Cervical Cancer Vaccine Effective at 5.5 Years

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — The investigational cervical cancer vaccine Cervarix remained 100% effective through 5.5 years in preventing cervical intraepithelial neoplasia lesions associated with human papillomavirus strains 16 and 18, Dr. Gary Dubin reported at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

The finding comes from the second interim analysis of the long-term follow-up phase of GlaxoSmithKline's primary efficacy trial for its bivalent HPV 16/18 vaccine, in which 1,113 women aged 15-25 years were randomized to receive the vaccine or placebo.

Safety, immunogenicity, and efficacy were initially evaluated for up to 27 months (Lancet 2004;365:1757-65), and the first interim analysis of the long-term follow-up phase was performed in October 2005 (Lancet 2006;367:1247-55). The final analysis will come at the end of 2007, said Dr. Dubin, vice president and director of GSK's Clinical Development and Medical Affairs, Prophylactic Vaccines, North America.

At 63-64 months following receipt of the first vaccine dose, ELISA titers to HPV strains 16 and 18 were both 11 times higher in the vaccine recipients than in the placebo group. From the end of the initial (27-month) study phase through a mean follow-up of 5.5 years, 1 incident HPV 16/18 infection occurred in a vaccine recipient, compared with 43 infections among the controls, giving a vaccine efficacy of 98.1%. The infection in the one vaccine recipient did not persist at 6 and 12 months, however, whereas 19 controls had persistent infection at 6 months and 9 infections persisted at 12 months.

A single incident HPV 16/18 infection occurred in a vaccine recipient, versus 43 infections among the controls, giving a vaccine efficacy of 98.1%.

As had been found at the two previous analyses, no vaccine recipient had HPV 16/18–related cytology classified as atypical squamous cells of undetermined significance (ASCUS) or greater, or cervical intraepithelial neoplasia (CIN) lesions. In contrast, 24 controls had HPV 16/18–related ASCUS or higher and 5 had HPV 16/18 CIN lesions at 5.5 years. Cervarix is formulated with a special adjuvant that has been shown to induce a higher and more persistent immune response, compared with vaccines formulated with aluminum salts only (Vaccine 2006;24:5937-49).

The vaccine also showed evidence of cross-protection against HPV types 45 and 31, the third and fourth most common strains associated with cervical cancer worldwide. Efficacy against incident infection with HPV 45 was 88%, and against HPV-31, 54%. Worldwide, 2.9% of all cervical cancers are attributed to HPV 31, 6.7% to HPV 45, 17.2% to HPV 18, and 53.5% to HPV 16 (Int. J. Cancer 2004;111:278-85).

In a separate immunobridging study involving 666 women aged 15-55 years, HPV 16/18 antibody titers were of the same order of magnitude as those associated with protection in the efficacy study. There is a need for an HPV vaccine in women over 25 years of age, because new infections with HPV cancer types are estimated to occur in 5.3% of women aged 25-55 years. Moreover, although new infections do decrease with age, the risk of persistence actually increases with age. "Our target is that women over 25 years are not denied access to the GSK cervical cancer vaccine," Dr. Dubin said.

A double-blind, randomized, controlled phase III efficacy trial involving 18,665 women aged 15-25 years in 14 countries is underway. The women received either GSK's HPV vaccine or the hepatitis A vaccine as a control on a 0-, 1-, 6-month vaccination schedule. The required number of events—HPV 16/18–associated CIN2 or higher lesions—were accrued in November 2006. Those data will be presented "in the near future." A study of the vaccine's efficacy in 5,700 women over 25 years of age is also ongoing, while trials looking at coadministration with other routine adolescent vaccines, safety and immunogenicity in HIV-positive women, and other local registration trials in several countries are planned.

Regulatory files for Cervarix were submitted to the European Union and internationally in 2006. In the United States, the biologic license application is "on target for submission by April 2007," Dr. Dubin reported. ■

Injection Site Pain Is Main Adverse Event for Gardasil

ATLANTA — Injection site pain is the most frequently reported adverse event following receipt of the quadrivalent human papillomavirus vaccine, Dr. Lauri Markowitz said at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

Through January 2007, the passive Vaccine Adverse Event Reporting System (VAERS) has received a total of 542 reports associated with Merck's quadrivalent human papillomavirus (HPV) vaccine (Gardasil), of which 5% were considered serious. No deaths were reported, said Dr. Markowitz of the CDC's National Center for HIV, STD, and TB Prevention.

