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The safety of human papilloma virus-blockers and the risk of triggering autoimmune diseases

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The safety of human papilloma virus-blockers and the risk of triggering autoimmune diseases

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Introduction: With the safety of human papilloma virus vaccine (HPVv) being questioned, this article aims to assess the risks and benefits of the commercially available HPVv. Within the last decade, two vaccines (Gardasil and Cervarix) have been put on the market to prevent infection with the most oncogenic HPV subtypes. Both vaccines contain aluminum adjuvants that are meant to cause a hyper stimulated immune response to prevent HPV infection.

Areas covered: The purpose of this paper is to consider the safety of these two vaccines based on the data from the U.S. Vaccine Adverse Event Reporting System (VAERS) and case reports.

Expert opinion: The current HPVv are both effective and generally safe. However, it should be noted that autoimmune side effects have been reported in several studies. Further research should be done to understand the relationship between HPVv and autoimmunity.

Keywords: adjuvant, aluminum, autoimmune/inflammatory syndrome induced by adjuvants, autoimmunity, guillain barré syndrome, human papilloma virus, postural orthostatic tachycardia syndrome, premature ovarian failure, vaccines

1. Introduction

Human papilloma virus (HPV) is a subtype of the papillomavirus family of viruses that infects nearly 80% of women in the first five decades of life [1]. There are > 100 different subtypes of HPV, with 40 of those subtypes causing genital or oropharyngeal infection [2]. HPV infects different areas of squamous epithelium, for example, HPV 6 and 11 cause genital warts, whereas HPV 2 and 4 cause warts on the hands or feet. Separately from warts, certain HPV genotypes have the potential to cause infected squamous epithelial cells (e.g., cells found in the uterine cervix) to undergo neoplastic transformation. The most notable neoplasm related to HPV is cervical cancer, with ~ 80% of cases being related to HPV types 16 and 18. Cervical cancer is the third most common cause of cancer in women, and the fourth most common cause of cancer-related death in women worldwide. Of the 275,000 cervical cancer deaths worldwide, it should be noted that 88% occur in developing countries that lack effective screening programs [3].

In order to prevent the development of cervical cancer, vaccines have been created. Vaccines are immune stimulants that result in sufficiently great immune response to cause prevention of disease. Immunity is achieved by injecting a compound containing three different substances. The first substance is called antigen, which is a specific protein sequence from the causative agent of the disease that directs the vaccine to the disease-entity in consideration. The second substance is a stabilizer, which is meant to keep the vaccine potent during transport and storage.
The third substance is called an adjuvant, which is a compound that acts to stimulate the immune response. Currently, two vaccines are commercially available against HPV infection; both are composed of HPV viral surface L1 antigens arranged into virus-like particles (VLPs). Cervarix contains HPV 16 and 18 L1 VLPs whereas Gardasil in addition to these two, also contains the L1 VLPs of HPV genotypes 6 and 11 which cause 90% of cervical warts. By preventing infection with HPV types 16 and 18, developers hope to reduce the post-infectious occurrence of cervical cancer [4]. In addition to the genotypes they protect against, the two vaccines differ in the adjuvants they utilize. Cervarix uses a double adjuvant system ASO4 composed of 3-O-desacyl-4′ monophosphoryl lipid A and aluminum hydroxide, whereas Gardasil uses aluminum hydroxysphate sulfate as an adjuvant [5].

In this review, we focused on HPV vaccines in an attempt to ascertain its safety taking into account the vaccine’s potential beneficial and deleterious effects.

### 2. Efficacy

In order for the anti-HPV vaccines (HPVv) to be considered effective, they should cause an increase in antibodies, prevent infection, and prevent post-infectious phenomena such as cervical cancer.

HPVv effectively produce an increase in antibodies when injected. Studies have shown that all patients who are injected with the HPVv will have a seroconversion. Most patients who underwent vaccination had an increase in antibodies 40-fold higher than what is observed in natural infection [6].

Studies have also shown that the HPVv is effective in preventing incidence and persistence of HPV 16/18 infection in fully vaccinated young women [7]. In a randomized control trial vaccine efficacy was 91.6% (95% CI 64.5 – 98.0) against incident infection and 100% against persistent infection (47.0 – 100) with HPV-16/18. As far as the ability to prevent post-infectious phenomena goes, the efficacy of HPVv in their ability to prevent cancer is a topic of debate [8].

