Preventive Medicine

Human Papillomavirus Vaccine – Where are We Now?

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Abstract

This paper attempts to review the currently available relevant information about the two widely distributed human papillomavirus (HPV) vaccines in use today and place it in an easily understandable and readable format for busy clinicians to access. The article briefly reviews the background of the HPV virus and cervical cancer. It details to the vaccines currently licensed for use in the United States, Gardasil and Cervarix, going over the mechanisms of action for both, as well as administration routes. Efficacy of the vaccines was discussed in terms of the available phase II and phase III trial data available to date. Vaccination in males, cost-effectiveness and social acceptance were also reviewed. A brief discussion about the future development of second generation HPV vaccines was included. Although the data collected to date are promising, there is still much to learn about exactly what the future impact of the HPV vaccine will be in the United States and globally. Further research and analysis are necessary to determine the long term medical, social, and economic impact of the HPV vaccine.
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Introduction

Cervical cancer is the second most common malignancy and the third leading cause of death in women worldwide.[1] One of the main factors associated with the development of the disease is human papillomavirus (HPV). Infection with high-risk types of HPV causes dysplasia in cervical epithelium, a precursor of cervical cancer.[2] Two vaccines against HPV have been developed and have proven to be effective on reducing the risk of cervical cancer and its precursors.[3] Since the U.S. Food and Drug Administration (FDA) approved Gardasil vaccine to protect against HPV diseases in June 2006, the publicity about it has died down, but many questions still remain to be answered.

HPV Virus

HPV viruses are double-stranded, non-enveloped deoxyribonucleic acid (DNA) viruses. The HPV genome is enclosed in a capsid shell comprised of major (L1) and minor (L2) structural proteins.[3] There are more than 100 known HPV genotypes and certain ones of these are associated with carcinogenesis. The most well known of these oncogenic subtypes are HPV types 16 and 18.[3] Other high-risk types include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, which have all been implicated in the development of cervical cancer.[4] HPV types 16 and 18 cause about 70% of all cases of invasive cervical cancer worldwide with type 16 having the most oncogenic potential.[3] Low risk types 6 and 11 cause most genital warts and respiratory papillomatosis.[5, 6]

Cervical Cancer

Annually, an estimated 400,000-500,000 women develop cervical cancer and approximately 265,000 women will die secondary to the disease.[1] Cervical cancer incidence rates vary greatly with the highest rates seen in countries which do not have organized screening programs in place.[9] Developing countries are where morbidity and mortality from cervical cancer is the highest and are also likely to be where a vaccine would have the greatest impact.[9]

The Vaccines

Currently, there are two different HPV vaccines widely available for use internationally.[4] Both use recombinant technology with purified forms of the major (L1) structural protein from the different virus types.[9] These then self assemble to form type specific virus-like particles (VLPs). The currently marketed vaccines do not contain viral DNA or live virus so they are non-infectious.[4] Gardasil, the

quadrivalent vaccine produced by Merck, contains VLP's for HPV types 6, 11, 16, and 18.[10] The vaccine is produced using the yeast Saccharomyces cerevisiae as a substrate and amorphous aluminum hydroxyphosphate sulfate salt as adjuvant. The vaccine contains no antibiotics, thiomersal or other preservatives.[10] It was first licensed in 2006 and is licensed for use in young adolescent girls to prevent cervical cancer and anogenital warts. Some countries have additionally licensed it for the prevention of anogenital warts in males.[11] In the U.S.A. Gardasil is currently approved for use in girls and young women ages 9-26 and has recently been approved for use in males. Three intramuscular injections of the vaccine are recommended. One at baseline and again after 2 months and 6 months.[12]

Cervarix, the bivalent vaccine produced by GlaxoSmithKline (GSK), contains VLP's for HPV types 16 and 18.[13] The vaccine is produced in Trichoplusia ni insect cell substrate using a baculovirus expression vector system with ASO4 adjuvant system containing aluminum hydroxide and 3-o-desacyl-4'-monophosphoryl lipid A.[13] The vaccine contains no antibiotics, thiomersal, or other preservatives. It was first approved for the European Union by the European Commission in 2007 for females from 10 years of age for the prevention of cervical cancer. The U.S. Food and Drug Administration just approved Cervarix for use in girls and young women ages 10-25 in October 2009.[12] Three intramuscular injections of the vaccine are recommended. One at baseline and again after one month and 6 months.[13] Both vaccines are available as a sterile suspension in single use glass vials or pre-filled syringes that need to be maintained at 2-8 °C.

The efficacy of the vaccines was determined by a globally agreed upon measurable efficacy endpoint. Because of ethical considerations and time constraints it was determined the use of histologically classified cervical intraepithelial neoplasias (CIN) of moderate or high grade be the measurable endpoint, as well as the development of cervical cancer.[14] Multicenter randomized double-blinded phase II and phase III trials that examined the clinical endpoints CIN2, CIN3, and/or adenocarcinoma in situ (AIS) were conducted in females for both the quadrivalent and the bivalent vaccines.[15,16]

