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REVIEW

Progress in the research on HPV vaccination: updates from the 25th International Papillomavirus Conference in Malmo, Sweden, 2009

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Introduction

The Human Papilloma Virus (HPV) is one of the most important oncogenic viruses for humans. Researches on its epidemiology, pathogenic mechanisms and preventive tools had an acceleration since preventive HPV vaccines started their way towards approval by regulatory authorities. An impressive number of articles have been published in international journals in the last years, and the same can be said about presentations and posters at congresses, meetings and symposia. One of the most important yearly events where new research data are usually anticipated, is the International Papillomavirus Conference, whose 25th edition was held in Malmo, Sweden, on May 8-14, 2009.
We summarise here a few particularly interesting selected studies presented at the Conference regarding Papillomavrus preventative vaccines.

Immune response after primary vaccination course: a comparative trial of two HPV prophylactic vaccines (Einstein et al.) [1]

Excellent clinical protection has been demonstrated so far for the two available HPV vaccines by several clinical trials and follow-up studies.
This study aimed at comparing the antibody responses measured one month after the administration of a complete course of vaccination either with the bivalent and the quadrivalent HPV vaccines.
In an observer-blind study, women (n = 1,106) were stratified by age (18-26, 27-35, 36-45 years) and randomized (1:1) to receive Cervarix™ (Months 0, 1, 6) or Gardasil® (Months 0, 2, 6). Antibody responses were evaluated in sera and in cervicovaginal secretions [CVS] by pseudovirion-based neutralization assay (PBNA, developed by NCI) and ELISA, and memory B-cell responses (sera) by ELISPOT assay.
In the According-To-Protocol (ATP) cohort (seronegative/DNA-negative before vaccination for HPV type analyzed), Geometric Mean Titres (GMTs) of serum neutralizing antibodies measured by PBNA at Month 7 were 2.3-4.8-fold higher for HPV-16 and 6.8-9.1-fold higher for HPV-18 with Cervarix™ compared with Gardasil®, across all age strata. In the Total Vaccinated Cohort (TVC) (women who received ≥ 1 dose), Cervarix™ induced significantly higher HPV-16 and -18 serum neutralizing antibody titers ($p < 0.0001$) for each antigen in each age stratum. Positivity rates for anti-HPV-16/18 neutralizing antibodies in CVS and circulating HPV-16/18-specific memory B-cell frequencies were higher for Cervarix™ compared with Gardasil®. Both vaccines were generally well tolerated. Rates of solicited symptoms were higher for Cervarix™, injection site reactions being most common. Compliance was high (84%) for both vaccines.

Comment. This study shows a significantly higher antibody response to the L1 protein of HPV 16 and 18 in women immunised with the bivalent compared to the quadrivalent vaccine. A higher titre of anti-L1 antibodies at the end of the immunisation course is likely to mean their longer-term duration, according to the experience of decay of antibodies registered after other vaccinations (for instance, hepatitis B). Future studies will hopefully clarify the exact role of antibody titres and of immunological memory for long-term protection. The recall effect of viral challenge at the mucosal level might play a role, but whether natural exposure to HPV induces an anamnestic response to L1 protein in vaccinees remains to be demonstrated. At the same time, the mechanism of protection conferred by vaccination has not been completely elucidated. The most likely hypothesis is that antibodies pass through from blood to the cervical mucus (natural site of infection and lesion), where they would be able to neutralise vaccine-types HPV virions. The implications of the response to this question are crucial to understand whether an elevated titre of anti-L1 is an obliged pre-requisite for long-term protection, or if immunity can rely also on the anamnestic response of memory B cells to nascent infection.

