrivalent vaccine. Serious vaccine-related events were reported in only 2 patients in each group of more than 7,000 women.

The effect of concomitant administration with other vaccines was evaluated in a study of 1,237 adolescents given the 9-valent HPV with quadrivalent meningococcal conjugate vaccine and tetanus, diphtheria, acellular pertussis (Tdap) vaccine or at separate visits.[2] Rates of seroconversion, evaluated one month post-dose, were similar between the two groups for each of the three vaccines. The incidence of injection site reactions was similar in the two groups, with the exception of a higher rate of swelling at the injection site in the concomitant administration group (14.4%) compared to the non-concomitant group (9.4%). The majority of the reactions were rated as mild to moderate in severity.

Contraindications and Precautions

The HPV vaccine is contraindicated in patients with a hypersensitivity reaction to previous doses or any of the vaccine components, including yeast.[2] Syncope is known to occur in some patients after receiving vaccines, including HPV vaccine; to minimize the risk, the manufacturer recommends that all patients be observed for 15 minutes following administration of a dose. The safety of 9-valent HPV vaccine during pregnancy has not been established and administration is not recommended. Efficacy and safety have not been established in children

younger than 9 years of age, adults over 26 years of age, or in immunocompromised patients.

Adverse Effects

The 9-valent HPV vaccine has been well tolerated during clinical trials, with most patients having only transient adverse effects at the site of injection.[2] Safety data are available from 13,234 patients who participated in one of the six clinical trials. Patients were evaluated at the time of vaccine administration and followed for 14 days after each injection. The most commonly reported adverse effects reported in girls 9 to 15 years of age included injection site pain (89%), injection site swelling (48%), erythema at the site (34%), and headache (11%).

Women 16 to 26 years of age reported similar symptoms, with injection site pain (90%), swelling (40%), or erythema (34%), and headache (15%). Adverse effects reported in boys 9 to 15 years of age included injection site pain (72%), swelling (27%), and erythema (25%). The presence of a temperature $\geq 100^{\circ}$ F was noted in 1-3% of girls and women after receiving a dose of the vaccine, with temperature $\geq 102^{\circ}$ F noted in 0-1%. Serious adverse events were reported in 2.3% of the patients enrolled in clinical trials, similar to the rate of 2.5% reported with the quadrivalent HPV vaccine. The serious reactions reported with the 9-valent HPV vaccine included fever, hypersensitivity reactions, an asthma exacerbation, headache, and tonsillitis.

Vaccine Administration

The 9-valent HPV vaccine is available in cartons of ten preservative-free single-dose vials or prefilled syringes.[2] The vaccine must be refrigerated until use. The time outside of refrigeration should not exceed 72 hours. The 0.5 mL dose should be administered by intramuscular injection in the deltoid region of the upper arm or the anterolateral aspect of the thigh. The manufacturer recommends that the second and third doses be administered at 2 and 6 months after the initial dose. The vaccine information sheet (VIS) for the 9-valent HPV vaccine is not yet available, but will soon be added to the CDC Vaccines and Immunizations website.

HPV Vaccination Rates

The first HPV vaccine, Gardasil®, entered the U.S. market in 2006. Its introduction was lauded as the first vaccine for cancer and its use was anticipated to significantly reduce the rates of cervical cancer as well as the more than $1 billion dollars spent annually for HPV prevention and treatment.[8] Nearly a decade later, these goals have yet to be realized. In spite of ACIP recommendations for routine immunization of both girls and boys at 11 to 12 years of age, immunization rates remain low. The percentage of girls between 13 and 17 years of age who had received at least one dose of the vaccine rose from 25% in 2007 to 57% in 2013, but has remained at that level. Completion of the three-dose series in 2013 was only 38%. In comparison, series completion rates in the UK and Australia are 60% and 71%, respectively.

Two recent papers have been published that focus on issues related to the low uptake of the HPV vaccine.[9,10] Rahman and colleagues at the University of Texas examined the regional differences in vaccination rates using the Behavioral Risk Factor Surveillance System 2012 data from 8 states.[9] Data from 3,727 adults between 18 and 26 years of age were used to determine the percentage who had received at least one dose of the HPV vaccine as well as the percentage who had completed the three-dose series. The percentages of women and men who had received at least one dose were highest in the Northeast (58.7% and 8.5%, respectively), with rates of 39% and 6.7% in the West and 30.4% and 4.9% in the South. Vaccine series completion rates showed similar regional differences, with the highest rates in the Northeast, 45.6% and 2.2%, compared to rates of 24.8% and 1.6% in the West and rates of 17.7% and 1.4% in the South.

The disparity in vaccine uptake remained even after adjustment for income and education. These numbers are particularly striking when viewed in light of the regional differences in invasive cervical disease. The South continues to experience the highest rates of cervical cancer in the United States. Based on their findings, the authors suggested two approaches to improve vaccination rates: utilizing visits for the influenza vaccine to initiate the HPV vaccine schedule and increasing insurance coverage or extending the Vaccines for Children program to include young adults from 19 to 26 years of age.