For the quadrivalent vaccine, in a combined analysis of four clinical trials with the primary composite endpoint was the combined incidence of HPV 16/18 related CIN 2/3, AIS, or cervical cancer, the vaccine was found to be 99% effective in the HPV naïve population and 44% effective in an intention-to-treat population of all women who had undergone randomization (those with or without previous HPV 16/18 infection).[18] In a second intention-to-treat analysis, there was an 18% reduction in overall rate of CIN 2/3 or AIS due to any HPV type.[17] In another study, the quadrivalent vaccine was found to be up to 100% effective in reducing the risk of HPV6/11-related genital warts in the population that was negative to 14 HPV types and able to reduce the risk of any genital wart irrespective of causal HPV by 62.0% in an intention-to-treat population.[18]

For the bivalent vaccine, the primary endpoint was to assess vaccine efficacy against CIN 2/3 that was associated with HPV 16 or HPV 18 in women who were seronegative at baseline and DNA negative at baseline and month 6 for the corresponding type.[19] Mean follow-up was 34.9 months after the third dose and vaccine efficacy was 98.1% in an analysis that took causality into consideration. An extended study to assess long-term vaccine efficacy in the prevention of incident cervical infection with HPV 16 or HPV 18 or both was done with 6.4 years of follow-up. Vaccine efficacy against CIN2/3 was 100% for lesions associated with HPV 16/18 and 71.9% for lesions independent of HPV DNA type.[19]

Safety

The Global Advisory Committee on Vaccine Safety (GACVS) is an expert clinical and scientific advisory body that was established by the World Health Organization to deal with vaccine safety monitoring. GACVS reviewed the safety profile of HPV vaccines at its nineteenth meeting in Geneva, Switzerland, December 2008. The committee reviewed the latest available data and publications on HPV vaccines and early post-marketing surveillance. They found the post-licensure data from the United States regarding Gardasil was reassuring with no evidence of previously undetected serious adverse events causally related to the vaccine.[20] They also reviewed several new scientific articles published since the GACVS meeting in June 2007 that addressed the specific observations of syncope, hypersensitivity, anaphylaxis and central demyelinating diseases. They concluded there was no convincing evidence to support an association between HPV vaccination and central demyelinating diseases[21] and that allergic reactions and syncope can occur after injection but the usual safety precautions should suffice.[20] The most common adverse events were reactions at the injection site and muscle pain.[20] There is limited data available on the inadvertent administration of HPV vaccines shortly before or during pregnancy, but what is available thus far does not establish a direct relationship between vaccination and miscarriage.[22] Further studies are needed in this area.

Vaccination in Males

To date, most of the research and publicity surrounding HPV infections and vaccination has focused on females. In October of 2009, the FDA licensed the quadrivalent HPV vaccine for use in males. A phase III efficacy study demonstrated that the efficacy for prevention of HPV types 6, 11, 16, or 18-related genital warts among males who received all 3 vaccine doses and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%. The efficacy for prevention of HPV 6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and regardless of baseline DNA or serology (intent to treat population), was 67.2%, and the efficacy for prevention of genital warts related to any HPV type was 62.1%.[12] HPV types 16 and 18 are well known for their association with cervical and vulvar cancers affecting females, but they have also been linked to oral cancers, anal cancer, and penile

caners.[23] The acceptance of HPV vaccine in the male population might not only play a role in reducing the incidence of cervical cancer, vulvar cancer and genital warts, but may also have a role in reducing the incidence of the above mentioned cancers that are primarily seen in the male population. Liddon et al. reviewed several studies regarding the acceptability among patients, parents and clinicians. They found that a preference to vaccinate females over males predominated in a majority of the studies among parents and health care providers.[24] Continued education about HPV related disease and cancer prevention may help with acceptance in the future. Further studies need to be conducted in this area to validate the use of the vaccine in males and look at long-term outcomes.

Cost-Effectiveness

Currently, cost-effectiveness models are being made based on assumptions and must be interpreted with caution. Most analyses are largely dependent upon the duration of vaccine induced immunity,[25] which is currently unknown, and the age at vaccination. Models in developed countries with well established screening programs already in place predict a good economic outcome if the majority of young pre-adolescent, HPV-naive girls can be vaccinated and if the vaccine-induced immunity is life-long.[25] Currently, Phase II trial data have established durations of efficacy for Cervarix and Gardasil lasting 6.4 and 5 years respectively.[26] In developing countries, where screening programs are not in place, the cost of the vaccine would have to be substantially lower than it currently is in high income countries for it to be cost-effective.[9] However, it is in these countries where the vaccines could potentially have the greatest impact in reducing mortality from cervical cancer.

Social Acceptance

A number of studies continue to show that older females (ages 13-17) are more likely to be vaccinated than preadolescent females.[27-29] Parents continue to be a barrier to the vaccination of preadolescent girls because of the perception that giving the vaccine may promote sexual activity or insinuate that their child is sexually active.[28] Unfortunately, this is the intended age group for the vaccine and the age group in which it is most efficacious.[29] Further education programs for parents and clinicians are needed to increase vaccination acceptability in this target age group.

A Look at the Future

The drawbacks to the current vaccines available for use today are that they only protect against a very limited number of HPV types,[26] they require cold storage, are injectable and expensive. Currently, second-generation vaccines, which will contain additional HPV serotypes to give better overall protection against cervical cancer as well as genital warts and other HPV related-diseases,[30] are under development. It will be years, probably decades, before this next generation vaccine becomes available for use.[30]

Conclusion

There are currently two vaccines to protect against certain strains of the HPV virus widely available for use today that show great promise in decreasing morbidity and mortality from a variety of HPV related disease. It seems that the data thus far show the most promise in sexually-naïve patients who have not been exposed to the virus.

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