Expert opinion

New paradigm for prevention of cervical cancer

Abstract

Human papillomavirus (HPV) infection is an event responsible for the development of cervical cancer and its premalignant dysplasia. Prophylactic vaccines based on virus-like particles (VLPs) have been successfully tested in clinical trials. They are safe, close to 100% effective in preventing persistent infection and premalignant disease, and are now being introduced onto the market. Vaccination should be offered primarily to young girls and adolescents 9–15 years of age. Vaccine introduction faces particular problems due to a bias towards sexually transmitted diseases and financing, especially in developing countries. However, it represents the first vaccine that has the potential to eradicate 70% of cervical cancer worldwide.

Keywords: Human papillomavirus; Prophylactic vaccination; Virus-like particles; Clinical studies

1. Introduction

Cervical cancer can be prevented by eliminating genital infections with oncogenic human papillomaviruses (HPV). This strategy of primary prevention comprises stopping a pandemic viral infection that (i) can affect nearly everyone, (ii) causes half a million cancer cases worldwide, and (iii) is responsible for 250,000 deaths among women each year.

When human papillomaviruses were detected in warts and cervical cancer for the first time in the early 1980s, only a few scientists predicted that this infection was an invariably necessary step in the induction of cervical cancer [1–4]. Today, we are witnessing the introduction of the first generation of prophylactic vaccines against the most prevalent HPV types in cervical cancer and genital warts. Molecular and epidemiological studies have proven that it is the two viruses, HPV16 and HPV18, out of approximately 18 “oncogenic” or “high-risk” types that are responsible for 70% of cervical cancers [5]. HPV6 and HPV11 induce 90% of genital warts, thus contributing significantly to anogenital disease and discomfort.

2. Prophylactic vaccines

Two major pharmaceutical companies have developed highly immunogenic and protective prophylactic vaccines, which in phase II and III clinical trials have thus far been shown to be safe and effective for up to 5 years. GlaxoSmithKline has developed a bivalent vaccine, Cervarix®, against HPV16 and HPV18, targeting anogenital cancers. Sanofi-Pasteur MSD/Merck has included HPV6, 11, 16, and 18 as a quadrivalent vaccine, targeting both genital warts and cancer (Gardasil®). Based on the recombinant expression of only one single capsid protein – L1 – in either insect cells or yeast, the production of virus-like particles (VLPs) generates a remarkably effective immunogen. VLPs of these most prevalent HPV types were combined with adjuvants to formulate vaccines capable of inducing virus-neutralising serum antibodies. Since VLPs are highly immunogenic per se, minute amounts of 20–40 μg are usually sufficient as an antigen. To further enhance the immune response, the standard adjuvant aluminium hydroxide was added (to both preparations) or is supplemented with GlaxoSmithKline’s proprietary AS04 containing MPL, a derivative of bacterial lipopolysaccharide, for Cervarix® (Table 1).

Initial studies showed that three injections induce virus-neutralising antibody titres in the serum that peak at approximately 100-fold higher than those induced after natural infection [6,7]. After an initial decline they level out, to at least around the level of those antibody titres induced after natural infection (Gardasil®) or well above 10-fold higher than these concentrations (Cervarix®).

Remarkably, the titres induced in the presence of AS04 seem to be higher and longer lasting. Follow-up observations are now available for >4.5 years and show no further significant decline in titres [8]. This promises a rather long-
lastingly immunized. Experience with adjuvant hepatitis B vaccine with AS04 produced comparable results, reaching antibody levels two-fold higher than the standard hepatitis B vaccine Engerix-B [9].

The study cohorts, which all together comprise about 50,000 participants, will be followed further in the future and are an exquisite sentinel cohort. They will be around 5–6 years ahead of the normally vaccinated population. Follow-up analyses will allow a determination of antibody levels and degree of protection [8,10].

Unfortunately, up to now, no direct comparisons of antibody titres of the two vaccines have been published, since each company has its own ELISA-based read-out system. Thus, the immunogenicity of the two vaccines cannot be compared directly.

For both vaccines the seroconversion rate is 100%. No abnegators have been reported and titres induced are comparably high throughout the vaccinated cohort. Therefore, it can be expected that the immunogenicity is reliable in all vaccinees and the success of vaccination will not have to be controlled after immunisation. Whether it will be deemed necessary to control or to boost titres later on will depend on the results of follow-up studies. For now, the measurement of IgG serum levels has been revealed to be a good correlate to protection. Other isotypes, such as IgM and IgA, were also induced, but turned out to be less long lasting or less detectable. Since serum IgG levels after natural infection do not seem to convey protection against reinfection with the same HPV type [11], additional mechanisms that prevent infection and disease should be present, but these remain to be defined.

