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Quadrivalent Human Papillomavirus (HPV) Recombinant Vaccine

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The approval of the first vaccine for human papillomavirus (HPV) by the Food and Drug Administration (FDA) on June 8, 2006 has been heralded as a major breakthrough in the prevention of cervical cancer. Each year, nearly 10,000 new cases of cervical cancer are diagnosed in the United States and approximately 4,000 women die from this disease. On June 28th, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended that the HPV vaccine be added to the childhood immunization schedule.¹

The currently available vaccine, a quadrivalent HPV vaccine, is indicated in females from 9 to 26 years of age for the prevention of cervical cancer, genital warts, and precancerous or dysplastic lesions including cervical intraepithelial neoplasia (CIN 1, 2, or 3) adenocarcinoma *in situ* (AIS), vulvar intraepithelial neoplasia (VIN 2 or 3) and vaginal intraepithelial neoplasia (VaIN 2 or 3) caused by HPV types 6, 11, 16, and 18.¹⁻⁵ This issue of *Pediatric Pharmacotherapy* will describe the quadrivalent HPV vaccine and review the available studies documenting its efficacy and safety in girls and women.

Vaccine Components and Immunogenicity

The quadrivalent HPV vaccine contains highly purified recombinant virus-like particles of the major capsid protein (L1) of HPV types 6, 11, 16, and 18. These four types are the cause of approximately 70% of cervical cancers, 90% of genital wart cases, and 35-50% of precancerous lesions. Each 0.5 mL dose of the vaccine contains approximately 20 mcg of HPV 6L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.²⁻⁵

Seroconversion has been demonstrated in approximately 99% of patients immunized. Administration of the HPV vaccine induces considerably higher levels of antibody than that produced after naturally occurring infection.⁶ In

a study of women 18 to 26 years of age, the quadrivalent HPV vaccine produced geometric mean titer (GMT) values of 582.2 for anti-HPV 6, 696.5 for anti-HPV 11, 3,889.0 for anti-HPV 16, and 801.2 for anti-HPV 18 at month 7 (one month following administration of the last dose in the three-dose series). Antibody titers then slowly decline, but appear to level off by month 24.² Antibody titers are still measurable five years after immunization.^{5,7}

In a study comparing immunogenicity in adolescent girls to adult women, GMT values in the younger patients were comparable or higher to those seen in adult women. Average GMT values in the adolescents (9 to 15 years of age) were 931.3 for anti-HPV 6, 1,305.7 for anti-HPV 11, 4,944.9 for anti-HPV 16, and 1,046.0 for anti-HPV 18 at one month post-vaccination. Titers in the 16 to 26 year old women were 542.4 for anti-HPV 6, 766.1 for anti-HPV 11, 2,313.8 for anti-HPV 16, and 460.7 for anti-HPV 18.²

Clinical Efficacy

The efficacy of the quadrivalent HPV vaccine or its components has been demonstrated in several clinical studies. The manufacturer has conducted two Phase II studies and two Phase III studies, enrolling more than 20,000 women between 16 and 26 years of age. All four were randomized, double-blind, placebo-controlled trials. Patients received either active vaccine or placebo at enrollment, and again at months 2 and 6. Efficacy was evaluated beginning at month 7 and follow-up ranged from 2 to 4 years.

The first Phase II study randomized 2,391 females to receive just the HPV 16 L1 component of the vaccine or placebo. There were no cases of HPV-16 CIN 2/3 or AIS in the vaccine patients and 12 cases in the placebo group (% efficacy 100, 95% CI 65.1, 100).

In the second Phase II study, 551 patients were randomized to either the quadrivalent vaccine or placebo. At follow-up, there were no cases of CIN 1, CIN 2/3, or AIS in the vaccine group,

compared to 3 cases in the placebo group (% efficacy 100, 95% CI -137.8, 100). There were no cases of genital warts in the vaccine group and 3 cases in the placebo group (100, 95% CI -139.5, 100).^{2-5,7}

Two multicenter Phase III trials (titled FUTURE I and II for Females United to Unilaterally Reduce Endo/Ectocervical Disease) were conducted to further evaluate the safety and efficacy of the quadrivalent HPV vaccine. FUTURE I assessed 5,442 girls and women over a period of 2.4 years. There were no cases of CIN 1, CIN 2/3, AIS in the vaccine recipients, compared to 37 cases in the placebo patients (100, 95% CI 89.5, 100). There were also no cases of genital warts in the vaccine group, compared to 29 cases in the placebo group (100, 95% CI 86.4, 100).²⁻⁵

FUTURE II enrolled 12,157 women for a two-year period. At follow-up, there were 4 cases of precancerous lesions in the vaccine group, compared to 43 cases in the placebo group (90.7, 95% CI 74.4, 97.6). There was one case of genital warts in the vaccine group, compared to 59 in the placebo group (98.3, 95% CI 90.2, 100). There were no cases of cervical cancer reported.^{2-5,8}

