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Review

On the relationship between human papilloma virus vaccine and autoimmune diseases

Paolo Pellegrino [a], Carla Carnovale [a], Marco Pozzi [b], Stefania Antoniazzi [c], Valentina Perrone [a], Dionigi Salvati [a], Marta Gentili [a], Tatiana Brusadelli [a], Emilio Clementi [b,d,*], Sonia Radice [a]

[a] Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, University Hospital "Luigi Sacco", Università di Milano, 20157 Milan, Italy
[b] Scientific Institute, IRCCS E. Medea, 23842 Bosisio Parini, Lecco, Italy
[c] IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan 20122, Italy
[d] Unit of Clinical Pharmacology, Consiglio Nazionale delle Ricerche Institute of Neuroscience, Department of Biomedical and Clinical Sciences, University Hospital "Luigi Sacco", Università di Milano, 20157 Milan, Italy

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ABSTRACT

The human papilloma virus (HPV) vaccines were introduced to reduce the incidence of cervical cancer. The bivalent vaccine is effective against HPV-16, -18, -31, -33 and -45 while the quadrivalent vaccine is effective against HPV-16, 18, 31, 6 and 11 types. The immunisation, recommended for adolescent females, has led to high vaccine coverage in many countries.

Along with the introduction of the HPV vaccines, several cases of onset or exacerbations of autoimmune diseases following the vaccine shot have been reported in the literature and pharmacovigilance databases, triggering concerns about its safety. This vaccination programme, however, has been introduced in a population that is at high risk for the onset of autoimmune diseases, making it difficult to assess the role of HPV vaccine in these cases and no conclusive studies have been reported thus far.

We have thus analysed and reviewed comprehensively all case reports and studies dealing with either the onset of an autoimmune disease in vaccinated subject or the safety in patients with autoimmune diseases to define the role of the HPV vaccines in these diseases and hence its safety. A solid evidence of causal relationship was provided in few cases in the examined studies, and the risk vs. benefit of vaccination is still to be solved. The on-going vigilance for the safety of this vaccine remains thus of paramount importance.

Contents

* Corresponding author at:Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, University Hospital "Luigi Sacco", University of Milan, Via GB Grassi 74, -20157, Milano, Italy. Tel.:+39 0250319683; fax: +39 0250319682
E-mail address: emilio.clementi@unimi.it (E. Clementi).

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1. Introduction

The infection by specific oncogenic serotypes of human papilloma virus (HPV) represents a key step in the pathogenesis of cervical cancers as well as ano-genital and some other non-genital malignancies [1–5]. These diseases have a high impact on public health, with cervical cancer representing the fourth most common cause of cancer-related death worldwide, although the vast majority of these deaths (88%) occurs in developing countries.

The high burden of this disease in developing countries is caused mainly by the lack of screening and treatment facilities as well as suboptimal nutrition and hygiene [6]. As the evolution from infection to invasive cancer is slow, countries with screening programmes witness a reduced incidence of cervical cancer from a rate of 50–80/100,000 observed in unscreened women to a rate of 4–8/100,000 [1,3].

According to the Finland cancer registry, cervical cancer has declined of about 75% over the past 60 years, primarily because at least 70% of the population participates into a continuous Pap screening programme [2]. The importance of cervical cancer screening is remarkable, as when 20–29 year old unvaccinated women stopped attending Pap screening, a four-fold increase in cervical cancer occurred within five years from screening cessation [2,7,8].

Along with pap screening two vaccines were developed to protect against the infection of the two serotypes most commonly related to cervical cancer [1–3,9,10]. These vaccines have different formulation as the bivalent vaccine contains 20 μg each of HPV 16 and HPV 18 L1 proteins, while the quadrivalent vaccine contains 40 μg of HPV 16, 20 μg of HPV 18, 20 μg of HPV 6 and 40 μg of HPV 11 [9,11]. The protection of quadrivalent vaccine against HPV 6 and 11 is meant to prevent the occurrence of genital warts, a minor issue in patients without HIV, and respiratory papillomatosis [9].

