

Research progress of HPV vaccine

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Abstract. HPV, whose full name is human papillomavirus, is common virus which can cause several kinds of disease includes all kinds of warts and even cancers. Studies show that almost 100% of cervical cancers are caused by HPV infection. Nearly 600,000 people worldwide are infected with HPV each year, and more than 300,000 of them die from cervical cancer. Efficient therapeutic vaccine has not been produced nowadays so prophylactic vaccine is the only choice for people who do not want to be infected by HPV. There are 4 types of proven vaccine of HPV in the world and they cover different subtypes, which mainly include bivalent HPV vaccine, 4-valent HPV vaccine and 9-valent HPV vaccine. Bivalent HPV vaccine can prevent more than 70% of cervical cancer caused by HPV. The 4-valent HPV vaccine can prevent 71% of cervical cancer caused by high-risk HPV viruses and about 90% of warts and other diseases caused by low-risk HPV viruses. 9-valent HPV vaccine, with a better protection, can prevent than 90% of cervical cancer. Moreover, various kinds of new vaccines of HPV are researching in the lab till today.

Keywords: HPV; Particle vaccine; Cervical cancer; 9-valent HPV vaccine.

1. Introduction

Human papillomavirus (HPV) is a group of Spherical, tiny, unenveloped circular double-stranded DNA virus. It can be divided into three categories according to the degree of risk: high risk, medium risk and low risk. In a recent research of HPV infection, in 542 HPV patients, 330 cases (60.9%) were single positive. Combined with other high-risk infections have 173 cases (31.9%), and 39 cases are with low-risk infection (7.2%) [1]. infection HPV can result in various kinds of diseases, such as warts and even cancers. Vaginal microecology of HIV-infected women is closely related to HPV infection, vaginal environment disorders are easy to cause HPV infection, and HIV infection and high-risk HPV infection may promote each other, continuous high-risk HPV infection may lead to cervical intraepithelial lesions, and may further develop into high-grade cervical epithelial lesions or even cervical cancer [2]. Almost 100% cervical cancer are generated by HPV infection. HPV infection can also cause many kinds of psychological problems.

In the recent researches of International Organization for Research on Cancer, nearly six hundred thousand of people get infected by HPV and over three hundred thousand of them died of cervical cancer every year in the world [3]. HPV can be spread by sexual transmission, contact transmission and mother-to-fetus transmission. Weaker immune system, smoking, messy sex life, disturbed sex hormone level can increase the risk of HPV infection, it can increase the risk of Depressive anxiety disorder in infected women [4]. Although many infected people can wipe out HPV by their own immune system, but once it cannot be wiped out by immune system or there is something damaged in the immune system of infected people, it will cause serious cancer, and HIV carriers are susceptible population of HPV [5]. In that case, the vaccination of HPV must be increase. In a study of the risk of HPV infection in immunocompromised people, immunocompromised women volunteer are 2 to 20 times more likely to be infected by HPV [6].

There are many kinds of vaccines guard against HPV on the basis of kinds of diseases they guard against. HPV vaccine has excellent HPV prevention effect on HIV-infected people, SLE infected people, organ transplant recipients, obese people, diabetic people and other people with low immunity. In the experiment, the immune response rate of HIV-infected people aged 18-25 years after HPV vaccine vaccination reached 100%, and that of SLE patients reached more than 76%. Obesity and diabetes have reached more than 98 percent. Depending on age, the number of transplants can be 50 to 75 percent.

To compare the functions of these vaccines. This review focus on the perniciousness of HPV virus and 4 kinds of effective vaccines people use to answer the virus. Including boundedness of existing vaccines and the introduction of new kinds of vaccines researching by scientists in the lab.

