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Current Status of HPV Vaccines

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Abstract

Cervical cancer is the second largest cause of cancer deaths in women worldwide, with ~500,000 diagnoses and 274,000 deaths annually. It remains a significant source of morbidity and mortality despite effective screening tools and treatments for its precursor high-grade cervical intraepithelial neoplasia (CIN). Increased understanding of cervical pathogenesis has led to the identification of human papillomavirus (HPV) as the etiological agent for cervical cancer and the development of preventive and therapeutic vaccines targeting HPV antigens for the control of cervical cancer. Herein, we discuss the current status of HPV vaccines.

Currently Approved Prophylactic HPV Vaccines

The commercialization of two prophylactic HPV vaccines, Gardasil® (Merck, NJ, USA) and Cervarix® (GlaxoSmithKline, Middlesex, UK), represents a milestone for prevention of cervical cancer (1). The vaccines target HPV L1 major capsid protein, which can assemble to form virus-like particles (VLPs) morphologically resembling native virions, to generate robust antibody responses and prevent HPV infection. Gardasil contains VLPs for HPV-16 and -18, associated with cervical cancer, and VLPs for HPV-6 and -11, associated with benign genital warts. Cervarix contains only HPV-16 and -18 VLPs. While both contain classical aluminum salt adjuvants, Cervarix also contains monophosphoryl lipid A, a Toll-like receptor 4 agonist that primes innate immunity and may stimulate adaptive immunity for enhanced antibody titers. The U.S. Food and Drug Administration (FDA) approved Gardasil for females ages 9–26 in 2006. In October 2009, the FDA approved Cervarix for use in females ages 10–25 and also approved Gardasil for use in males ages 9–26 to prevent genital warts and to prevent the spread of cervical cancer. These recent events may further impact cervical cancer rates.

Issues Faced by Current Preventive HPV Vaccines

While current preventive HPV vaccines are promising for global prevention of cervical cancer, there are remaining issues:

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1. Cost

The high cost, need for refrigeration and multiple doses of the commercial preventive HPV vaccines preclude their widespread implementation in developing countries, which have >80% of cervical cancer cases. Gardasil and Cervarix each require 3 doses costing ≥$100/dose. For low-income countries, the per-dose cost may need to be <$5 for affordable vaccination (2). Employment of basic structural units of the HPV capsid assembled from 5 L1 monomers, termed L1 capsomers, represents a potential alternative since they are more thermo-stable and cheaper to produce than VLPs. L1 capsomers produced in *E. coli* (3) and expression of L1 in recombinant *Salmonella enterica* serovar Typhimurium (4) were shown to induce protective antibodies in preclinical models. Other options include needle-free administration routes to lower complexity and cost of vaccination.

2. Duration of Vaccine Efficacy

Duration of HPV vaccine efficacy is crucial in deciding whether cervical cancer is merely postponed or truly prevented. Analyses have indicated that duration must last at least 15 years for cost-effective prevention of cervical cancer (1). While Cervarix and Gardasil are highly efficacious in preventing HPV-16/18-associated lesions, the duration of efficacy beyond 6.4 years for Cervarix and 5 years for Gardasil is unknown. In a head-to-head trial, Cervarix was shown to have somewhat higher antibody titers for HPV-16 and HPV-18 than Gardasil, but it is unclear if this will translate into a more durable response (5). It will be important to follow up on these vaccines to see if two doses are sufficient, or if additional booster shots are required.

3. Coverage of HPV types

Gardasil and Cervarix contain VLPs for HPV-16 and -18, which account for up to 75% of cervical cancers, with >10 HPV types accounting for remaining cases. Unfortunately, these vaccine-elicited antibody responses are primarily type-restricted to genotypes covered. While limited partial cross-protection has been observed against homologous HPV genotypes, the duration of cross-protection is unknown. L1 vaccines containing VLPs for multiple HPV types may broaden protection; Merck is recruiting for Phase III clinical trials of a nine-valent vaccine, V503 (www.merck.com). Another promising method involves L2 minor capsid protein, which is highly conserved across HPV genotypes. Efforts have focused on boosting the immunogenicity of L2 by linking together short amino acid sequences of L2 from different oncogenic HPV types (6). While multimeric L2 showed robust antibody responses in preclinical models against multiple HPV types, it is not as immunogenic as VLPs. Upon successfully finding an appropriate adjuvant, this approach will be explored in clinical trials.

