Largest Study to Date Supports Gardasil's Safety in First Year of Use

BY HEIDI SPLETE
Senior Writer

ATLANTA — Clinicians can be more confident about the safety of Gardasil, the quadrivalent human papillomavirus vaccine, because postlicensure safety data from the first year of widespread use confirm that serious adverse events associated with the vaccine are rare.

"Postlicensure safety reporting for HPV4 has occurred at relatively high levels, as is expected for a newly licensed product that has garnered significant public attention," said Dr. John Iskander, who presented the postlicensure data at the June 2007 meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

Dr. Iskander presented safety data from the United States Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD), two vaccine surveillance mechanisms supported by the CDC.

"The data encompass the first 11 months of the U.S. experience with Gardasil," said Dr. Iskander, an officer at the CDC's Immunization Safety Office.

The postlicensure data are likely to increase comfort levels for doctors when they talk to patients about the HPV4 vaccine.

"Now [that] the vaccine has been out for about a year, it is beginning to develop a safety record, so it should make the practitioner feel more confident in the safety of the vaccine," Dr. Joseph Bocchini Jr., the American Academy of Pediatrics' liaison to ACIP and chairman of the department of pediatrics at Louisiana State University, Shreveport, said in an interview.

More than 5 million doses of Gardasil have been distributed as of the end of March 2007, according to the vaccine's manufacturer (Merck), although the exact number of doses that have been administered is uncertain at this time, Dr. Bocchini added.

So far, the HPV4 overall vaccine adverse event reporting rate is 33 per 100,000 doses, and the serious adverse event reporting rate is 1.8 per 100,000 doses, based on VAERS data.

A total of 1,763 adverse events related to use of the HPV4 vaccine had been reported to the VAERS as of May 8, 2007. Of these, 87% involved the use of HPV4 alone. Nearly 70% of the reports involved girls and women aged 9-26 years (the age range used in prelicensure clinical trials).

"A substantial proportion of vaccine events began on the day of vaccination (39%), or in the days [immediately] following vaccination," Dr. Iskander noted. Similarly, 42% of serious adverse events occurred on the day of vaccination, with an average onset time of 1 day afterward. A total of 857 vaccine events (49%) were reported after a single dose of HPV4.

The most common symptoms in reports of serious adverse events were vomiting (14%), syncope (12%), fever (11%), nausea (11%), and headache (11%). Similarly, the most commonly reported symptoms associated with vaccine use were dizziness (13%), injection site pain (10%), syncope (10%), and nausea (9%).

Although data on associations between HPV4 use and reports of Guillain-Barré syndrome are limited, the VAERS data included 13 reports of GBS in patients who received HPV4. Of these, 11 cases occurred in girls aged 13-16 years; one case occurred in a 50-year-old woman, and the age of the other patient is unknown. More than half of these cases involved coadministration of Menactra and Gardasil.

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Dr. John Iskander of CDC said serious adverse events involving HPV4 vaccination have rarely been reported, for a rate of 1.8/100,000 doses.

The VAERS data also included two nonfatal cases of thromboembolism in patients who received the HPV4 vaccine.

In addition, 11 serious event reports from VAERS involved syncope, all of which occurred within 10 minutes of vaccination. "Current recommendations suggest a 15-minute waiting period after vaccination … to avoid syncope," Dr. Iskander noted. Many of the frequently reported adverse events are common in the general population and do not have a specific relationship to this vaccine or to vaccinations in general.

Dr. Iskander also presented details on four cases of death in patients who had been vaccinated with HPV4. The cases included a 12-year-old girl who died of myocarditis after developing ventricular tachycardia, a 19-year-old girl who died from sudden cardiac death and pulmonary embolism (her autopsy showed multiple blood clots), a 14-year-old who died from multiorgan system failure due to influenza B viral sepsis, and a fourth case for whom few data were available except her use of oral contraceptives; her death was associated with blood clots.

Gardasil has been covered under the national Vaccine Injury Compensation Program since Feb. 1, 2007, but no claims alleging injuries as a result of HPV4 had been filed as of June 7, 2007, Dr. Iskander reported. Complete vaccination coverage data are not yet available, but vaccine uptake is being followed using the VSD. The CDC's VSD sites are monitoring 68,266 doses of Gardasil given between Aug. 6, 2006 and May 13, 2007, for a variety of safety outcomes including Guillain-Barré syndrome, seizure, syncope, stroke, thrombosis, and pulmonary embolism.