2. Basic information of HPV

HPV virus have currently known over 150 kinds and over 200 subtypes. HPV can be detected in 90% cervical and 75% penile cancer tissue, and HPV16 infection was predominant in all of these cases. Cervical cancer caused by HPV is one of the leading causes of death in women with cancer. Near 300000 people from all parts of the world die of cervical cancer every year. HPV infection can be divided into two basic types due to different infected position: mucosal infection and skin infection. Skin infection usually evolve into benign infection. It is often caused by HPV 1,2,3,4 and 10 and can generate many kinds of thymion on human's hands, feet and face (usually in adolescents). In regard to mucosal infection, however, usually infect mucosal on the surface of genital tract and respiratory tract of human, some of the high-risk types can cause serious cancers like cervical cancer, vulvar cancer, anal cancer, prostate cancer and bladder cancer. HPV16 mucosal infection can be detected among almost 50% of all cervical cancer patients. Moreover, other high-risk HPV virus like 16,18,31,33,45 also have closely connection with cervical cancer.

Natural immunity and adaptive immunity of the human immune system will control and eliminate the infected HPV, because most of the infection is self-limited. Studies show that more than 90% of infected people will clear the virus within three years, but because HPV has multiple mechanisms to escape the immune system, a small number of people will remain infected [7]. There is no therapeutic vaccine against HPV at present. Once people infected by high-risk HPV virus, physiotherapy and drug therapy can be common ways for them to pull through. Microwave, laser, freeze, fulgerize and various kinds of other physical methods are used to eliminate the warts or tumours. It is suitable for most clinical conditions, has the advantages of accurate positioning, no bleeding, low recurrence rate and little damage to surrounding normal tissue. However, the depth of treatment requires skilled operator control, and deep wounds heal slowly, especially in the external genital area, which is prone to bleeding and infection. Drug therapy is another way of HPV treatment which is really convenience. HPV drugs are usually external use and self-medication, but a course of treatment would be from 4 to 16 weeks, which is time-consuming. Operative treatment would be considered when HPV patients have extensive damage. Operation and matched chemotherapy can easily eliminate the focus of HPV virus. Immunotherapy is a new treatment method for HPV infection in recent years. Drugs such as interferon and transfer factor can quickly clear the lesion and reduce the probability of recurrence. Nowadays we generally use comprehensive treatment to prevent recurrence and achieve clinical cure. Firstly, physical methods are used to remove the tumor as much as possible. Secondly, the application of immune drugs and immune preparations injection would be proceeded. After these steps, benign tumours produced by HPV virus would be clear gradually. However, it is hard for patients (especially young women who were not pregnant before) with advanced malignant neoplasm to pull through completely. Therefore, vaccination before getting infected is extremely important for guarding against and curing HPV infection.

3. The vaccine of HPV

There are various kinds of HPV vaccine in the world at present, and can be divided into three categories according to their functions and the types of HPV virus they prevent: Bivalent HPV vaccine, 4-valent HPV vaccine and 9-valent HPV vaccine.

3.1. Bivalent HPV vaccine

Bivalent HPV vaccine, commonly called as HPV vaccine, can prevent 2 kinds of high-risk subtypes of HPV virus (HPV16 and HPV 18) for women from 9 to 45 years old. There are 2 kinds of Bivalent HPV vaccine currently on the market: Cervarix and Cecolin.

Cervarix is a Bivalent HPV vaccine developed by a British company (GSK) in 2007 and approved in the European Union. It adopts three intramuscular injections. The vaccine contains 20 micrograms of VLP components of HPV16 and HPV18, and adds AS04 adjuvant, which can prevent more than 70% of cervical cancer caused by HPV. However, because the vaccine does not contain the VLP component of low-risk HPV subtypes, it does not prevent warts caused by low-risk HPV viruses [7]. In the clinical trial of Cervarix, 18,729 female volunteers aged 15 to 25 years were vaccinated with Cervarix and the results showed that the vaccine provided approximately 98.1% protection against HPV16 and HPV18 related viruses. At the same time, the vaccine also has a good long-term performance. HPV antibody levels in the volunteers remained very high (almost 98%) four years after vaccination. In addition, the vaccine also has a certain cross-protection effect. In another climate test, a group of 12 to 13 years old female volunteers receive Cervarix vaccine. After seven years, not only the infection and transmission of HPV16 and HPV18 reduced by 89%, but also the infection of other subtypes such as HPV31, HPV33, HPV45 reduced by more than 80% [7].