Therapeutic HPV Vaccines

The existing global burden of HPV-associated lesions and cervical cancer emphasizes the urgent need for therapeutic HPV vaccines. Current preventive vaccines exert no therapeutic effects and it would take years of mass vaccination to see reduced cervical cancer rates due to high prevalence of HPV infections and slow rate of cervical carcinogenesis. In contrast to antibodies induced by preventive vaccines, therapeutic vaccines aim to generate cell-mediated immune responses using killer T cells that actively destroy HPV-infected cells. Hence, therapeutic vaccines may exert immediate effects on lowering HPV-related disease incidence.

While definitive objectives have been achieved in developing preventive HPV vaccines, overall progress in therapeutic HPV vaccine development has been slower. Vaccination to control cervical cancer has been evaluated in several forms, such as live vector-based,

peptide/protein-based, nucleic acid-based and whole cell-based therapeutic HPV vaccines targeting HPV E6 and E7 oncoproteins (for review, see (7)). The promising preclinical data has led to the evaluation of several therapeutic vaccine candidates in early phase clinical trials.

Long overlapping peptides have stirred enthusiasm for therapeutic HPV E6/E7 peptide-based vaccines as they may limit the obstacle of MHC restriction by broadening the range of antigenic epitopes. A vaccine comprised of 13 overlapping peptides representing HPV-16 E6 and E7, formulated in Montanide ISA 51 adjuvant, was shown to be safe and well-tolerated in earlier trials and has most recently demonstrated great efficacy in a Phase II trial, leading to complete clinical responses in 9 of 19 evaluable HPV-16-positive high-grade vulvar intraepithelial neoplasia patients (8).

DNA vaccines employing strategies to enhance vaccine potency have also stimulated great interest. Microencapsulation of DNA vaccine can prevent DNA degradation by nucleases for efficient delivery. Amolmigene bepiplasmid (ZYC101A), a DNA vaccine comprised of plasmid DNA encoding HPV 16/18 E6/E7 proteins encapsulated in poly(glycolide-lactide) biopolymer, has advanced to Phase II/III clinical trials and is undergoing investigation in CIN 2/3 patients (9). Other vaccine-potentiating approaches include intracellular targeting strategies that utilize the understanding of antigen processing/presentation pathways. One example is Sig/E7(detox)/Hsp70, a DNA vaccine encoding a signal sequence for the endoplasmic reticulum linked to an attenuated form of HPV-16 E7 and fused to immunostimulatory Hsp70. A Phase I clinical trial employing Sig/E7(detox)/Hsp70 boosted with recombinant vaccinia virus encoding HPV-16/18 E6/E7 fusion protein (TA-HPV) with or without imiquimod is in progress in CIN 2/3 patients (10). Additionally, a Phase I trial evaluating CRT/E7(detox), a DNA vaccine encoding modified HPV-16 E7 linked to calreticulin, delivered via clinical-grade gene gun, in patients with high-grade CIN has recently begun (W Huh, personal communication).

Future Outlook

While it is clear that HPV vaccines will not eliminate the need for effective cervical screening and treatment for many years to come, they can substantially reduce the burden that cervical cancer imposes on women and health services in the long run. Although significant challenges remain in achieving broad coverage of adolescents and reducing the cost of these vaccines, the implementation of two commercial preventive HPV vaccines has exciting prospects. Additionally, with continuing progress into advanced stages of clinical trials and further exploration of combinatorial strategies, there is great promise for significant advances in the field of therapeutic HPV vaccine development.

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