PRESENT ASPECTS OF HPV INFECTION
Part II

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Abstract: *People are living surrounded by an environment of omnipresent HPV viruses. A part of these viruses brings about certain lesions, some benign, some of malign potential. Some of these viruses infect the mucous membrane (especially the anogenital one) with a large frequency among the young patients causing cervix cancer (in women), anal and penis cancer, in men. In most of the cases, cervical HPV infection is temporary and asymptomatic. The most spread HPV viruses of oncogenic risks are the types 16 and 18. The screenings for cervix lesions consist in Pap test or liquid-base cytology for detecting HPV virus. Depending on the type of lesion, certain management strategies have been suggested. Today, in order to prevent the HPV cervix infection, the HPV vaccine is being used, being available as a bivalent vaccine (for 16 and 18 HPV types) and as a quadrivalent vaccine (for 6, 11, 16 and 18 HPV types). These vaccines have proved to be very efficient in 5-year studies, so that certain countries have adopted strategies of mass vaccination.*

Keywords: *HPV, cervix dysplasia, cervix cancer, vaccine*

Rezumat: *Omul trăieşte înconjurat de un mediu în care virusurile HPV sunt omniprezente. O parte din aceste virusuri provoacă diferite leziuni, unele benigne, altele cu potenţial malign. Unele dintre aceste virusuri infectează mucoasele (mai ales cele anogenitale) cu frecvenţă foarte mare la pacienţii tineri, la femei fiind cauza cancerului de col, iar la bărbaţi aceste virusuri pot cauza cancer anal şi de penis. Infecţia cervicală cu HPV este în majoritatea cazurilor pasageră şi asimptomatică. Tipurile HPV cele mai răspândite, cu risc mare oncogen sunt 16 şi 18. Screeningul leziunilor de col uterin se face prin citologie pe lamă (examen Papanicolau), sau prin citologie în mediu lichid cu detectarea virusului HPV. În funcţie de leziune, s-au propus o serie de strategii de management. Pentru prevenţia infecţiei cervicale cu HPV, la ora actuală se utilizează vaccinul contra HPV, acest vaccin existând în două forme, vaccin bivalent (contra HPV 16 şi 18) sau un vaccin quadrivalent (contra HPV 6,11,16,18). Aceste vaccinuri s-au dovedit foarte eficiente pe studii de până la 5 ani, astfel încât unele ţări au adoptat strategii de vaccinare în masă.*

Cuvinte cheie: *HPV, displazie cervicală, cancer de col uterin, vaccin*

Screening and management of the female patients with positive HPV.

In the Unites States, mortality due to cervix cancer decreased with 70%, following the introduction of the screening tests (Papanicolau). Generally, in the U.S.A., this screening is recommended to be initiated approximately 3 years after the first sexual contact, but not above the age of 21. The test should be done yearly and regarding the women above the age of 30 and who had three negative tests in antecedents, the test might be done every two or three years. Screening might be stopped in the women above the age of 65/70 who had three or more consecutive negative tests in the last 10 years. If HPV test is used, the interval between smears may increase up to three years, on condition that HPV be negative. (8)

The treatment of the cervical lesions brought about by HPV may include different approaches according to the lesion: condylomas may be treated surgically, through an excision with the cold or electrical surgical knife or with LASER, cryotherapy, photodynamics, immunotherapy with interferon or imiquimod and with antiviral agents; according to their gravity, cervical lesions may benefit from a simple loop-excision conization or hysterectomy. (8)

If, following a routine examination, HPV with high oncogenic risk was detected, but with negative smear, colonoscopia should not be immediately recommended, but to repeat the smear and the HPV test one year after.

The present oncologic classification of Babeş Papanicolau smears is made taking into account the Bethesda guidelines, the old Papanicolau classification being practically abandoned. According to the lesion detected upon the cytological examination, different management options are suggested.