Long-term efficacy of a prophylactic human papillomavirus type 16 vaccine (Rowhani-Rahbar et al.) [2]

The first protptype vaccine, against HPV 16 (never available for commercial use) was administered in a clinical trial a mean of 8.5 years ago (range: 7.2-9.5 years). This follow-up study was intended to evaluate the long-term efficacy of this precursor of the present quadrivalent vaccine (Gardasil®) in 290 women who had participated in a phase IIb randomised controlled trial (RCT) of this vaccine in Seattle (November 1998-January 2004). During the RCT period, one woman exhibited HPV-16 infection by HPV DNA detection at a single visit (month 12) in the vaccine group; 15 women exhibited HPV-16 infection and 5 women developed HPV-16-associated CIN in the placebo group. During the extended follow-up period, no woman exhibited HPV-16 infection or developed HPV-16-associated CIN in the vaccine group; 6 women exhibited HPV-16 infection (vaccine efficacy [VE] = 100%; 95% confidence interval [CI]: 25%-100%) and 3 women developed HPV-16-associated CIN (VE = 100%; 95% CI: < 0%-100%) in the placebo group. Approximately 86.3% of vaccine recipients remained HPV-16 competitive Luminex(R) immunoassay seropositive at 8.5 years. Overall,throughout the combined RCT and extended follow-up periods, 1 woman exhibited HPV-16 infection and no woman developed HPV-16-associated CIN in the vaccine group; 21 women exhibited HPV-16 infection (VE = 96%; 95% CI: 73%-100%) and 8 women developed HPV-16-associated CIN (VE = 100%; 95% CI: 47%-100%) in the placebo group.

Comment. The virtual 100% efficacy of the monovalent vaccine against HPV type 16 is reassuring in view of the required long-term effectiveness vis-à-vis the long foreseen sexual life after administration of prophylactic vaccination at pre-adolescent age. However, it must be underlined that each vaccine formulation may have different characteristics also regarding the long-term effectiveness, and therefore long-term protection of the quadrivalent vaccine cannot be directly inferred from data of one of its precursors.

Final phase III efficacy analysis of Cervarix™ in young women (J Paavonen et al.) and Cross-protective efficacy of Cervarix™ against oncogenic HPV types beyond HPV-16/18 (R. Skinner et al.) [3, 4]

The former of these two studies (representing in reality two sub-sets of results of the same study) reports the data on the final outcome of the phase 3 clinical trial of the bivalent 16/18 AS04 adjuvanted vaccine (Cervarix™, GlaxoSmithKline), after the interim analysis published in The Lancet by the same Authors in 2007 [5].

The primary objective was to evaluate vaccine efficacy (VE) against HPV-16/18 CIN2+. Secondary and exploratory objectives included VE against CIN2+ associated with any oncogenic HPV types, CIN2+ overall (i.e., irrespective of HPV type detected in the lesion) and safety. The study population consisted of 18,644 women 15-25 years (total vaccinated cohort; TVC), who received either HPV-16/18 vaccine (n = 9,319) or a control vaccine (HAV) (n = 9,325) at Months 0, 1, 6. Cervical samples were collected every 6 months for HPV DNA typing; gynecological and cytopathological examinations were performed every 12 months. Efficacy analyses were performed in the According-To-Protocol cohort for Efficacy, (i.e., those meeting all eligibility criteria, complying with the protocol procedures, without any protocol violations, who were given three vaccine doses, had normal or low-grade cytology at baseline, and were valuable for efficacy) (ATP-E; vaccine = 8,083; control = 8,069; mean [SD] follow-up: 34.9 [6.41] months after dose three), in the TVC and the TVC naive (a subset of the TVC that included subjects who had normal or low-grade cytology at baseline, who received ≥1 vaccine dose, were seronegative for HPV-16/18 and DNA negative for 14 oncogenic HPV types at baseline; vaccine = 5,822; control = 5,819). Safety was assessed in all valuable women.

Vaccine efficacy (and relevant 96.1% confidence intervals -CI) against HPV-16/18 CIN2+ in the According-To-Protocol for Efficacy population was 92.9% (79.9;98.3) in the pre-defined primary analysis (defined as a positive HPV16 or HPV18 result as detection of either type by SPF10-LiPA25 system or by type-specific PCR in vaccinated and non vaccinated cohorts), and 98.1% (88.4;100) in an analysis that assigned probable HPV causality in lesions containing multiple HPV types; and was 98.4% (90.4; 100) in the TVC naive. Overall, VE against CIN2+ was 30.4% (16.4; 42.1) in the TVC (regardless of baseline cytological, serological and DNA status) and 70.2% (54.7; 80.9) in the TVC naive. Rates of adverse events (including serious adverse events and medically significant conditions) were generally similar between groups.