Another Bivalent HPV vaccine come out recently is Cecolin. It is a new 2-valent HPV vaccine developed by Xiamen University in China in 2019. The vaccine uses recombinant expression of *Escherichia coli* to obtain vaccine antigens, namely VLP of HPV16 and HPV18 (containing 40 and 20 micrograms, respectively). In a clinical trial involving 7,372 female volunteers aged 18 to 45 in 2020, Cecolin's vaccine achieved 100% protection against HPV16 and HPV18 infection and almost 98% protection against later persistent infection. However, the vaccine has been on the market for only a short time, so it is difficult to determine whether it has the ability to cross-protect between different subspecies [7].

3.2. 4-valent HPV vaccine

The 4-valent HPV vaccine protects against the four subtypes of HPV, HPV6, HPV11, HPV16, and HPV18. Unlike the 2-valent vaccine, the 4-valent HPV vaccine can prevent 71% of cervical cancer caused by high-risk HPV viruses and about 90% of warts and other diseases caused by low-risk HPV viruses. There is currently only one 4-valent HPV vaccine on the market, Gardasil4. The vaccine is given as a three-shot intramuscular injection for women between the ages of 9 and 26.[7]

Gardasil4 was developed by Merck in the United States in 2006. It was tested in more than 10 clinical trials before being marketed. In a 2007 clinical trial involving 12,167 women aged 15 to 26, the vaccine was nearly 98 percent effective against cancer caused by the HPV16 and HPV18 viruses. In a 2008 clinical trial in women aged 24 to 45, the vaccine achieved more than 83% protection against HPV16 and HPV18 infections, and a staggering 100% protection against diseases related to HPV6 and HPV11 infections. In addition, this vaccine has not had serious adverse reactions in multiple clinical trials, which is enough to prove that its safety is higher than that of traditional bivalent vaccines [7]. In a 2008 clinical trial in China, among 3,006 female volunteers aged 20 to 45 years, Gardasil was more than 91% effective against cervical HPV infection after 6 months and more than 97% effective after 12 months. In addition, in a 2011 clinical trial of men aged 16 to 26 years, Gardasil was more than 90% effective against HPV6, HPV11, HPV16, and HPV18. Other more clinical trial data prove that this vaccine against other high-risk HPV viruses (such as HPV31, HPV33, HPV45, etc.) transmission and infection also has a certain preventive effect[7].

3.3. 9-valent HPV vaccine

9-valent HPV vaccine can prevent a total of 9 HPV virus subtypes of HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52 and HPV58, can prevent more than 90% of cervical cancer caused by HPV virus infection, is currently the most comprehensive prevention of a vaccine. There is currently only one 9-valent HPV vaccine on the market. It is named Gardasil9.

Gardasil9 vaccine is a 9-valent HPV vaccine developed by Merck in 2014, which simultaneously contains the VLP components of the above 9 HPV virus subspecies, the total antigen is up to 270 mg, using three intramuscular injections, suitable for women 9 to 26 years old and men 9 to 15 years old. The vaccine protects against cervical cancer caused by seven high-risk HPV strains and warts caused by several low-risk HPV strains. According to a 2017 clinical trial involving 14,215 female volunteers aged 16 to 20. The protection rate of cervical cancer caused by various types of HPV virus infection is more than 97%, and compared with other 2-valent and 4-valent vaccines, Gardasil9 vaccine vaccinators have no significant reduction in antibody concentration in the body for at least 6 years, which can prevent more than 90% of cervical cancer, with a wider range of protection and better safety [7].

4. Other vaccines in development

In addition to these vaccines already on the market, a number of preventive and therapeutic vaccines are in development or clinical trials. Currently, the prophylactic HPV vaccines on the market are all prepared with VLP of L1 protein as the antigen. However, due to the high specificity of various subtypes of HPV virus, it is difficult to make vaccines using VLP of a single antigen protein to cover all subtypes of HPV virus. Therefore, the development of new HPV vaccines needs to consider how to make the vaccine have a wider range of protection.