Regarding the management of the patients with ASCUS, there are three accepted options. The first option is represented by the HPV test, which should be repeated one year after, if negative and if it is positive for high oncogenic risk HPV type, colonoscopy or biopsy is recommended. If the test comes positive for reduced oncogenic risk HPV type, it is suggested to repeat the

cytological examination 6 months after. The second option is to repeat the smear 6 months after and if it comes positive again, colonoscopy or biopsy is suggested and if it is negative, the test should be repeated one year after. The third option suggests the colonoscopy or the biopsy immediately. In the case of the young women below the age of 25, if the HPV test reveals an oncogenic HPV, they are suggested to repeat the cytological examination, as well as to make a colonoscopy or a biopsy. Regarding the menopausal women, the intravaginal estrogen therapy may be suggested, as well as to repeat the smear and if this comes positive, colonoscopy or biopsy will be recommended; if the smear turns to be negative, the smear will be repeated 6 months after. The LSIL lesions management is similar and the approach of the other types of lesions (ASC-H, HSIL, CIN 1/2/3), as well as that of the lesions detected upon colonoscopy or the cervix lesions that are histologically confirmed followed well-established protocols. (9)

Strategies for preventing the HPV infection

HPV prevention is made by using the condom, by the reduction of the number of the sexual partners, by the development of the sexual negotiation aptitudes, first sexual contact delay, abstinence, HPV vaccination. Until the introduction of the HPV vaccination, the condom use has been the most efficient and accepted method among the young, although it did not prove entirely efficient, as a series of studies and meta-analyses proved. (3,10)

HPV vaccines

There are vaccines obtained through genetic engineering (there is no risk for HPV infection) and contain L1 VPL (virus like particles), which have a very strong antigenic power. Seroconversion was obtained in all patients after vaccination, while the antibodies titre and their establishment in time were significantly higher after the natural infection.

Today, there are two vaccines on the market, a quadrivalent one that contains VLP for the types 6/11/16/18 and a bivalent one that contains VLP for 16 and 18 types. (10) The quadrivalent vaccine is produced by Merck & Co and has L1 VLP, which was obtained through a recombined vector of Saccharomyces pombe. It contains the 6/11/16/18 types of 20/40/40/20 µg/dosage each, using an immunologic adjuvant based on aluminium. It is administered 3 dosages intramuscularly, at 0,2 and 6 months. (10)

The bivalent vaccine is produced by GSK Belgium; L1 VLP is obtained through a recombined vector of baculovirus. It contains the 16 and 18 types of 20/20 µg/dosage each, ASO4 being used as adjuvant, containing aluminium hydroxide and monophosphoril-lipide A. It is administered intramuscularly in 3 dosages at 0,1 and 6 months. Due to the fabrication technique, as well to the use of baculovirus as a vector, the spatial conformation of L1 VLP and its resemblance to the natural capsid of the virus are higher in this vaccine, so the antibodies formed are more specific.

After vaccination, a new strategy of screening could be introduced – in the UK, Papanicolau test was introduced every 2 years, starting with the age of 24. (8) Markov statistical model estimates the vaccination for the 12-year old patients in percentage of 100%, with a vaccination efficiency of 95% (against HPV 16 and 18). This will bring about a reduction of the mortality rate due to cervix cancer with 76% and a reduction of the HSIL lesions with 66%. (10,16)

Until now, there have been no studies to compare the two vaccines directly, so the comparison is indirectly based on the data offered by the production companies and by the clinical studies made for each vaccine. The quadrivalent vaccine was conceived and tested clinically on the young female patients at the beginning of their sexual life, which have a very good immunocompetence. This vaccine has been tested on patients up to the age of 25 and offers protection against the genital condylomas, which has the largest incidence in this particular age. The bivalent vaccine is a vaccine with a very large antigenity, the levels of the antibodies being kept high for a large period of time and the immune response is very good in the patients above the age of 25. This vaccine has been tested on the patients up to the age of 55.

