Cervical Cancer Vaccine Effective at 5.5 Years

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — The investigational cervical cancer vaccine Gardasil remained 100% effective through 5.5 years in preventing cervical intraepithelial neoplasia lesions associated with human papillomavirus strains 16 and 18, Dr. Cary 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, through March 15, 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 27 months (1-year) study phase through a mean follow-up of 5.5 years, 1 patient with 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 as 6 and 12 months, however, whereas 19 controls had persistent infection at 6 months and 9 infections persisted at 12 months.

Injection site pain was the most frequent 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 342 reports associated with Merck’s quadrivalent human papillomavirus (HPV) vaccine (Gardasil), of which 3% 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 lower 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, followed by dizziness (11%), syncope (11%), fever (9%), and nausea (9%). More than 99% occurred in females, reflecting the sex distribution of the study population. The vaccine currently is recommended for nearly half (47%) of those reporting adverse events were aged 13-18 years, and another 18% 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 (Men-actra) and 9 and 13 days earlier. It was unknown 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 commented.

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

—Miriam E. Tucker

Nonvaccine HPV Infections Common

BY PATRICIE WENDLING
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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 (ASC-US) or greater leukocyte atypia (LAA) associated with intracutaneous 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 31 and 33, the third and fourth most common strains associated with cervical cancer worldwide. Efficacy against incidence infection with HPV 45 was 88%, and against HPV 51, 53/54. Worldwide, 29% of all cervical cancers are attributed to HPV 31, 6.7% to HPV 45, 17.2% to HPV 18, and 53.3% to HPV 16 (Int. J. Cancer 2004;112:278-85).

In a separate immunogenicity study involving 666 women aged 15-35 years, HPV 16/18 antibody titers were of the same order of magnitude as those associated with the vaccine. 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% 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 elderly patients, and other local registration trials in several countries are planned.

Regulatory files for Cervarix were submitted to the European Commission in July 2006 and are under review nationally in 2006. In the United States, the biologic license application is “on target for submission by April 2007,” Dr. Dubin reported.