In the other presented subset of the study, the TVC-naïve cohort of women was considered (Mean [SD] follow-up: 39.5 [8.99] months). Vaccine efficacy (VE) (96.1% CI; p-value) against CIN2+ was: 100% (82.2, 100; $p < 0.0001$) for HPV-31 /45, 68.2% (40.5, 84.1; $p < 0.0001$) for the 5 most frequent oncogenic types (HPV-31 /33 /45 /52 /58), 68.4% (45.7, 82.4; $p < 0.0001$) for the 10 most frequent oncogenic types (HPV-31 /33 /35 /39 /45 /51 /52 /56 /58 /59), 66.1% (37.3, 82.6; $p < 0.0001$) for A9 species (HPV-31 /33 /35 /52 /58) and 77.3% (36.0, 93.7; $p = 0.0009$) for A7 species (HPV-39 /45 /59 /68). Cross-protection was further substantiated by VE against individual HPV types including 31, with 92·0% VE (66.0 to 99.2; $p < 0.0001$) against CIN2+, and 45, for which statistically significant protection was demonstrated against 12-month persistent infection, VE 63.0% (18.4, 84.7; $p = 0.0049$) [6]. Overall VE against CIN2+ associated with 14 oncogenic types, including vaccine types (HPV16 /18 /31 /33 /35 /39 /45 /51 /52 /56 /58 /59 /66 /68) was 77.7% (63.5, 87.0; $p < 0.0001$).

Comment. The final results of the phase III trial of the bivalent vaccine confirm the high protective efficacy of the vaccine against CIN2+ lesions due to HPV 16 /18. The 93% efficacy in the ATP-E population resulting from pre-specified criteria (designed irrespective of the high probability of multiple HPV types infection) is further improved (98%) when an algorythm is used to assign causality to one of different HPV types present in a lesion.
The overall results of efficacy against CIN2+ due to all HPV types in the Total Vaccinated Cohort Naive (about 70%) are a proxy of the expected impact of vaccination on total CIN2+ lesions in the pre-adolescent cohorts, who are the main object of routine immunisation programmes. On the other hand, the about 30% efficacy against all CIN2+ lesions in the TVC cohort represent the potential impact of catch-up vaccination policies including sexually-active young women who might be immunised when already infected by HPV.
Data on cross protection towards CIN2+ and persistent infection caused by vaccine-related HPV types represent another very important result, since they mean a potentially further 10-15% preventable pre-cancerous lesions in addition to those caused by HPV 16 and 18. As a matter of fact, vaccine types 16 and 18, together with HPV 31, 33 and 45 (types for which cross-protection is particularly important and desirable, and that was demonstrated at variable level for the bivalent vaccine) cause altogether about 82% of all cervical cancers.

Rapid decline in warts after national quadrivalent HPV vaccine program (Fairley et al.) [7]

Since Australia was the first country to offer free of charge vaccination with HPV vaccine to several cohorts of girls (12-18 year old since April 2007) and to women (26 year old through general practices since July 2007), and due to the short incubation period between infection and manifestation of genital warts, that country represents the best place where to verify the impact of the HPV vaccine in the field following extended immunisation programmes.
The aim of this study was to measure the proportion of new clients with genital warts at Melbourne Sexual Health Centre (MSHC) from January 2004 to December 2008. Thirty-six-thousand-fifty-five new clients attended MSHC between 2004-2008 and genital warts were diagnosed in 3,826 (10.6%; 95% confidence intervals (CI): 10.3-10.9). Clinical prevalence ratios (RR), and 95% CIs were calculated for the proportion of new clients with genital warts for 2004-2007 combined compared to 2008. The proportion of new clients with genital warts was significantly lower in 2008 than 2004-2007 for men (RR = 0.82 [95% CI, 0.75-0.90]) and women (RR = 0.62 [95% CI, 0.54-0.72]). Analysis of subgroups found only women <28 years (RR = 0.52 [95% CI, 0.44-0.63]) and heterosexual men (RR = 0.83 [95% CI, 0.74-0.92]) but not homosexual men (RR = 0.93 [95% CI, 0.73-1.17]) or women ≥ 28 years (RR = 0.91 [95% CI 0.70-1.17]) had a significant fall in genital warts in 2008 compared to 2004-2007. From January to December 2008 there was a significant decline in the monthly presentations for warts among women < 28 years (p for trend = 0.03).