For the vaccination of healthy young individuals whose characteristics still need to be defined, the safety of the vaccines is of utmost importance. Both preparations had an excellent safety profile. Local site and systemic reactions were generally mild and nearly indistinguishable between the vaccine and placebo groups. There was no discontinuation of the immunisation protocol due to adverse reactions. Not a single serious adverse event that occurred due to the exposition of the vaccine was reported from the studies that have been published up to now. During the follow-up period no new onset of any chronic disease was reported [8]. Again, the long-term follow-up and the application of phase IV studies will have to verify this important issue. For example, in polio prevention, vaccine-associated paralytic poliomyelitis occurred in one case per 2.4 million doses distributed [12]. The HPV VLP vaccine, however, is based on recombinant technology, which does not carry any risk of infectivity.

The most promising and surprising result of the vaccination trials was the outstanding effectiveness of the vaccines used. Even during the initial proof-of-principle study of a monovalent HPV16 VLP vaccine, 100% effectiveness in protecting against persistent HPV infection and cervical dysplasia was recognized [10,13]. The following phase III studies confirmed these results. There was an approximately 90% reduction of incident infection and cytological anomalies, and 100% effectiveness against persistent infection and protection against cervical intraepithelial neoplasia (CIN) [6,7]. Moreover, during long-term observation it became obvious that not only the HPV types contained in the vaccines were controlled, but infections by some other HPV types were also reduced. The genetically closely related types HPV45 (95%) and HPV31 (54%) were found to be significantly less frequent in persons vaccinated with Cervarix®. Such cross protection may enhance the effectiveness of the vaccine to prevent 80% of cervical cancers [8].

### Table 1
Comparison of emerging vaccine formulations: Sanofi-Pasteur MSD/Merck vs. GlaxoSmithKline

<table>
<thead>
<tr>
<th>Company</th>
<th>SP MSD/Merck</th>
<th>GSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Gardasil®</td>
<td>Cervarix®</td>
</tr>
<tr>
<td>Target disease</td>
<td>Genital warts, cervical dysplasia, and cancer</td>
<td>Cervical dysplasia and cancer</td>
</tr>
<tr>
<td>Application (months); injection</td>
<td>0, 2, 6: 0.5 ml i.m.</td>
<td>0, 1, 6: 0.5 ml i.m.</td>
</tr>
<tr>
<td>Target HPVs</td>
<td>6/11/16/18 quadrivalent</td>
<td>16/18 bivalent</td>
</tr>
<tr>
<td>VLP amount</td>
<td>20/40/40/20 µg</td>
<td>20/20 µg</td>
</tr>
<tr>
<td>Adjuvants</td>
<td>Amorphous aluminium hydroxyphosphate sulphate</td>
<td>Amorphous aluminium hydroxyphosphate sulphate + MPL (AS04)</td>
</tr>
<tr>
<td>Production</td>
<td>Yeast (Saccharomyces cerevisiae)</td>
<td>Insect cells (SF9)/baculovirus</td>
</tr>
<tr>
<td>Approval granted</td>
<td>June 8th, 2006</td>
<td>Approval pending</td>
</tr>
<tr>
<td>Essential publication</td>
<td>Villa et al. [7]</td>
<td>Harper et al. [6,8]</td>
</tr>
<tr>
<td>Safety</td>
<td>Well tolerated, few minor adverse events</td>
<td>Well tolerated, few minor adverse events, no vaccine-related SAE</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>100% seroconversion</td>
<td>100% seroconversion</td>
</tr>
<tr>
<td>Antibody titres (depending on HPV type)</td>
<td>Comparable to 1–19 times of natural infection (3 years)</td>
<td>14–17 times of natural infection (4.5 years)</td>
</tr>
<tr>
<td>Efficacy, preventing persistent infection (%)</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Efficacy, preventing CIN (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cross protection against incident infection</td>
<td>Not shown</td>
<td>HPV45 (95%), HPV31 (54%)</td>
</tr>
</tbody>
</table>

VLP: virus-like particles; CIN: cervical intraepithelial neoplasia; SAE: serious adverse event.
3. Implementation

Reducing 80% of cervical cancers could result in the prevention of 400,000 cancer cases in women and approximately 200,000 deaths worldwide. There is the potential risk that other HPV types will fill in the niche when HPV16 and HPV18 are eliminated. Recent epidemiological data, however, show that of all high-risk HPV types, HPV16 and 18 confer the highest risk of dysplasia over a period of up to 10 years [14,15].

