Gardasil 96% Effective Against Premalignancies

BY BRUCE K. DIXON
Chicago Bureau

CHICAGO — The quadrivalent human papillomavirus vaccine, which protects women against HPV types 6, 11, 16, and 18, also prevents the abnormal growth of precancerous cells in the cervix associated with these four types.

This finding, from the international phase IIb/III Quadrivalent HPV Vaccine Study, was reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

These premalignancies, known as cervical intraepithelial neoplasia (CIN), are a major contributor to health care costs resulting from screening, research, and treatment, Dr. Sven-Eric Olsson said at the conference, which was sponsored by the American Society for Microbiology.

Through 3 years of follow-up, the vaccine was 96% effective in preventing CIN related to HPV types 6, 11, 16, and 18, and vaccine efficacy was significant for all four of the HPV types, though somewhat less so for HPV 11, said Dr. Olsson, with the Karolinska Institute at Danderyds Hospital in Stockholm.

The Food and Drug Administration–approved quadrivalent HPV vaccine (Gardasil; Merck & Co.) is recommended by the Centers for Disease Control and Prevention for use by women aged 9-26 years. The four targeted HPV types are responsible for 70% of cervical cancers and 90% of genital warts, according to the CDC.

The investigators drew data from more than 18,000 women aged 16-26 years who were enrolled in one of three randomized trials sponsored by Merck.

Through 3 years of follow-up, the vaccine was 96% effective in preventing cervical intraepithelial neoplasia related to HPV types 6, 11, 16, and 18.

The cohort of women was evenly divided to receive either vaccine or placebo at day 1, month 2, and month 6. Subjects underwent cervicovaginal sampling at day 1 and month 7 and Pap testing at day 1 and 6- to 12-month intervals for up to 48 months.

All of the specimens were HPV typed and histologically diagnosed by a four-member blinded pathology panel, said Dr. Olsson. He has given lectures for Merck but has no financial stake in either Merck or GlaxoSmithKline, which has filed with the FDA for approval of Cervarix, a bivalent HPV vaccine protecting against types 16 and 18.

Primary per protocol vaccine efficacy analysis included subjects who received all three of the doses, were sero- and PCR-negative to the four HPV types at day 1 and PCR-negative through month 7, and had no major protocol deviations.

Dr. Olsson reported that in the group that received the vaccine, there were 6 cases of HPV 6/11/16/18 CIN, compared with 148 cases in the placebo group, providing the vaccine efficacy of 96%.

"And for CIN [grade] 2 or worse, including adenocarcinoma in situ, there was 1 case in the vaccine group and 76 cases in the placebo arm, for a 99% efficacy rate," he said, adding that vaccine efficacy against HPV 6/11/16/18–related CIN ranged from 95.5% to 100% based on CIN grade. (Grade 1 is low-grade squamous intraepithelial lesion; grades 2 and 3 are high-grade squamous intraepithelial lesions.)

The single case of CIN 3 in the vaccinated group (there were 46 in the placebo arm) was a Brazilian woman who was positive for HPV 52 at day 1 and at 32 months was shown to be positive for both 52 and 16. She subsequently underwent a loop electrosurgical excision procedure.

"The lifetime risk of acquiring an HPV infection for sexually active people is 50%, and approaches 75% in some settings," Dr. Olsson explained, adding that HPV causes cervical cancer in 3%-4% of unscreened women. "When we do the screening, we reduce the frequency of cervical cancer, but in doing so we create a new disease ... CIN."

A separate analysis of data from this same cohort of women suggests that in these women, aged 16-26 years, Gardasil vaccination reduces the overall incidence of Pap abnormalities regardless of the HPV types involved.

In a poster presentation, the researchers analyzed the impact on rates of abnormal Pap tests in women who, at day 1 of the study, had a negative Pap test and were DNA negative to 14 common HPV types and seronegative to the four vaccine HPV types discussed above.

In this generally HPV-naïve population, Gardasil prevented almost half of high-grade squamous intraepithelial lesions, compared with placebo. "Given these results, the impact on HPV 6/11/16/18–related Pap abnormalities is expected to be dramatic," the authors wrote. ■

Recent Cancer Data Support HPV Vaccine Approval for Young Men

BY SHARON WORCESTER
Southeast Bureau

Recent data linking human papillomavirus with oropharyngeal cancers, which typically occur in men, suggest a need for stepped-up efforts to gain approval for use of the HPV vaccine in young men and adolescent boys, according to Dr. Erich Sturgis and Dr. Paul M. Cinciripini, of the University of Texas M.D. Anderson Cancer Center, Houston.