Comment. In spite of the clear limitations that every field evaluation performed in a relatively short time interval inevitably has, this study is suggestive of a marked impact of extended vaccination programmes on the incidence of genital warts among vaccinated women, and supports some benefit being conferred to men. A reduction in genital wart diagnoses in heterosexual but not homosexual men is consistent with reduced heterosexual transmission of HPV as a result of female vaccination.

Quadrivalent HPV vaccine effficacy against male genital disease and infection (Giuliano et al.) [8]

Although HPV-related diseases undoubtedly exert their pathogenic potential mainly in women, however also men experience benign diseases (especially genital warts) and pre cancerous and cancerous lesions of the genital and anal area. This study examined the efficacy of the quadrivalent HPV L1 virus-like particle vaccine against incidence of HPV 6/11/16/18-related external genital lesions (EGL) (external genital warts, penile/perineal/perianal intraepithelial neoplasia, and penile/perineal/perianal cancer) as well as genital HPV 6 /11 /16 /18 infection in young men (heterosexual men and men having sex with men).
A cohort of 4,065 young men aged 16-26 years received quadrivalent HPV vaccine or placebo at enrollment, month 2, and month 6. Subjects underwent detailed genital exams as well as sampling from the penis, scrotum, and perineal/perianal region at enrollment, month 7 and at 6-month intervals afterwards. After enrollment, all new lesions were biopsied for pathological diagnosis and PCR testing. Efficacy analyses were performed in a per-protocol population seronegative at day 1 and HPV DNA-negative from day 1 through month 7 to the relevant vaccine HPV type. Median follow-up was 2.3 years (starting from month 7).
Among 1,397 vaccine subjects and 1,408 placebo subjects, efficacy against any HPV 6/11/16/18-related external genital lesion was 90.4% (95% CI: 69.2, 98.1). Vaccine efficacy against condyloma and PIN was 89.4% (95% CI: 65.5, 97.9) and 100% (95% CI: <0, 100), respectively. Vaccine efficacy against HPV 6/11/16/18 persistent infection and DNA detection at one or more visits was 85.6% (97.5% CI: 73.4, 92.9), and 44.7% (95% CI: 31.5, 55.6), respectively. Slightly more injection-site adverse experiences were seen among vaccine recipients.

Comment. Although present vaccination programmes are limited to women in the vast majority of countries, it is not excluded that an enlargement of such programmes might be desirable in the future to male populations. This study provides evidence of the efficacy of the quadrivalent HPV vaccine against external genital lesions in young men, both hetrosexual and homosexual, thus representing useful data to this potential aim.

Conclusions

The studies on HPV vaccination presented at the 25th International Papillomavirus Conference in Malmo confirm the key role that vaccines have in the struggle against one of the most impacting viral diseases on human health. An impressive amount of data confirm the excellent performance of available vaccines, whose safety and efficacy profile (also thanks to the unforeseen cross protection they provide) is significantly greater than the initial forecasts.

The main challenge now, in addition to the continuing development of new generation products, will be that of implementing functioning immunisation programmes, particularly needed in low-income countries, where the burden of HPV related diseases is very high also due to the difficulty in setting up effective screening programmes.

Strong commitment will be needed by industrialised countries both to offer protection to more cohorts of their citizens, but also to join efforts in order to provide vaccine doses, and to help countries most in need to build the infrastructures and the manpower capacity that will allow all the world population to benefit from an essential, life saving medical technology like HPV vaccination.

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