Cervarix Is Effective Against CIN2+ Lesions

BY MIRIAM E. TUCKER

ATLANTA — The efficacy of GlaxoSmithKline's human papillomavirus vaccine against cervical intraepithelial neoplasia grade 2 or higher has been confirmed in a final analysis of phase III data from more than 18,000 women in 14 countries.

And in a separate head-to-head comparison involving a total of more than 1,100 women, immune responses to the oncogenic HPV strains 16 and 18 were significantly better with GSK's Cervarix than with Merck & Co.'s HPV vaccine Gardasil, Dr. Gary Dubin said at the June meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

GSK's phase III data on Cervarix were submitted to the Food and Drug Administration in March 2009 and are still under review. The vaccine is currently licensed in more than 95 countries including 27 in the European Union, according to Dr. Dubin, vice president, North American clinical development, GSK.

The final analysis enrolled 18,644 women aged 15-25 years in a double-blind, randomized, controlled trial using the hepatitis A vaccine as the control. Mean follow-up was 39 months after the first of three doses.

The primary objective was to assess efficacy against the development of cervical intraepithelial neoplasia–2 (CIN2+) associated with HPV-16 and HPV-18 in women who were DNA negative and seronegative at baseline and DNA negative at 6 months for the HPV type considered in the analysis. The final analysis was conducted when at least 36 cases of the primary end point were observed in the according-to-protocol cohort.

Cervarix also showed efficacy against CIN2+ lesions caused by nonvaccine types that are genetically related to the vaccine types HPV-16 and HPV-18.

Among the 14,656 seronegative women who had received all three doses of study vaccine, the overall efficacy of Cervarix against HPV-16/18 CIN2+ lesions was 93%. In total, 4/7,344 Cervarix recipients and 56/7,312 controls were found to have HPV-16/18 DNA in lesions during follow-up. Irrespective of baseline serostatus, vaccine efficacy was 91% for HPV-16/18.

In the subset of 11,641 totally vaccinated naive women, defined as those who at baseline had normal cytology, had no HPV DNA for 14 oncogenic types, and were seronegative for HPV-16 and HPV-18, Cervarix efficacy was 98% against HPV-16/18 CIN2+ lesions. For the total vaccinated cohort of 18,644 women, vaccine efficacy against HPV-16/18 CIN2+ lesions was 53%, reflecting the fact that many women in this cohort had preexisting lesions, he said.

Irrespective of HPV lesion type, the efficacy of Cervarix in the naive women was 70% against CIN2+ lesions and 87% against CIN3+ lesions. For the total vaccinated cohort, irrespective of HPV lesion type, Cervarix efficacy was 30% for CIN2+ lesions and 33% for CIN3+ lesions.

Examination by the cumulative incidence over time showed that lesion development occurred at the same rates in the vaccine and control groups until about month 18, when the curve separation became apparent.

This is because most of the lesions detected during the first 18 months of the trial were derived from preexisting infections. Only after there was a "washout" of these lesions did the prophylactic effect of the vaccine become apparent, Dr. Dubin pointed out.

Cervarix also had a significant impact on colposcopy referrals, with reductions of 26% in the naive group and 10% in the total vaccinated cohort. Cervical excision procedures were also affected, with reductions of 10% in the naive and 25% in the total vaccinated group compared with the placebo group.

Cervarix also showed efficacy against CIN2+ lesions caused by nonvaccine types that are genetically related to vaccine types, particularly HPV-31 (related to HPV-16) and HPV-45 (related to HPV-18), Dr. Dubin said.

A safety analysis showed identical rates of serious adverse events (7.5% with both Cervarix and hepatitis A vaccine) and of new-onset autoimmune disease (0.8% for both). There were similar rates of medically significant conditions (32% with Cervarix vs. 32% with placebo), congenital anomalies (0.7% vs. 0.5%), and spontaneous abortions (9.1% and 8.7%).

The head-to-head comparison was the first for the two licensed vaccines using the same methodology for immunogenicity and safety.

The primary objective was to compare the geometric mean titers of HPV-16 and HPV-18 serum neutralizing antibodies at month 7 following vaccination in women aged 18-26 years. A secondary end point was serum neutralizing geometric mean titers at month 7 in women aged 27-35 and 36-45 years.

The observer-blinded study was conducted at 40 U.S. centers in a total of 1,106 women randomized to receive Cervarix or Gardasil according to the recommended administration schedules: 0, 1, and 6 months for Cervarix and 0, 2, and 6 months for Gardasil. Placebo injections were given to the Gardasil group at 1 month and the Cervarix group at 2 months.