The aim of most vaccines is to prevent initial infection with a bacteria or virus; however, HPVv are different in that their main purpose is to prevent the post-infectious development of cervical cancer [8]. Before being introduced to the general public, the vaccines were found to be highly effective (99%) against premalignant HPV 16- and 18-associated cervical intraepithelial neoplasia (CIN2)+ lesions as well as genital warts, vulvar or vaginal intraepithelial neoplasia lesions, in 16 – 26 years old women with no current HPV infection at the time of initial vaccination. They showed no therapeutic efficacy in women who were already infected at the time of receiving the HPVv [4,9]. However, the longest follow up data was for 5 years in Gardasil and 9.4 years in Cervarix.

This is concerning, as it takes 20 – 40 years for invasive cervical cancer to develop [10-12]. Data thus far have shown that Cervarix is 93% effective at preventing CIN 3 regardless of HPV type. Gardasil is 47% effective at preventing CIN 3 regardless of HPV type [13]. In addition to this, data collected by the World Health Organization shows that the high mortality from cervical cancer is due to the lack of PAP screening coverage rather than HPV16/18 infection in women with high-grade lesions and cervical cancer [6,14]. For these reasons, it has been argued that PAP screening can prevent just as many cervical cancer cases as the HPV vaccines without the risks of exposing healthy patients to potential vaccine-related adverse drug reactions (ADRs) [6].

### 3. Vaccine safety in general

In general, vaccines have proven to be safe to the general public, with the benefits far outweighing the risks [15]. The most common minor side effects associated with vaccination are pain, redness, tenderness or swelling at injection site, fatigue, headache, itching at injection site, nausea, dizziness, fever, or a mild rash. Most of these side effects will go away within several days. These side effects are associated with most vaccines and compromise the majority of ADRs. Although very rare, serious side effects have been reported including intussusception, allergic reactions and seizures leading to brain damage [16-20]. Recently, a link between autoimmunity and vaccination has also been suggested. The connection has been well documented and is a topic of heavy research. In a healthy individual, vaccination will cause an appropriate immune stimulation; however, some individuals can have an abnormal response. In patients predisposed to autoimmunity, such as patients with genetic predisposition, vaccine exposure can pose a bigger challenge to the immune system. Different HLA alleles are linked to the susceptibility to develop different autoimmune diseases [21,22].

**Genetic predisposition to vaccination has been a topic of emerging research. For example, febrile seizures have been a well-known side effect of the measles, mumps and rubella (MMR) vaccine. Recently researchers have found two specific**
loci associated with febrile seizures. The knowledge of a genetic predisposition can help doctors to either avoid, or to be better prepared for ADRs associated with vaccinations. A recently published article discusses the future of genetic testing in reference to vaccination. The ability to know how a patient may respond to a vaccine may lead to a more personalized vaccine regime, thus decreasing risk of potential ADRs [23,24].

Vaccines, such as infections, activate immune-mediated mechanisms to induce a protective effect. A complex vaccine may theoretically be more immunogenic than a simple vaccine. Vaccines harbor added complex agents, for example, adjuvants including aluminum, which may induce autoimmune disease [25]. Preservatives are more often found in viral vaccines compared to bacterial vaccines suggesting that the preservatives may be the inciting culprits [26].

The challenge presented by complex vaccines may lead to the development of a range of autoimmune disorders. It has been shown that patients in the 1970s who were vaccinated with an H1N1 vaccine were more likely to develop Guillain Barré Syndrome (RR-7/1) [27,28]. Other examples of autoimmunity following vaccination include rheumatoid arthritis, MS, or vasculitis following HBV vaccination as well as the relatively new syndrome known as Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) [20,29,30].

ASIA is a hyperactive immune response, which entails four different conditions exhibiting similar signs and symptoms: siliconosis, macrophagic myofasciitis syndrome, Gulf war syndrome and post-vaccination phenomena. The most frequently reported symptoms include chronic fatigue, myalgia, myositis, arthralgia, neurological manifestations, fever, dry mouth and cognitive alterations. The syndrome was suggested to occur in genetically predisposed individuals following exposure to adjuvants which can include silicon, aluminum, pristane and infectious components, all of which seem to induce similar symptoms in both animal and human models [31-33]. The wide spectrum of symptoms that are covered by the umbrella of ASIA challenges the idea that a physician should look for a specific autoimmune disease following vaccination or adjuvant exposure, and should instead focus on the individual symptoms [34]. The rationale for this is further supported by the fact that clinically diagnosable autoimmune diseases often evolve over a longer period of time (i.e., several months) following initial manifestation of apparently non-specific symptoms. Indeed, there are many reported cases of autoimmunity following HPV and other vaccines where, although the first manifestations of symptoms normally occurred within the first 3 weeks and following the first or second vaccine injections, the definite clinical manifestation and final diagnosis of the disease was made months later [35-37].