Vaccination in men was taken into consideration, but it has not been introduced in the current practice yet, with the exception of few countries, such as Australia and Mexico, due to the fact that the direct impact of HPV infection on men is reduced and the studies that show the exact efficiency of the vaccine, as well as the optimum vaccination age are still undergoing. Men are a reservoir (in a recent study made on 463 men, aged between 18 and 40 years old and who did not have genital condylomas history, the presence of HPV strains was proved in 51.2%), as well as a very important virus transmission vector. Contagiousness is high and HPV is bringing about perineal and genital condylomas in men, too (6,11), as well as penis and anal cancer. Regarding the penis cancer, HPV types 16 or 18 were proved in 77.5% cases. Regarding the patients with only one sexual partner during their entire life, it was proved that the sexual promiscuity of the partner increases 7 times the risk for cervix cancer. HPV detection in the sexual partner is associated to a 7-time increase of the cervix cancer. (3,11,17). There were studies that assessed the infection risk and which were made on the patients who were initially HPV negative, resulting that the largest infection risk is related to a new sexual partner. (3)

In order to establish the *vaccination efficiency*, as well as the age groups where vaccination should be applied, a pharmacoeconomic model was issued. According to this model, vaccination should be made in both genders at the age of `12 up to the age of 26 for a catch up. In Great Britain, the experience of vaccination against the German measles proved that, for an efficient control, both men and women should be vaccinated; by extrapolating this experience, HPV vaccination is indicated in men, too. (11)

The efficiency of the long term vaccination is essential, eliminating the need for the booster dose. After the administration of the quadrivalent vaccine, the levels

of Ig are increasing; they decrease two years after and remain constant for 5 years. After the administration of the bivalent vaccine, the levels of Ig are high and remain high for about 3,5, years. HPV vaccines induce a strong immunologic memory, so that upon a possible re-vaccination (with a single dose), the levels of immunoglobulins increase rapidly and are higher than after the initial vaccination. The mathematical modeling analyses used anticipate the fact that, after vaccination, 99% of the women will have blood detectable antibodies during their entire life. Today, the Nordic countries are conducting two trials, regarding the III and the IV stage, aiming at detecting the long term efficiency of the HPV vaccination against the cervix cancer and the CIN3 lesions. These trials will be ready in 2015 and 2020.

Vaccination efficiency of the quadrivalent vaccine regarding the 5-year studies is of 98-100% in the women aged between 16 and 23 years old, only one case of CIN3 being reported in the vaccinated women.

Regarding the bivalent vaccine, vaccination efficiency was studied on the patients with an average age of 23, proving that seropositiveness remained >98% for a period of time of at least 4,5 years. 51 and 53 months after, the antibodies titre was of 17, respectively 14 times higher than the natural titre for HPV 16, respectively 18. (12,14,15,19)

Cross-protection.

After the natural infection (that determines the occurrence of antibodies), the data regarding the protection against re-infection or cross-protection are contradicting. Most of the studies show that there is no such protection. After vaccination, there are clear data that confirm the cross-protection. In vitro, the data regarding the quadrivalent vaccine show a cross-protection with HPV 45. Clinical data regarding the bivalent vaccine show a cross-protection with HPV 31/45/52. The cross-protection is not as efficient as the direct protection. (13)

CONCLUSIONS

HPV infection is extremely spread in humans, but only a small part of viruses produces lesions with clinical importance (condylomas of pre-cancerous or cancerous lesions). Out of these viruses, the 16 and 18 viruses are the most frequently involved in the pre-malign or malign lesions all over the world. It is known, that if the HPV infection does not take place, a series of cancer types (especially the cervix cancer) may be prevented. As a result, HPV vaccines were conceived and developed. Vaccination is an efficient method for HPV protection and, in consequence, against the lesions brought about by this virus. The age groups where this vaccine proved its efficiency (proved by the clinical studies) are between 12 and 25 years old. (19) Preliminary data (especially after the vaccination with the bivalent vaccine) revealed that the vaccination age could be extended. Vaccination in men is being studied. Long term protection remains to be proved, but the present data are promising. Some countries have already adopted policies of mass vaccination. (18) As a matter of fact, vaccination may be proposed individually (but not as a strategy of mass vaccination) to any woman who has no counter-indications and who has no active HPV infection. Today, there are no data which should support the cost efficiency relation for the systematic determination of HPV before vaccination. (19) Vaccine is not suggested to the already infected women, due to the fact that there are no studies that should prove its efficiency. The active viral infection is not a vaccine counter-indication.

Today's studies try to prove the efficiency of the vaccination in children, even in those of a very young age. These studies are quite promising, with a large practical applicability in the developing countries. (19)

Today, there are experimental vaccines whose administration will be nasally, under the form of aerosols. (20)

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