Although the incidence of most types of squamous cell carcinomas of the head and neck have declined over the past 20 years, in tandem with declines in the prevalence of smoking, the incidence of oropharyngeal cancers has remained stagnant—a trend that may be attributable to the growing incidence of oncogenic HPV-associated cancers, the authors stated in the report (Cancer 2007 Oct. [doi:10.1002/cncr.22963]).

"We encourage the rapid study of the efficacy and safety of [HPV-16/18] vaccines in males and, if successful, the recommendation of vaccination in young adult and adolescent males," they wrote.

They praised efforts to promote the recently approved HPV-16/18 vaccination of young women and adolescent girls to reduce the incidence of cervical cancer and dysplasia, but warned that limiting vaccination programs to women and girls would delay potential benefits of preventing the HPV-16/18 oropharyngeal cancers in males.

Dr. Cinciripini has acted as a consultant for GlaxoSmithKline, the manufacturer of Cervarix, a vaccine against HPV 16/18.

Their recommendation is based on a number of factors. Data have confirmed an increase in the incidence of oral tongue cancer in young adults and of oropharyngeal cancers—particularly tonsil and base of tongue cancer—in those younger than 45 years.

In addition, the literature consistently shows a link between oncogenic HPV and oropharyngeal cancers, with HPV DNA being identified in about half of all oropharyngeal cancers and in a particularly high proportion of oropharyngeal cancers in nonsmokers. More than 90% of HPV-positive oropharyngeal cancers are a result of HPV-16.

"The association is also quite strong with a significant risk of oropharyngeal cancer reported in epidemiologic case-control studies by numerous independent investigators and after adjustment for smoking and alcohol exposures," the authors wrote.

The similarities between HPV-related oropharyngeal cancer and cervical carcinogenesis, and the "biologic plausibility of the HPV carcinogenesis model all support HPV causality of a proportion of oropharyngeal cancers," they noted.

The mode of transmission of HPV in patients with HPV-related oropharyngeal cancer is not clear, but some reports suggest that the sexual history of oncogenic HPV-positive oropharyngeal cancer patients mirrors that of women with cervical cancer, and it is likely that risk factors such as multiple sexual partners and oral-genital sex play a role, they stated.

Lending further credence to this possibility is the reported increase in the frequency of oral sex in adolescents, which could be a contributing factor in the increase in HPV-associated oropharyngeal cancers in young adults.

Data from the Swedish Cancer Registry show that the prevalence of HPV-16 in oropharyngeal cancer specimens increased from 23% in the 1970s to 28% in the 1980s, 57% in the 1990s, and 68% in the 2000s, despite dramatic declines in smoking prevalence. ■

HPV-16/18 Vaccine Found to Not Clear Existing Infection

BY MARY ANN MOON
Contributing Writer

In women who test positive for human papillomavirus DNA, the bivalent HPV-16/18 vaccination does not induce or accelerate clearance of the infection, according to a phase III study.

Human papillomavirus (HPV) vaccination induces cell-mediated immune responses that are traditionally involved in the eradication of infection, and it has been suggested that the vaccine might benefit women who are already infected, perhaps by enhancing viral clearance. Researchers examined the issue using a cohort drawn from a large, ongoing randomized clinical trial of vaccine efficacy.

The subjects in the main study of vaccine efficacy were nearly 7,500 women aged 18-25 years who resided in Costa Rica, where cervical cancer screening programs incorporate HPV DNA testing along with Pap tests. "Because current management protocols often involve retesting HPV-positive women within months of an initial HPV-positive result before treatment decisions are made, understanding the impact of vaccination on viral clearance in the first 6-12 months following an initial HPV-positive result would be informative," wrote study investigators Dr. Allan Hildesheim of the National Cancer Institute, Rockville, Md., and his associates.

The investigators assessed viral clearance in a subset of 2,055 subjects who were positive for HPV DNA and received either a control immunization or the bivalent HPV-16/18 vaccine that contains viruslike particles only from HPV-16 and HPV-18. This formulation has been approved for use in Australia and is under review for use in the United States and other countries, they noted.

Clearance rates for HPV-16 and/or HPV-18 were not significantly different between the active treatment and placebo treatment groups either 6 months after the initial vaccination was given (33.4% vs. 31.6%) or at 12 months, when the entire series of vaccinations was completed (48.8% vs. 49.8%). In addition, there was no evidence of a vaccine effect in any of several subgroups studied.

The trial was funded by the National Cancer Institute and the National Institutes of Health. Although Dr. Hildesheim reported having no conflicts of interest, other study investigators reported receiving financial support through royalties and employment from GlaxoSmithKline—manufacturer of the vaccine used in the study—and Merck. ■