Cervarix induced significantly higher serum neutralizing antibody titers than did Gardasil. In women aged 18-26, antibody titers for Cervarix were 3.7-fold higher against HPV-16 and 7.3-fold higher against HPV-18 compared with results for Gardasil. In women aged 27-35 years, those differences were 4.8-fold and 9.1-fold, and for 36- to 45-year-olds, 2.3-fold and 6.8-fold.

Positivity rates at month 7 for HPV-16 and HPV-18 antibodies measured in cervicovaginal secretions were higher with Cervarix than with Gardasil. The frequency of circulating antigen-specific memory B cells at month 7 was 2.7-fold higher with Cervarix vs. Gardasil for HPV-16 and HPV-18, and the frequency of CD4+ T-cell responses at month 7 was also significantly higher with Cervarix compared with Gardasil for both HPV-16 and HPV-18. These data confirm differences in immunologic response between the two vaccines, Dr. Dubin said.

"Although the importance of these differences is unknown, they may represent determinants of duration of protection against HPV-16/18 and/or protection against nonvaccine types. Disease modeling will help determine how the observed differences in vaccine profiles may translate into differences in public health impact," he said, adding that the current data "indicate that the GSK HPV vaccine is likely to provide long-lasting protection against cervical cancer." ■

Severe Anemia May Not Be Obvious at AUB Presentation

BY BETSY BATES

CHICAGO — Few symptoms or clinical examination findings distinguished severely anemic patients from other women who presented for urgent evaluation of abnormal uterine bleeding, a retrospective cohort study showed.

Of 350 patients who presented to the emergency department for heavy menstrual bleeding, 122 (35%) were anemic, defined as having a hemoglobin concentration of less than 12 g/dL, while 48 (14%) were moderately to severely anemic, defined as having a hemoglobin concentration of less than 10 g/dL.

Only increasing age (relative risk, 1.04) and the presence of both tachycardia and hypotension (RR, 3.11) were associated with severe anemia, reported Dr. Kristen A. Matteson at the annual meeting of the American College of Obstetricians and Gynecologists.

"Our take-home message is that clinical symptoms and bleeding history are poorly predictive for moderate to severe anemia," said Dr. Matteson of the department of obstetrics and gynecology at Brown University, Providence, R.I.

Because no presenting symptom or physical finding can rule out clinically important anemia, she suggested that "a low threshold should be maintained for performing a hemoglobin concentration."

'Diagnosis and management of heavy menstrual bleeding are dependent on what a woman says about her blood loss because clinically we do not have practical means to "measure" bleeding.'

The median age of women in the study was 32 years. Nearly 70% were non-Hispanic white, and 20% were non-Hispanic black. Almost one in four had received outpatient care for abnormal uterine bleeding (AUB) in the prior 3 months, but, 49% had a concurrent medical condition that could affect treatment options for the condition, Dr. Matteson pointed out. These concurrent diagnoses included breast, endometrial, or ovarian cancer; cardiovascular disease; depression; diabetes; gastrointestinal diseases; migraine; seizure disorders; and thromboembolic disorders.

The duration of the current bleeding episode was more than 7 days in 55% of the study population. A combination of heavy and irregular bleeding was reported by 65%, and more than half reported passing clots or flooding. Neither the amount of bleeding recorded on examination nor bleeding patterns described by the patients were associated with moderate to severe anemia.

"We were not surprised that the amount of bleeding actually seen by the provider was scant in the majority of patients because abnormal uterine bleeding can be very unpredictable and episodic," noted Dr. Matteson. "Diagnosis and management of heavy menstrual bleeding are dependent on what a woman says about her blood loss because clinically we do not have practical means to 'measure' bleeding."

When a woman reports extremely heavy bleeding that affects her life at home and work, but has little bleeding during a 30-minute medical appointment, the disparity can lead to frustration on the part of both the physician and patient, she said. Studies have shown that such patients "often report dissatisfaction with their interactions with health care providers."

Dr. Matteson said mild anemia is generally asymptomatic in patients who do not have cardiovascular disease. Severe anemia, on the other hand, can lead to cardiac events in some patients and may require blood transfusions. Anemia that is moderate to severe can cause extreme fatigue, reducing productivity and quality of life.

Dr. Matteson reported no financial conflicts of interest. ■