Several studies have been done to identify at-risk patients. In particular, it has been found that other patients who might be at particular risk include patients with a prior history of post-vaccination phenomena, patients with an established autoimmune disease, patients with a history of allergic reactions, and individuals who are prone to autoimmunity by either a positive family history of autoimmunity, genetic factors, or the presence of autoantibodies [22].

4. HPV vaccine safety

In pre-licensure studies Agorastos et al. assessed 60,000 women who were vaccinated with HPVv. When compared to placebo groups, the most common local reactions included pain redness and swelling at the injection site. Patients receiving the vaccine also experienced more cases of fever, nausea and dizziness [38].

The ADRs associated with Gardasil and Cervarix are reported in the U.S. Vaccine Adverse Event Reporting System (VAERS). VAERS has several limitations. The main limitation is that it is a passive surveillance system, meaning the reported ADRs may or may not be related to vaccine at all, they just happened to occur in the time period following vaccination. Another issue with VAERS being a passive system is that as little as 5% of ADRs are estimated to be reported. It should also be noted the report of a medical condition observed after vaccination does not mean that a causal relationship between such condition and vaccination has been established, just that it occurred after vaccination. Despite these limitations, VAERS can provide useful data on national trends that may require additional attention [39].

Gardasil was introduced in 2006 and Cervarix in 2009. In the time since, VAERS has reported that there have been 21,301 ADRs, with 3,310 of them being considered serious. The total number of emergency room visits by women ages 6 – 29 years totaled 834, 760 were permanently disabled, and 69 deaths occurred. Gardasil was associated with 65.9% of serious ADRs, 80% of permanent disability, and 62% of deaths [8,20].

Post-licensure data is similar to the pre-licensure data in that the most commonly reported ADRs are local site reactions, headache and fatigue [40]. Block et al. showed that 82.9% of the patients who received Gardasil experienced redness and swelling, whereas 77.4 and 44.9% of patients had swelling when injected with an aluminum-containing placebo and a non-aluminum-containing placebo, respectively [41]. Several studies have observed an increase in syncope among young women who received the vaccination; however, the conclusion was that many of the episodes could have been avoided with the recommendation that patients sit for 15 min after injection. Other commonly reported adverse events include fatigue, gastrointestinal symptoms, arthralgia, myalgia, rash, fever and urticaria [42,43].

It should be emphasized that individual case reports of adverse reactions following HPVv do not necessarily establish causality. International bodies, whose role is to oversee vaccine safety, have all found HPVv to be safe for use, with the side effect profile to be minimal. The Global Advisory Committee for Vaccine Safety (GACVS) have closely monitored the safety of HPVv and based on clinical data.
have concluded that the benefit-risk profile remains favorable. GACVS also state that there is currently no scientific evidence that aluminum-containing vaccines cause harm, that the presence of aluminum at the injection site is related to any autoimmune syndrome, and that HPV DNA fragments are responsible for immune-mediated phenomena (44,45). In order to establish a link between causality and coincidence, baseline data on the incidence of autoimmune diseases in populations before and after vaccination needs to be obtained, as no study has yet to provide this data.

Serious adverse events have been suggested following clinical studies, the most concerning of which have been related to the onset or exacerbation of autoimmune disorders. It should be noted that many of these case studies are coincident with HPV vaccination and are a weak form of evidence regarding the association. It is only through more sophisticated studies that hypotheses regarding their association can be tested.

Guillain–Barré Syndrome (GBS) is an immune-mediated acute polyneuropathy. There have been several vaccines in the past, which have resulted in the onset of GBS (27,28), as such, research has been aimed to show that HPVv does not induce onset of GBS. Some studies have suggested an increase in cases among young women receiving the vaccine (46); however, multiple studies have since found that there is no higher incidence of GBS of patients receiving HPVv (47-49).

Postural orthostatic tachycardia syndrome (POTS) is a disease of unknown etiology but some studies have found increased antibodies and suggest it is of an autoimmune origin (50). Case reports of patients who developed POTS 2 weeks following vaccination with HPVv suggests a relationship between the events (51,52). A study recently published by Danish researchers analyzed a group of 53 patients who developed autonomic dysfunction in the 2 months following exposure to the HPV vaccine. The patients were all gathered from a Syncope Unit and all exhibited similar symptoms after having been vaccinated with Gardasil. The most prevalent symptoms reported were headache, dysautonomic symptoms, excessive fatigue, cognitive dysfunction and widespread pain of a neuropathic character. The symptoms in 98% of the cases were so severe that patients had to take 2 months of work off in order to cope (52). Researchers found that the frequency of symptoms in all of the patients corresponded to patients with POTS (53,54).