Roberts and colleagues explored the concept of parental vaccine hesitancy in an article published ahead of print in *Vaccine*. More than any other vaccine, the HPV vaccine has been the focus of parental and societal concerns regarding its association with a sexually transmitted disease. The authors used a modified version of the Parent Attitudes about Childhood Vaccines (PACV) survey to evaluate the issues surrounding parental hesitancy to accept HPV vaccination for their teenage children. The results of 363 surveys were analyzed from parents of adolescents between 11 and 17 years

of age in six pediatric clinics at either the University of Oklahoma Health Sciences Center or the Medical University of South Carolina. Vaccination status was assessed for the HPV vaccine as well the quadrivalent meningococcal vaccine and Tdap. At the time of the visit when the survey was completed, the overall vaccination coverage rate was 45% for ≥ 1 dose of the HPV vaccine, 73% for the meningococcal vaccine, and 84% for Tdap.

Thirty-nine percent of parents noted that they had concerns about the HPV vaccine efficacy and 41% had concerns about adverse effects. Nearly half of the parents (45%) disagreed with the statement "Teens can get all of the vaccines that are due at a single visit." Agreement with the question "Have you ever delayed a vaccine for reasons other than illness or allergy?" was associated with a higher rate of HPV vaccine refusal than acceptance (8.7% versus 5%, p = 0.048). Disagreement with the statement "I am able to openly discuss concerns about vaccines with my teen's doctor." was also associated with a higher rate of HPV vaccine refusal (6% versus 1.2%, p = 0.046). The overall score on the modified PACV score failed, however, to predict which adolescents would be vaccinated at that visit. While the survey was useful in identifying reasons for parental vaccine hesitancy, it did not predict HPV vaccine uptake. The authors acknowledge that additional methods are needed to better illuminate vaccine-specific parental concerns.

Summary

While the introduction of the 9-valent HPV vaccine offers additional protection against strains known to produce cancer, the low level of HPV vaccine uptake throughout the United States lessens the potential benefits of the vaccine on an individual and societal basis. New initiatives, at the local as well as the state and national levels, are needed to inform the public of the efficacy and safety of the vaccine.

The editors would like to thank Dr. J. Owen Hendley for serving as our guest editor for this issue of the newsletter.

References

1. U.S. Food and Drug Administration. FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV. December 10, 2014. Available at: http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news (accessed 2/23/15).
2. Gardasil® 9 prescribing information. Merck & Co., Inc. February 2015. Available at: http://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf (accessed 3/7/15).
3. Walker M. ACIP: 9-valent HPV vaccine OK to use. MedPageToday. February 27, 2015. Available at: http://www.medpagetoday.com/MeetingCoverage/ACIP/50234 (accessed 3/7/15).
4. Jenco M. ACIP approves meningitis vaccines for high-risk patients. AAP News. March 2, 2015. http://aapnews.aappublications.org/content/early/2015/03/02/aapnews.20150302-1 (accessed 3/7/15).
5. Serrano B, Alemany L, Tous S, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. Infect Agents Cancer 2012;7:38. Available at: http://www.infectagentscancer.com/content/7/1/38 (accessed 3/7/15).
6. Serrano B, Alemany L, de Ruiz PA, et al. Potential impact of a 9-valent HPV vaccine in HPV-related cervical disease in 4 emerging countries (Brazil, Mexico, India and China). Cancer Epidemiol 2014;38:748-56.
7. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.
8. Centers for Disease Control and Prevention. Human papillomavirus vaccination: recommendation of the Advisory Committee on Immunization Practices (ACIP). Morbid Mortal Weekly Report 2014;63(5):1-29.
9. Rahman M, Islam M, Berenson AB. Differences in HPV immunization levels among young adults in various regions of the United States. J Community Health 2015: E-pub ahead of print. DOI 10.1007/s10900-015-9995-2.
10. Roberts JR, Thompson D, Rogacki B, et al. Vaccine hesitancy among parents of adolescents and its association with vaccine uptake. Vaccine 2015: E-pub ahead of print. DOI 10.1016/j.vaccine.2015.01.068.

Formulary Update

The following actions by the Pharmacy and Therapeutics Committee at their February 2015 meeting:

1. Cadexomer iodine gel (Iodosorb®) was added.
2. The warfarin dosing policy was updated to include an option for morning dosing in addition to evening dosing.
3. The policy on sublingual administration of tacrolimus capsules was updated.
4. Immune globulin for IM use was deleted due to lack of use.
5. Homatropine hydrobromide 2% and 5% ophthalmic solutions were deleted due to manufacturer discontinuation.
6. Smaller sizes of lidocaine 1% (2 mL) and lidocaine 1% with epinephrine 1:100,000 (10 mL) vials were added to reduce waste.
7. Vasopressin and haloperidol injection were added to the basic override list.