In order to achieve this goal, vaccine development from around the world plans to extend the vaccine's immunity to various HPV viruses by using novel antigens and improved adjuvants. GSK is using a novel adjuvant, AS04, in its new 2-valent HPV vaccine Gervarix, which enhances the vaccine's immunogenicity and prolongs the durability of the immune effect. In addition, a preventive vaccine using HPV L2 protein as an antigen protein is also being developed. L2 protein is a potential antigen protein with broad immunogenicity, but experimental data to prove this is still lacking. Moreover, experiments have shown that the antibody concentration induced by L2 protein in human body is much lower than that of existing L1 protein, in addition, the safety of this new protein as an antigen protein remains to be studied.

In addition to preventive vaccines, therapeutic vaccines for HPV are also being developed. Preventive vaccines do not eliminate existing HPV infections and lesions. Based on the current research on the carcinogenic mechanism of HPV, E6 protein and E7 protein are considered to be the most important carcinogenic proteins [8,9], so most of the current therapeutic vaccines are developed to target these two proteins. These vaccines present disease-causing proteins to antigen-presenting cells in various ways, and activate various immune responses to clear viral infection and infected cells. Therapeutic vaccines that have begun to be developed include live carrier vaccines, subunit vaccines, DNA vaccines and DC vaccines.

The live carrier vaccine inserts the genes for the E6 and E7 proteins into a non-toxic biological carrier (bacteria or viruses) and is injected into the human body, using the replication of the live carrier in the human body to achieve the transmission of the antigen. This vaccine can induce a strong human immune response and is extremely immunogenic. However, there are also many disadvantages, such as low safety (especially for people with partial immune function loss), and poor immune effect due to the immune response to the live carrier itself exceeding the immune response to HPV. Subunit vaccines skip the vector and directly deliver proteins or peptides to human cells. This vaccine is safe, stable and easy to produce, but the lack of support of the vector makes its immunogenicity very low, requiring the use of adjuvants or other stimulating molecules to enhance the therapeutic effect. DNA vaccine inserts the gene fragment of HPV virus into the plasmid, and then injected into the human body for expression, generating HPV antigen and activating immune response to achieve the purpose of treating HPV infection. This vaccine is safe and stable, easy to produce, and can be continuously expressed in the human body to produce antibodies, repeatedly strengthening human immunity to HPV virus. DC cells are dendritic cells whose main function is to take, process and present antigens. DC vaccine can directly transfer antigens to DC cells and trigger

immune response. However, due to the limitations of current technology, researchers cannot extract DC cells that meet the quantity and quality requirements from patients every time, and the production time and cost of this vaccine are long. Large-scale production is currently difficult.

5. Limitations and future development

According to a survey in USA, the vaccination of HPV is outstanding lower than expected [10]. The HPV vaccine works best if given to children between the ages of 9 and 10. But the virus is more sexually transmitted, so not many parents are aware of vaccinating their children (especially boys). Therefore, in the future HPV vaccine development plan, it is very important to do a good job of publicity about the harm of HPV virus and the protective effect of vaccine. In addition, the current market price of HPV vaccine is relatively expensive, and the relatively cheap nucleic acid vaccine and DC vaccine technology is not mature, and the current inactivated and attenuated vaccines have no advantages compared with nucleic acid vaccines in long-term protection. People have a narrow choice of HPV vaccines. There is an urgent need to introduce a new, affordable and high-quality vaccine as soon as possible. Overall, there is still a long way to go to promote and improve the HPV vaccine. Works of scientists in the future are beset with difficulties.

6. Conclusion

The damage caused by the widespread spread of HPV is well known. However, unlike smallpox, which achieved global immunity with a vaccine, the dangers of HPV have only been well understood in recent years. Because the severity of the disease varies greatly (some subtypes cause only some warts, while others can cause cancer), and the route and speed of transmission of the HPV virus and the extent of the spread of the population is far less than other influenza, people do not pay as much attention to HPV as other equally troublesome diseases. Previous vaccine development efforts have been limited to inactivated and attenuated vaccines. Due to the concern about cervical cancer cases in recent years, more and more young women tend to receive HPV vaccine early, and the increase in demand has also indirectly promoted the development of vaccines, many new vaccines have passed clinical trials and are ready to be marketed in a few years. As the government began to publicize the dangers of HPV. By then, the threat of HPV may have faded.

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