Analysis of overall study results by the manufacturer revealed a reduction in the incidence of HPV disease-related procedures (excision, laser or cold knife conization) by 16.5% and a reduction in surgeries to excise genital lesions by 26.5% in the vaccine recipients compared to those given placebo.²

Contraindications and Precautions

The quadrivalent HPV vaccine is contraindicated in patients with a known hypersensitivity to any component of the vaccine, including yeast, or in those who have had hypersensitivity reactions with a previous dose of the vaccine. Vaccination may be delayed in patients with a febrile illness, but low-grade fever or mild upper respiratory tract infections are not considered contraindications to administering the vaccine. Patients with an impaired immune response, due to underlying illness or the use of immunosuppressive medications, may have reduced antibody response to the vaccine. Because the HPV vaccine is an intramuscular injection, patients with bleeding disorders or those who are taking anticoagulants may be at risk for hematoma after injection.²⁻⁵

In reproduction studies in rats, the quadrivalent HPV vaccine has not been associated with teratogenic effects. The effects of the vaccine on

a developing human fetus, however, are not known. The manufacturer recommends that the vaccine be given to a pregnant woman only if clearly needed. In clinical trials, the rate of adverse events in women who became pregnant after receiving the vaccine were no different than in those receiving placebo. Prescribers should contact the manufacturer's pregnancy registry at 800-986-8999 to report any pregnancy during the period around vaccination.²⁻⁵

Adverse Effects

In clinical trials, the most common adverse reactions reported with quadrivalent HPV vaccine administration were injection site reactions and fever. Using data accumulated in five clinical trials, the most frequently reported adverse effect was pain (reported in 84% of patients versus 49-75% of patients given placebo), followed by swelling and erythema (reported in 25% of HPV vaccine recipients compared to 1-18% of those given placebo), and pruritus (3% in the vaccine group versus 1-3% in the placebo group). Fever within 15 days of vaccination was reported in 10% of the HPV vaccine group and 9% of the placebo group.²⁻⁵

Other adverse reactions reported after HPV vaccine administration included headache (0.03% in vaccine recipients compared to 0.02% in controls), gastroenteritis (0.032% versus 0.01% in controls), appendicitis or pelvic inflammatory disease (0.02% versus 0.01% in controls).²⁻⁵

Dosing

The quadrivalent HPV vaccine (Gardasil®) is administered in a three dose series, with the second dose given 2 months after the first dose, and the third dose given six months after the first dose. The ACIP recommends administration to girls beginning at the 11-12 year physician visit. It is administered as an intramuscular injection, in either the deltoid or the anterolateral area of the thigh.^{2,3} According to the ACIP, the quadrivalent HPV vaccine may be given concomitantly with the hepatitis B vaccine, the tetanus-diphtheria-acellular pertussis vaccine, and the conjugate meningococcal vaccine.¹

Availability and Cost

Gardasil® is manufactured by Merck and is available in single-dose vials or prefilled syringes. It must be refrigerated and protected from light until use. The average wholesale cost is \$119.75 per dose. The HPV vaccine was approved for the Vaccines for Children program on June 29, 2006.¹

Several cost-benefit analyses have been conducted which suggest a positive overall effect from routine HPV vaccination.^{9,10} Using a mathematical model with a cost-effectiveness ratio of less than \$60,000 per quality-adjusted year of life saved, Goldie and colleagues suggested a program to immunize adolescent girls at age 12 and begin screening (Pap tests) every three years starting at age 25 to provide an estimated overall lifetime reduction in cervical cancer risk of 94% compared to no intervention.¹⁰ Other models have produced similar results, with incremental differences based on the cost and efficacy of the vaccine, as well as the duration of immunity produced.

Summary

The quadrivalent HPV vaccine has the potential to produce a significant reduction in the number of women who develop cervical cancer. While more long-term surveillance studies are needed to determine its efficacy, the availability of this vaccine is a major step towards eradication of HPV-related disease.

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Pharmacology Literature Review

Antistaphylococcal products

As the frequency and severity of staph infections continue to rise, there has been increasing interest in the development of methods for both active and passive immunization against these organisms. This article describes the products currently under development, including a capsular polysaccharide vaccine (StaphVAX®) and several immunoglobulin products (Altastaph®, INH-A21, tefibazumab, Aurograb®, and pagibaximab). Unfortunately, at this time, Phase III trials with StaphVAX and INH-A21 have failed to demonstrate significant benefit. The author of this review discusses the problems with these products and the need for continued research in this area. Deresinski S. Antistaphylococcal vaccines and immunoglobulins: current status and future prospects. *Drugs* 2006;66:1797-806.