Other vaccination programs against hepatitis, polio, and childhood infections have proven to be cost-effective and efficient health care measures. WHO programs even made it possible to eradicate smallpox. For HPV no animal interim reservoir for the propagation of the virus exists and a sterilizing immunity can be induced in humans. Thus, the elimination of certain HPV types seems possible. It must be emphasized that screening for precancer at an early stage needs to be continued, even if in a modified way, due to the presence of oncogenic HPV types not covered by these vaccines.

Clearly, the impact of a vaccination program in South America, Africa, and parts of Asia, where 80% of cervical cancers occur, has to be distinguished from those of other geographical regions. While in the so-called developing countries the aim must be to reduce the cancer burden at a low cost, in the so-called developed world the same applies, but in addition the aim will also be to reduce the overall costs of screening and health care. This will be accomplished due to modified algorithms and reduced numbers of repeat PAP smears and surgical interventions.

Both companies have submitted approval applications. Gardasil® was filed with the FDA and EMEA in December 2005. After a fast-track evaluation process the FDA granted approval on June 8th, 2006. The vaccine is now available on the US market. Introduction onto the European market can be expected by the end of 2006. Cervarix® filed with the EMEA in March 2006 and is expected to be available in spring 2007. If vaccination is readily implemented, benefits will already be seen in a couple of years. About 30% of high-risk HPV infections, 40–50% of cytological abnormalities, and 50–60% of high-grade CIN may be avoided within 5–10 years, thus leading to considerable cost savings. The ultimate goal is a reduction in the incidence of cervical cancer (Fig. 1). The success of vaccination, however, depends on framework conditions like coverage and age at vaccination [16]. There are intangible costs that are hard to measure, but alleviation of the psychological distress associated with genital warts, abnormal PAP results, and treatment for pre-neoplasia or cancer adds considerably to the purely economic health savings.

A prerequisite for the elimination of genital infection with HPV is the establishment of a widespread and consequent vaccination program. The primary target population will be girls and young adolescents of both sexes, 9–15 years of age, just before initiation of sexual activity. Vaccinating younger children is not advisable due to the fact that the duration of protection has not yet been established. As a catch-up young adults and older women may also be vaccinated. High-risk groups like men who have sex with men, those who are iatrogenically immuno-suppressed, or HIV-infected persons may benefit from vaccination. It was shown that vaccinating women who are currently infected with HPV or who are serologically HPV-positive neither worsens health conditions nor inhibits antibody induction for the accompanying HPV types in the vaccines [17]. In contrast, HPV-positive but seronegative women vaccinated with Gardasil® gained 27% protection against developing CIN, which was not observed in seropositive vaccinees [18].

Whether boys should be vaccinated is controversial. Protection from HPV6/11-induced genital warts is conferred by Gardasil® and will also make vaccination attractive to the male population, while HPV16/18-caused disease is rare in males. With regard to cancer, immunisation of boys will contribute to the overall protective herd immunity effect of immunisation programs [19,20]. It may not substantially
reduce the cancer burden in women [21]. For health care providers cost-effectiveness is an important issue. Depending on the modelling method, vaccination of boys may turn out to be cost-effective.

4. Practical issues

The introduction of a vaccine against a sexually transmitted virus certainly faces particular difficulties. Ethical, religious, cultural, and social issues have to be taken into consideration [22]. This is an issue in particular when matronized and/or patronized young adolescents of 9–15 years of age are the main target group of a vaccination program. Adequate communication strategies must be developed and information needs to be transmitted in an adoptable way. Consensus statements, recommendations, and guidelines will have to be expressed by the relevant authorities [23]. Politicians, health care providers, and physicians of all the specialties involved will be instrumental in conveying information to parents of adolescent teenagers and the general public. It will need a common effort and a concerted action in order to reach and motivate those who are to be vaccinated. It means targeting an uninformed population that has never heard of HPV and cannot relate a viral infection to the means targeting an uninformed population that has never heard of HPV and cannot relate a viral infection to the

In conclusion, having a vaccine available for the primary prevention of HPV infection, means that researchers have accomplished a long-promised goal: giving mankind a tool to reliably eradicate a large proportion of a certain cancer disease. We hope that everyone will unambiguously support the introduction of this vaccine.

References

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