The protection offered by these two vaccines extends to persistent HPV 31 infection, while only the bivalent vaccine could prevent persistent infections also from HPV 45 and 33 types [1,3,7].

Considerations on the clinical efficacy of these vaccines should take into account several important "real-world" factors including: efficacy against oncogenic HPV strains not covered by the vaccine and possibility of increased frequency of infections with these types; efficacy in women acquiring multiple HPV types; and effects in women with pre-existing HPV infections [12]. Although the results from clinical trials showed >97% HPV vaccine efficacy against HPV-16 and 18 related CIN-2/3 precancerous lesions, the corresponding figures against CIN-2/3 lesions caused by all high-risk HPV types associated with cervical cancer were only 16.9% in the per-protocol population. Thus, most likely, the true HPV vaccine efficacy lies somewhere between 16.9% and 70% [13].

A recent analysis found an increased cervical cancer incidence when vaccination was not accompanied by appropriate screening programmes [1,7,8], and that combining screening with vaccination does not significantly lower the incidence, while decreasing the number of women with abnormal screening tests [1].

In this view, it is important to better define the safety profile of HPV vaccines, especially considering their possible role as triggers of autoimmune diseases. Such definition is of paramount importance, as would allow physicians to provide a full and open discussion guiding women to make a decision for their cervical cancer protection [1]. In addition the introduction of a new vaccine in a population always raises concerns in terms of safety [14,15]. As expected based on previous experience with the introduction of other vaccines in a large cohorts of adolescent, several cases of adverse drug reactions have been reported also for the HPV vaccines, some of which being autoimmune diseases [16].

Numerous reports have thus raised the possibility of a causal relationship between vaccination and autoimmune diseases and hence on vaccine safety, without however providing a conclusive answer [15–19].

In this view, we have reviewed all available information on HPV vaccine safety in patients with autoimmune diseases and about the risk for healthy subjects to develop an autoimmune disease after vaccination; we provide an updated indication about the possible side effect of these vaccines.

2. Autoimmune diseases

2.1. Method of analysis

We carried out a PubMed search up to 2013 using the terms: "Autoimmune disease" OR "Multiple sclerosis" OR "Systemic lupus erythematosus" OR "Guillain–Barré syndrome" OR "Acute disseminated encephalomyelitis" OR "Demyelinating diseases" OR "Rheumatoid arthritis" OR "Juvenile idiopathic arthritis" OR "Inflammatory bowel disease" OR "Primary ovarian failure" AND HPV vaccine. We considered studies that included case reports and series, case–control studies, post-marketing surveillance programmes and published analyses by the Vaccine Adverse Event Reporting System (VAERS), a US-based national vaccine safety surveillance programme. We carried out an initial screening by reading each abstract to identify the articles meeting these inclusion criteria, which were conclusively assessed after a thorough analysis of their content. The retrieved studies were then entirety read to assess appropriateness. Citations from each included articles were examined in order to identify any other published study potentially meeting inclusion criteria. We limited the research to article written in English.

2.2. Acute disseminated encephalomyelitis (ADEM) and other demyelinating diseases of the central nervous system

Acute disseminated encephalomyelitis is classically described as a monophasic demyelinating disease of the central nervous system that typically follows an infection or, with a lower frequency, a vaccination. As highlighted in Table 1 numerous cases have been reported in the literature [20–24].

In most of the patients described in these reports, the pathology onset occurred within few days after the second or third vaccine shot [20–24]. The therapy response was generally good in all cases and no fatalities due to this condition were described [20–24].

ADEM following vaccination is a clinical entity poorly described in terms of epidemiological features [25]. Based on the reports to the VAERS and the European adverse event database, we recently showed that HPV vaccine is amongst the ones most commonly related to ADEM reports [25].

The incidence of ADEM following immunisation with the HPV vaccine is unknown, but the reporting rate was estimated to be $0.26/10^6$ (CI 95%: $0.16/10^6$–$0.37/10^6$) [23]. Such estimation was achieved considering the reports to the VAERS database and the doses of vaccine distributed in the same period [23].

Along with ADEM, other diseases characterised by demyelination of the central nervous systems have been reported. In a recent case series, