A Status Report on Human Papillomavirus Vaccines

Human papillomavirus (HPV) vaccine research is advancing at a rapid pace. GlaxoSmithKline (GSK) and Merck & Co., Inc. have each developed first-generation prophylactic vaccines, and it is anticipated that a vaccine will be registered for use in 2006. GSK currently has Phase 3 clinical trials under way and Merck has completed some of its Phase 3 clinical trials with others under way. While product development has been fueled primarily by developed-country markets, these vaccines are likely candidates for early introduction into developing countries, where the burden of cervical cancer disease is highest.

Overview of vaccines

Virus-like particle (VLP)-based HPV vaccines tested in women aged 15 to 23 demonstrated that the vaccines were well-tolerated and highly immunogenic, and they conferred type-specific protection against new and persistent HPV infection and type-specific cervical intraepithelial neoplasia (CIN).

Merck Vaccine

Merck is developing an L1 VLP vaccine based on recombinant yeast technology. It is being developed to protect against infection by HPV types 16 and 18, the HPV types that cause the most cases of cervical cancer, as well as the two types that cause most genital warts (types 6 and 11). A large Phase 3 study is underway, involving 25,000 women aged 16 to 23 in 33 countries in North America, Latin America, Europe, Southeast and East Asia, Australia, and New Zealand. This study will establish vaccine efficacy and safety for up to 3.5 years after vaccination.

Koutsky et al.'s placebo-controlled, double-blind trial of an HPV 16 VLP vaccine (Merck) involved more than 2,000 women (aged 16 to 23) who received three doses of vaccine over a six-month period; the trial produced very encouraging results. After four years, the vaccine was shown to be 100 percent effective in preventing persistent HPV 16 infections and HPV 16-specific CIN.[1,2] A Phase 2 study of the current vaccine involving more than 500 women and men over 36 months found that a combined incidence of persistent infection or disease related to HPV type 6, 11, 16, or 18 was reduced in women by 90 percent in comparison to a placebo group.[3] In a more recent trial involving over 12,000 women aged 15 to 26, the vaccine showed 100 percent efficacy against HPV 16/18-related CIN 2/3.[4]

Other smaller, bridging studies are also underway, such as one examining immunogenicity and safety among boys and girls aged 9 to 15. Another study is examining efficacy and safety among women aged 24 to 45.

GSK Vaccine

GSK is developing an L1 VLP vaccine based on recombinant baculovirus technology. It is being developed to protect females against infection by HPV types 16 and 18. GSK is conducting a Phase 3 study in North America, Latin America, Asia, and Europe involving 18,000 women aged 18 to 25. The United States National Cancer Institute is also evaluating this vaccine in a Phase 3 study in Costa Rica involving 12,000 women aged 18 to 25. In Harper et al.'s randomized, double-blind, placebo-controlled trial of the GSK vaccine, more than 1,100 women in North America and Brazil aged 15 to 25 received three doses of the vaccine over a six-month period. Follow-up at 27 months found a vaccine efficacy rate of 92 percent against new infection and 100 percent against persistent infection.[5] GSK is also implementing bridging studies involving preteens, adolescent girls, and women over the age of 25. Table 1 summarizes the current status of these first-generation vaccines.

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Table 1. Current status of first-generation vaccines

Manufacturer	Vaccine type	HPV types	Status
Merck & Co., Inc.	L1 VLP (Gardasil™) based on recombinant yeast technology	16, 18, 6, 11	Phase 3 underway; regulatory FDA submissions expected late 2005; launch expected 2006.
GlaxoSmithKline (GSK)	L1 VLP (Cervarix™) based on recombinant baculovirus technology	16, 18	Phase 3 underway; expected regulatory filing in EU and internationally expected 2006.

Further research needs

Several critical research questions remain about HPV vaccines. Studies are under way to help clarify some of these questions, including:

- The ideal age of vaccination.
- The potential for co-administration with other vaccines in the same visit.
- The efficacy and safety of vaccination in areas with high HIV/AIDS prevalence.
- The efficacy of HPV vaccination among boys (with HPV infection and genital warts as endpoints).

Other research questions that may be important include vaccine efficacy with different numbers or timing of doses, and assessments of vaccine uptake in programs focusing on girls only versus girls and boys. It also will be important to assess vaccine safety, efficacy, and acceptability in Africa, where no studies have been implemented to date except in South Africa.

Lastly, programmatic and operational research that demonstrates how the vaccine can be successfully introduced in countries where the need is greatest will be very important. These studies will inform donors and guide countries in making decisions about how to best introduce HPV vaccine as part of efforts to reduce cervical cancer incidence in developing countries.

References

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