Serious adverse events involving HPV4 have rarely been reported; the reported deaths in vaccine recipients don't appear to be causally related to vaccination, Dr. Iskander said. But the CDC will continue to collaborate with the Food and Drug Administration, the World Health Organization, and other organizations to monitor postlicensure surveillance and other communication related to HPV4.

At future ACIP meetings, the postlicensure safety data for Gardasil may be considered in conjunction with safety data on the bivalent HPV vaccine recently submitted to the FDA by GlaxoSmithKline, said Dr. Lauri Markowitz, a member of ACIP's HPV working group. If the GSK vaccine, HPV-008 (Cervarix), is approved by FDA, the working group will review data and discuss including vaccine preference, and whether doses of the two could be interchangeable. ■

Bivalent HPV Vaccine Shows 90% Efficacy

BY ROBERT FINN
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A bivalent vaccine for human papillomavirus manufactured by GlaxoSmithKline has shown greater than 90% efficacy against high-grade cervical intraepithelial neoplasia, according to interim results from a large, randomized controlled trial published online in the Lancet.

The study, led by Dr. Jorma Paavonen and colleagues, is called the Papilloma Trial to Prevent Cervical Cancer in Young Adults (PATRICIA), and involves 18,644 women, aged 15-25 years, from 14 countries in Europe, Asia, and North America. The participants were randomly assigned to receive three injections of the human papillomavirus (HPV) vaccine or a hepatitis A vaccine at months 0, 1, and 6 (Lancet 2007; DOI:10.1016/S0140-6736[07]60946-5).

The study was sponsored by GlaxoSmithKline. Several study investigators were employees of the company, and others, including Dr. Paavonen of the University of Helsinki received consulting and lecture fees from the pharmaceutical firm.

The vaccine, Cervarix, has not yet been approved by the Food and Drug Administration. If it is approved, it will be competing against Merck's already released HPV vaccine, Gardasil. Cervarix is a bivalent vaccine, active against HPV types 16 and 18, which account for 70% of all cases of cervical cancer. Gardasil is a quadrivalent vaccine, active against HPV types 6 and 11 (the cause of 90% of genital warts) in addition to types 16 and 18.

In the current study, only 2 of the 9,319 women receiving Cervarix developed cervical intraepithelial neoplasia (CIN) of grade 2 or 3 and related to HPV 16 or 18, compared with 21 of the 9,325 women in the control group. This translates into an efficacy of 90%.

The vaccine also showed 89% efficacy against grade 1 or higher CIN.

Virtually all the women receiving the HPV vaccine (99.5%) had developed antibodies against HPV 16 and 18 after the second of the three injections.

In an accompanying editorial, Dr. Jessica A. Kahn of the University of Cincinnati and Dr. Robert D. Burk of the Albert Einstein College of Medicine, New York, described these results as "encouraging," while sounding a note of caution (Lancet 2007; DOI:10.1016/S0140-6736[07]60947-7).

They noted that the follow-up time was only about 15 months, which is short compared with the several decades over which cervical cancer often evolves. The enrollment criteria in the trial were relatively narrow, so it's unknown whether seroconversion rates, antibody titers, and efficacy rates will be as high when the vaccine is distributed to a wider population.

Dr. Kahn and Dr. Burk also emphasized that the vaccine was not without side effects. Although generally well tolerated and safe, the HPV vaccine caused significantly more local adverse events such as pain, redness, and swelling, than did the hepatitis A vaccine. Risks of general adverse events, including arthralgia, fatigue, and myalgia, also were significantly higher in the HPV group.

Dr. Kahn and Dr. Burk stressed the need for the vaccine to be made available in less-developed regions of the world, where cervical cancer makes the largest contribution to years of life lost to cancer. "Poverty is strongly associated with high-risk HPV infection and cervical cancer," they wrote. "If those who live in poverty cannot access highly effective interventions such as HPV vaccines, disparities could worsen dramatically."