The Prospects of HPV Vaccination in Cervical Cancer Prevention: Results of a New Independent Trial

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Summary: Herrero and colleagues show that in a phase III randomized trial in Guanacaste, Costa Rica, the use of a human papillomavirus type 16 (HPV16) and HPV18 ASO4-adjuvanted vaccine (Cervarix) resulted in complete efficacy against 12-month persistent HPV16 and HPV18 infections and partial protection against HPV31, 33, and 45 in HPV-naive young women ages 18 to 25. Cancer Discovery; 1(5): 377–80. ©2011 AACR.

Commentary on Herrero et al., p. 408 (6).

INTERNATIONAL CONTEXT OF HUMAN PAPILLOMAVIRUS VACCINES

There are currently two human papillomavirus (HPV) vaccines: Gardasil (Merck and Co., Inc.) and Cervarix (GlaxoSmithKline Biologicals). Gardasil targets two oncogenic HPV types (16 and 18) and two nononcogenic HPV types (6 and 11) responsible for genital warts and respiratory papillomatosis. Cervarix targets two oncogenic HPV types (16 and 18) and is formulated with a novel adjuvant, ASO4, included to boost the immune response. Phase III clinical trials have already been done and HPV vaccines are currently licensed in 120 countries (1, 2). To date, these two vaccines have shown a very high efficacy against predefined end point lesions [HPV16- or HPV18-related cervical intraepithelial neoplasia of grade 2 (CIN2) or higher (CIN2+)], adequate safety and tolerability profiles, high immunogenicity, long-term duration of protection in the range of 7 to 8 years, and strong indications of immune memory induction. Interestingly, some degree of cross-protection against CIN2+ related to other HPV types (HPV31 for both vaccines and HPV33 and 45 for Cervarix) has been documented. Therefore, in properly vaccinated populations, the global estimates of the protection against cervical cancer of the currently available vaccines range from strictly high rates of cervical cancer. Thus, the vaccination trial in Guanacaste is likely to be perceived as the reference for HPV vaccination in many countries in the region.

The initial intent of the research team was to generate a useful HPV vaccine on its own [some components of the virus-like particles (VLP) technology used in the production of vaccines are under NCI patents] but later decided to use Cervarix, which at the time was entering phase III trials. The reasons for this choice have not been fully disclosed, but the external validation of novel technology for screening, and more recently, they are contributing a full phase III HPV vaccination trial for the prevention of cervical cancer.

Costa Rica is considered a developing country in which cervical cancer remains a preventive priority among women. Standardized incidence rates are in the range of 17.5 to 18.9 per 100,000 women. Cervical cancer ranks second in frequency among cancer in women of all ages and first among women ages 15 to 44 (5). Data from Costa Rica should be largely applicable to extensive areas in Latin America, a region with consistently high rates of cervical cancer. Thus, the vaccination trial in Guanacaste is likely to be perceived as the reference for HPV vaccination in many countries in the region.

The Guanacaste HPV Vaccination Trial

The Guanacaste province, located in the northern part of Costa Rica, has been one of the emblematic study locations in the HPV field. For the last two decades, studies jointly run by the local epidemiologic team and scientists at the National Cancer Institute (NCI) in the United States have generated critical data on the natural history of HPV infections and the validation of novel technology for screening, and more recently, they are contributing a full phase III HPV vaccination trial for the prevention of cervical cancer.

The Guanacaste trial is significantly smaller (N = 7,466 women, ages 18–25) than other phase III trials with either Cervarix (Patricia study, N = 18,644 women ages 15–25) or Gardasil (Future II study, N = 17,622 women ages 15–26). Thus, the power to evaluate vaccine efficacy (VE) against the less common HPV types individually (i.e., HPV31, 33, and 45)
or to circumvent the complexities of the causality attribution in the presence of multiple infections is lower than in the other vaccine trials. Consequently, the authors decided (for this article) to use 12-month persistent infection as the central end point for VE evaluation, which is a more distant, yet more frequent, surrogate to cervical cancer than the conventional CIN2+ end point. They also decided to present composite end point analyses by grouping viral types: HPV16; HPV18; HPV31+33+45; “other” oncogenic; and “any oncogenic.” Individual evaluation of each HPV type, however, is available in the supplementary tables accompanying the article by Herrero and colleagues (6). While persistent infection is now generally acceptable as an end point, the report of the trial does not include data on the HPV16 or 18 CIN2+ end points, thus limiting the ability to fully compare the results with those of other vaccination trials. However, some VE results against 6- and 12-month persistent infections have been reported for the Patricia trial and are largely consistent with the results of the Guanacaste trial.