Premature ovarian insufficiency (POI) is defined as a hypergonadotrophic hypogonadism developing before the age of 40 (55). Little et al. described three cases of young women ages 16 – 18 that presented with POI following administration of HPVv. Little argues that in preclinical trials of Gardasil the time period was not sufficient for POI to be identified in young women (56). Post-licensure data also does not take POI into account as one of the major studies assessed ADRs as emergency room visits; however POI does not generally require emergency admission (57). The largest study to date failed to assess menstrual cycle aberrations, which are indicative of menstrual dysfunction (58). VAERS has 104 reported cases of amenorrhea following vaccination; however data on FSH levels was recorded in only one individual (59). The lack of data regarding POI suggests that further research should be done to assess whether it may be a consequence of HPVv.

Systemic lupus erythematosus (SLE), the mother of autoimmunity, has also been suggested to be associated with HPVv. Data from VAERS showed that patients vaccinated with Gardasil were more likely to have SLE (OR = 5.3, 95% CI = 1.5 – 20.5) (60). In addition to this, Gatto et al. reported six cases of patients who presented with SLE and SLE-like symptoms post-vaccination. The study observed both a temporal relationship to vaccination as well as similar symptoms amongst the SLE patients (55). Soldevilla et al. also observed SLE exacerbations in three patients following HPVv. Reports have shown increased HPV infections in SLE patients and that infection can even worsen SLE symptoms. However, Soldevilla et al. concluded that despite the SLE exacerbation following HPVv, patients with SLE should still be advised to have an HPVv vaccination (61). A prospective study following 27 SLE patients ages 12 – 26 years old immunized with Gardasil found that the vaccine was safe and well tolerated (62). Currently, evidence suggests a relationship between SLE and HPVv, and further studies should be done in order to better understand their relationship (30).

When discussing a vaccine that contains an aluminum adjuvant, it is appropriate to consider ASIA within the parameters of ADRs. Studies often fail to take into account the fact that the ADRs may not always fall under a well-defined autoimmune-disease like GBS or SLE. Many of the often-reported symptoms of myalgia, weakness, paraesthesias and arthralgias (a ‘forme fruste’ of a defined autoimmune condition) could be symptoms of ASIA, and thus be overlooked (30,31). A recent study analyzed the incidence of symptoms that fall under the umbrella of the ASIA syndrome following HPV vaccination based on data from VAERS. The researchers found an estimated reporting rate was of 3.6 cases per 100,000 doses of HPV vaccine distributed (95% CI 3.4 – 3.7) (63).

5. Discussion

A possible explanation for autoimmune disorders in HPV vaccination patients is that if the patient has been previously exposed to either the vaccine, the infection itself, or other viruses with similar composition, the body may have a pathological response. This anamnestic response could then lead to the sudden onset of autoimmunity. The adjuvants present within vaccination coupled with the relatively short period of administration of vaccines are meant to produce a potentiated immune response and may cause the immune system to react more aggressively than it would with an infection (18).

Another possible explanation for the role of the immune system is through molecular mimicry (64). The recombinant proteins found in Gardasil may be the reason for an increased association with autoimmunity. It was found that Gardasil
vaccination leads to a 40-fold increase in anti-HPV antibodies when compared with natural infection with HPV [6] and antibody titers against HPV-16 and 18 have found to be increased 11-fold 5.5 years following injection [65]. Patients vaccinated with Cervarix were found to have anti HPV-18 antibodies 10 times higher than those with a natural infection 8.4 years after the initial treatment. The increased antibody production by adjuvants may suggest that there may be a higher risk of autoimmunity than in natural infections, especially in subjects previously prone to develop autoimmune diseases [22].