Clinical trial design

This concise review covers the basics of clinical trial design, with an emphasis on drug trials. This article, while likely to be of interest to most clinicians, may be especially useful for students and new practitioners. The authors highlight 10 key factors in developing a sound clinical trial, including: ethical issues, sampling criteria, blinding, randomization, choice of analytic methods, group comparisons, end point selection, interpretation of results, trial duration, and the issue of traditional versus equivalence testing. Glasser SP, Howard G. Clinical trial design issues: at least 10 things you should look for in clinical trials. *J Clin Pharmacol* 2006;46:1106-15.

Erythema multiforme after meningitis vaccine

The authors of this case report describe a 20 year old college student who developed erythema multiforme within two weeks of administration of the conjugate meningococcal vaccine. The rash resolved in four weeks. Although not previously reported with meningococcal vaccine, erythema multiforme has been associated with administration of diphtheria-tetanus-pertussis, measles-mumps-rubella, *Haemophilus influenzae* type b, hepatitis B, pneumococcal, and varicella vaccines. Based on the potential for more serious dermatologic reactions, such as Stevens Johnson Syndrome, with repeat exposures, the authors recommend that patients who develop erythema multiforme following vaccination not be given additional doses. Studdiford J, Oppenheim L, McCann E, et al. Erythema multiforme after meningitis vaccine: patient safety concerns with repeat immunization. *Pharmacotherapy* 2006;26:1658-61.

Management of focal-onset seizures

This extensive review covers the therapeutic options currently available for the management of focal seizures. The authors cover the diagnosis and classification of partial seizures, as well as antiepileptic drug selection, monitoring, and dose titration. Specific concerns with drug selection in children and the elderly are addressed, as well as the use of antiepileptics in women of child-bearing potential. Johannessen SI, Ben-Menachem E. Management of focal-onset seizures: an update on drug treatment. **Drugs 2006;66:1701-25.**

Otitis media review

This review, by clinicians from the University of Pittsburgh, covers a wide range of therapies for patients with otitis media with effusion. In addition to discussing antibiotic use, the authors review the role of decongestants, antihistamines, corticosteroids, and surgical interventions, including myringotomy with tube insertion and adenoidectomy. They also address the role of vaccines in preventing disease. While the article itself is brief, the reference list includes over 100 citations. Mandel EM, Casselbrant ML. Recent developments in the treatment of otitis media with effusion. **Drugs 2006;66:1565-76.**

Rifampin in neonates

In this study, the pharmacokinetic profile of rifampin was evaluated using 123 serum samples collected from 21 neonates. After an average IV dose of 8.5±2.1 mg/kg/day, the peak and trough concentrations were 4.66±1.47 mg/L and 0.21±0.20 mg/L. There was a significant linear relationship between dose and peak rifampin concentrations, but with a high degree of interpatient variability. The mean pharmacokinetic parameters were: volume of distribution 1.84±0.59 L/kg, clearance 0.28±0.11 L/kg/hr, and elimination half-life 4.9±1.7 hrs. Based on their findings, the authors concluded that the currently recommended dosing regimen of 10 mg/kg given once daily is adequate to achieve desired serum concentrations. Pullen J, Stolk LML, Degraeuwe PLJ, et al. Pharmacokinetics of intravenous rifampicin (rifampin) in neonates. **Ther Drug Monit 2006;28:654-61.**

Safety of corticosteroids for asthma

A number of studies have been conducted to evaluate the safety profile of long-term use of corticosteroids. The author of this review describes the findings of long-term studies (those lasting > 1 year) of inhaled corticosteroid use in children with asthma. The article focuses on three areas: growth (reported in 14 studies), bone mineral density (reported in 4 studies), and

cortisol levels (reported in 10 studies). While there was some evidence of a small decrease in growth during initial therapy, particularly with doses greater than 200 mcg, there were no studies demonstrating significant differences in final adult height. None of the studies showed significant effects on mineral density or plasma or urinary cortisol levels. Pedersen S. Clinical safety of inhaled corticosteroids for asthma in children: an update of long-term trials. **Drug Safety 2006;29:599-612.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/27/06:

1. Levetiracetam (Keppra®) injection was added to the Inpatient Formulary for the treatment of seizures in patients unable to take the drug orally. The IV dose and interval should be the same as the PO regimen.
2. Ramelteon (Rozerem®) was added to the Inpatient and Outpatient Formularies for the treatment of insomnia characterized by difficulty with sleep onset. This agent is a melatonin receptor antagonist with high affinity and selectivity for human MT₁ and MT₂ receptors.
3. Ranolazine extended-release tablets (Ranexa™) was also added to both Inpatient and Outpatient Formularies. It is used in the treatment of chronic angina and is restricted to use by Cardiology.
4. Ferrous gluconate 325 mg was added back to the Inpatient Formulary for use in the GCRC.
5. Levalbuterol (Xopenex®) was rejected. If this product is needed, it may be obtained through the current non-formulary request process.
6. The Adverse Drug Reaction Quarterly Report and the Quarterly Report of Non-Formulary Drug Use were presented. For more information, contact Drug Information Services at 4-8034.

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