In this respect, it would be useful if a pooled analysis of the Patricia and Guanacaste trials could be performed using stronger end points (i.e., CIN3) and similar criteria to deal with the issue of multiple infections to advance the quantitative understanding of the cross-protection effect. Furthermore, for future vaccine studies, trials that combine regulatory-driven and scientifically or public health-driven objectives could potentially save time. The combined academic and commercial approach in conducting these studies may prove to be essential in forthcoming population-wide preventive trials in which different combinations of HPV vaccination and novel screening technologies, including potential conflicting interests, will need to be articulated.

**CRITICAL RESULTS**

**Vaccine Protection**

In this issue, Herrero and colleagues (6) confirm the expected 95% to 100% protection against HPV16 and 18 persistent infections in HPV-naïve young women. Further, VE against HPV16 and 18 persistent infections in the 4 years of observation increased over time in both cohorts (according-to-protocol (ATP) and intention-to-treat (ITT)) to an astonishing 100% and 94.3%, respectively. The results are consistent with those of other vaccine trials that have also repeatedly reported a trend in increasing efficacy over time, when the burden of cases to be related to prevalent infections has materialized. The ITT results showing a significant increase in VE over time strongly suggest that HPV16 and 18 vaccination of women already exposed to the virus protects them against reinfection and persistence of infection with HPV16 and 18.

Comparison of VE across four age groups in the 18- to 25-year range in the ATP and ITT cohorts strongly suggests that efficacy is not age-dependent, but HPV status-dependent. In Guanacaste, VE in the ATP cohort was 95.9%, 86.6%, 95.7%, and 82.2% for ages 18 to 19, 20 to 21, 22 to 23, and 24 to 25, respectively (test for trend not included), whereas in the ITT cohort, VE clearly decreased from 68.9%, 42.8%, and 51.5% for ages 18 to 19, 20 to 21, and 22 to 23 to a nonsignificant 21.8% for ages 24 to 25. The high VE against 6-month persistent infection in older HPV-naïve women is directly supported by at least one other vaccine trial of Gardasil recruiting women up to age 45 (7).

Finally, it is important to note that these results pertain to women in Costa Rica, a high-risk country for cervical cancer, and that recruitment was conducted irrespective of the sexual activity or HPV status of the women at study entry. In the trial’s population, the prevalence of HPV infection was high (28% at recruitment), as was the risk of new infections over a 4-year period (3%–4% persistent infection in the ATP cohort and 7%–9% in the ITT cohort).

Taken together, the findings of a very high VE in the ATP cohort across ages 18 to 25 and of a significant VE in the ITT cohort up to ages 22 to 23 support the proposal of massive vaccination of young adult women at least to age 23. The protection against reinfection afforded over time in the entire age range of 18 to 25 has the potential to expand the proposal to target ages beyond the 25-year age limit, an arbitrary limit imposed by the study design. These recommendations should be particularly attractive in populations who have limited access to high-standard screening and diagnostic programs.

**Vaccine Cross-Protection**

This study also confirmed partial protection of Cervarix against persistent infection by HPV31, 33, and 45 in a combined end point analysis. However, the individual evaluation of VE by type produced fluctuating results. In some instances, this could be attributed to a small number of observations, but for several viral types, the number of HPV infections and 12-month persistent infections was large. It is worth considering that persistent infection is indeed a surrogate of CIN2+ but a more distant surrogate of cervical cancer; therefore, lack of VE against persistency may not be fully informative about VE against cervical cancer.

The added value of using viral persistency as an end point is that it avoids the complexity of causality attribution in the presence of multiple infections, a situation that has plagued the major vaccine trials that used CIN2+ as end points particularly to evaluate protection against individual HPV types other than 16 and 18.

It would therefore be worthwhile to standardize the analysis and end points such as CIN2+ or CIN3+ irrespective of HPV type, a reasonable alternative that might help future vaccine trials as well as regulatory bodies.

**THE CONFIRMATORY VALUE OF AN INDEPENDENT TRIAL**

The possibility of biased results from trials supported and largely analyzed and published by the product’s manufacturer often has been raised and exploited by some antivaccine groups to the detriment of vaccines being accepted and used by the public.