A total of 2.1 million doses of Merck's HPV vaccine had been distributed through December 2006. The adverse event reporting rate, 25/100,000 doses, is slightly higher than that seen with other vaccines but "not unexpected for a new vaccine," she noted.

Injection site pain was the most commonly reported adverse event (18%), followed by dizziness (11%), syncope (11%), fever (9%), and nausea (9%). More than 99% occurred in females, reflecting the population for whom the vaccine currently is recommended. Nearly half (47%) of those reporting adverse events were aged 13-18 years, and another 38% were aged 19-26 years. Only 7% were aged 9-12 years, 6% were over 26 years of age, and the rest were less than 9 years.

There were three reported cases of Guillain-Barré syndrome (GBS), two of whom had simultaneously received the meningococcal conjugate vaccine (Menactra) 9 and 13 days earlier. It was not known whether the third GBS case had received other vaccines at the same time. An association between Menactra and GBS has been reported, although it is not yet clear whether the relationship is causal (MMWR 2006;55:1120-4).

Facial palsy was also reported in three cases, all within 1 day of receiving Gardasil. Two of those individuals had received influenza vaccine—one live attenuated and one inactivated—at the same time. The background rate of facial palsy in the general population is 30/100,000 per year.

"We can confidently say that the observed [rate] is much less than expected," Dr. Markowitz commenteted.

Physicians are encouraged to report all clinically significant adverse events in patients following receipt of vaccines to VAERS, online at www.vaers.hhs.gov, by phone at 800-822-7967, or by fax at 877-721-0366.

—Miriam E. Tucker

Nonvaccine HPV Infections Common

BY PATRICE WENDLING
Chicago Bureau

NEW ORLEANS — Infections with genotypes not contained in the newly approved human papillomavirus vaccine are common among adolescent girls positive for the virus, Dr. Roshan George said at the Southern regional meeting of the American Federation for Medical Research.

She presented results from the first 32 patients, aged 16-18 years, in an ongoing genotype study of adolescents with atypical squamous cells of undetermined significance and human papillomavirus (HPV) infection. None of the girls had been immunized with the new vaccine containing HPV genotypes 6, 11, 16, and 18 (Gardasil).

Genotype results available from 29 of the 32 girls identified 53 isolates, of which 38% were vaccine genotypes and 62% were nonvaccine genotypes.

Sixteen girls (55%) were infected with more than one genotype, seven (24%) with more than two genotypes, and two girls (7%) were infected with four genotypes, said Dr. George, a pediatrician with Louisiana State University Health Sciences Center in Shreveport.

Just 17% of girls were infected only with genotypes covered by the vaccine, 38% were infected with the vaccine genotypes plus other types, and 45% were infected only with genotypes not covered by the vaccine.

"[These data support] recommendations that cervical screening should be continued even in females receiving the vaccine," Dr. George said.

Epidemiology studies have shown an HPV prevalence rate of 25%-40% in young women.

Of 53 isolates identified in results from 29 of 32 girls, 62% were nonvaccine genotypes.

DR. GEORGE

Adolescents acquire HPV rapidly after sexual initiation, and often have concomitant sexually transmitted diseases.

"I was definitely not surprised that almost 55% had a concomitant STD, but I was surprised to see that 50% were pregnant, two had four genotypes, and 45% were not covered by vaccine strains," Dr. George said in an interview. "That's why it's important we keep screening."

Dr. George recommends that HPV genotyping, which is not federally approved for this application, should be performed only in those patients with abnormal cytology or carcinoma in situ on their routine Pap test.

The investigators extracted DNA from ThinPrep liquid Pap smear specimens taken from the patients and used polymerase chain reaction to amplify HPV targets overnight before using xMAP (Luminex) bead-based assay technology to detect the DNA.

The reagent beads or microspheres are embedded with HPV probes that are color coded into subsets specific for 1 of 19 HPV genotypes. Thus, each of the 19 probes is associated with a microsphere of a specific dye color and will bind to its complementary target DNA, Dr. George explained.

High-risk HPV genotypes 16 and 18, which cause 70% of cervical cancers, were found in 19% and 5.6% of isolates. Low-risk types 6 and 11, which can cause genital warts and lead to low-grade dysplasia, were found in 5.6% and 7.6% of isolates. HPV genotypes 57, 45, 31, 35, and 58 were also found in roughly 7.5% of isolates. No detectable genotype was found in two specimens and one patient had a low-risk type not detected by the assay, the investigators reported.

The study was funded by the Digene Corp., which markets the reagents used in the study. ■