The aluminum adjuvant in vaccines is poorly excreted most likely due to its tight association with the antigen and specific way by which this complex is processed by the immune system. The route of administration also plays a crucial role in toxicokinetic of any pharmaceutical compound. Thus, although the half-life of enterally or parenterally absorbed aluminum from the body is short (~24 h), such is not the case with the intramuscularly injected aluminum. For example, the cumulative amount of aluminum hydroxide (the most commonly used form of vaccine adjuvant) excreted in the urine of adult rabbits as long as 28 days post intramuscular injection was <6% as measured by accelerator mass spectrometry [66]. Current research also suggests that the Al adjuvants can form complexes with other vaccine excipients. HPV L1 gene DNA contaminants were recently found in Gardasil via a highly sensitive PCR technique. The detected HPV DNA was found to be firmly bound to the insoluble, proteinase-resistant fraction, presumably consisting of the amorphous aluminum hydroxylphosphate sulfate adjuvant nanoparticles [67]. The same HPV DNA fragments were later detected in postmortem blood and splenic tissue obtained at autopsy of a formerly healthy teenage girl who suffered a sudden unexpected death in sleep 6 months after three intramuscular HPVv injections [68]. These observations suggest that the aluminum–HPV DNA complex may persist in the body long term, presumably because the complex is resistant to degradation by endonucleases thus potentially increasing the risk for adverse immune responses.

The yet unclear link between adjuvants and autoimmunity further demonstrates the need for more research in order to better understand the risks factors that may lead to disease induction.

6. Conclusion

The Human Papilloma Virus has >100 different genotypes, which lead to both warts as well as cervical cancer secondary to infection. HPV genotypes 16 and 18 are the most associated with cervical cancer.

Current evidence shows Gardasil and Cervarix have proven to be effective in preventing HPV infection as well as in preventing the development of warts. The effectiveness of the vaccine to prevent secondary cancers remains controversial, as it takes roughly 20 years for cervical cancer to develop and the longest period tested was 9.4 years.

The HPV vaccines are considered safe and most reactions are mild and limited. In general, serious ADRs have not been shown to be associated with the vaccine, and the World Health Organization has found the benefits of HPVv to outweigh the risks. However, autoimmunity following vaccination has been an area of increasing interest. Although the occurrence is rare and the relationship has not been proven, several studies suggest a relationship between HPVv and onset of autoimmune diseases like SLE. Further research should be done to discover the relationship between HPVv and autoimmunity and future genetic studies should be done to identify patients who may be at risk of developing autoimmunity following vaccination.

7. Expert opinion

The key findings in the research on the HPVv have shown that the vaccine is effective in preventing infection. The ability of the HPVv to prevent subsequent cervical cancers remains a topic of debate, as it’s effectiveness in decreasing the risk of cancer has not been directly proven. The only method that can directly prove its effectiveness is time, as the development of cervical cancer takes up to 20 years. During this period, a lot of research can be done in order to better understand all of the risks and predispositions for ADRs associated with the vaccination. More information could be gathered to ascertain whether or not HPV vaccination would be as effective in preventing cervical cancers as implementing a proper PAP screening program would be. This is because patients who have been vaccinated are not exempt from having a regular PAP smear.

Further research also needs to be done in order to establish whether a link between any autoimmune phenomena associated with the vaccination are purely coincidental or whether this is a relationship that deserves more scrutiny.

In order to better understand the relationship, a more active surveillance system must be implemented in order to ascertain more accurate results of adverse reactions to the HPV vaccine. It would be extremely useful to establish an active surveillance program for ADRs associated with HPVv; however, the likelihood of this occurring remains extremely small. Such a study would require tremendous resources which would be difficult to obtain considering the fact that the number of reported ADRs within the VAERS system is relatively low.

As the HPVv is approved and supported by the World Health Organization, the vaccine is likely to be used worldwide. However, Gardasil is being replaced with Gardasil9, a vaccination which has even higher antigenic load for seven cancer causing HPV types, as well as double the aluminum adjuvant. The current Gardasil will be phased out, and the scientific data which has been gathered thus far will no longer be useful. Gardasil9, which has no known long-term duration, and little clinical trial information collected thus far will have to be reassessed and both the efficacy and safety
will have to be analyzed once again. The data on Gardasili9 looks promising, as it prevents infection from several other genotypes of HPV. However, with this increased viral load comes increased risk of ADRs, which need to be thoroughly investigated before being introduced to the general population.

If a more concrete relationship between HPVv and autoimmunity were to be established, other research that could be of interest would be to learn which genes are responsible for the susceptibility of developing an autoimmune disease, much like what was done with the MMR vaccine in relation to febrile seizures. The possibility of having personalized vaccination is a field of growing interest which could lead to a fewer ADRs and can lead to a greater number of people within the population to get vaccinated.

Other areas of interest lie in the use of aluminum adjuvants. Current research is being done around the globe to assess the safety of aluminum adjuvants. If significant negative data is gathered regarding its safety, it is possible that HPVv could employ a different adjuvant altogether.

Overall the data regarding the HPVv has shown that is it generally safe and effective; however, risks are always associated and care should be continually taken in order to prevent any unnecessary harm coming to the general population.

**Declaration of interest**

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