The HPV vaccine trial in Guanacaste offers an interesting opportunity to validate the critical results on safety and efficacy in a study that has been run and analyzed independently from industry. Several lessons can be learned from the Guanacaste trial process. The preparation of the trial included significant interaction and discussions of the research...
team with external advisors and industry to reach a scientific agreement on which vaccine to use and the master guidelines of the study design (e.g., end points, vaccine dose, clinical protocols, HPV testing systems). To that extent, it is important to note the similitude with the Patricia trial in critical aspects of the protocol and laboratory technologies for HPV testing (8, 9).

The Guanacaste study has already been presented in publications and in oral communications with analyses of potential public health interests that seem to have been of lower priority in the industry-driven trials. These include the early report of the nontherapeutic effect of the bivalent vaccine (10), confirmed also for the larger phase III trials; the suggestion of the potential value of two doses versus three doses (11); studies on anal lesions (12); and some safety studies (13).

In general, industry-driven trials give priority to publishing the results in agreement with the regulatory agencies that will determine vaccine licensing and establish the clinical indications. Some of the results of the Guanacaste trial should stimulate additional analyses and publications by the larger phase III trials that have the power to validate the findings with significantly more statistical power. Other smaller demonstration trials are being organized in Japan, China, and India as part of the regulatory requirements for licensing in these countries.

One of the limitations of these external validation trials is that they tend to be isolated projects and not part of a comprehensive research plan that includes, for example, immunologic investigations on doses and schedules, bridging studies of younger and elderly age groups, studies of interference with other vaccines, male vaccination studies, larger safety data banks, linkage to basic research on vaccine development and mechanisms of action, and a series of other ancillary studies that are typically organized by the larger industry-funded projects.

However, the confirmatory results are also useful because they externally validate the general methodology of the larger Patricia and Future trials including the advisory implication of external scientists and analysts and the organization of expert panel supervision for monitoring quality, the assessment of end points, safety, ethics, advisory boards, and writing committees.

The HPV vaccine trials offer a reproducible methodology that can be used in future vaccine trials (HPV and other) that may not benefit from the organization of independently run trials outside manufacturers’ studies.

RESULTS OF VACCINE INTRODUCTION AND FUTURE PROSPECTS

Since 2006, efforts to introduce HPV vaccines into routine vaccination programs and, most importantly, into developing countries have been a large part of the international public health agenda. Early results from Australia have indicated that in the years following massive vaccination of women the occurrence of genital warts is dramatically reduced (14). Population-based results on the reduction of CIN1+ and CIN2+ in populations receiving high coverage at ages ranging from adolescence to 18 (i.e., the United Kingdom, using Cervarix) or 25 years (i.e., Australia, using Gardasil) are expected in 2012 to 2017. The limitations of current vaccines are known and include the lack of therapeutic effect; the still poorly known effect of the cross-protection effect; and, as a consequence of the two, the requirement to continue screening programs among vaccinated women. Of no less importance is the initial high cost of the vaccines in the years of introduction, which dominated the age range indications in developed countries and largely delayed the arrival to developing countries (1).

Future prospects for the prevention of cervical cancer are now being clarified and the Guanacaste trial will help in the efforts to introduce HPV vaccination into developing countries. The recent announcement of a low-cost vaccine offered by Merck (MSD) to the GAVI Alliance countries has piqued great interest. In developed countries, priority generally has been given to vaccinating individuals in the adolescent age range with a variable interval for catch-up vaccination, and protocols are being developed to assess the best screening options for HPV-vaccinated women. In the medium term, novel vaccines will appear that either will increase the number of HPV types used as antigens for a broader coverage of the oncogenic spectrum or will use other technologies that will equally target a wider range of viral types.

Along with the progress made in the screening field, cervical cancer prevention now enters a phase in which the technologies for preventing the disease in defined populations are available. Attention now must shift to the political and public health arenas, where important decisions need to be made and resources found to move one of the most prevalent cancers in women onto the list of eradicable diseases.

Disclosure of Potential Conflicts of Interest

F. Bosch has consulted for the MSD International Steering Committee, provided expert testimony for GlaxoSmithKline at the Food and Drug Administration and European Medicines Agency (EMA) hearings, and is a member of the GlaxoSmithKline and Sanofi Pasteur MSD speakers bureaus. X. Castellsagüé has received institutional research grants and personal payments for consultancy and lectures, including service on speakers bureaus, from Sanofi Pasteur MSD, Merck, and/or GlaxoSmithKline. S. de Sanjose has received institutional research grants from Merck, personal payment for consultancy from Qiagen, and personal payment for lectures, including service on speakers bureaus, from Qiagen, Sanofi Pasteur MSD, and GlaxoSmithKline.

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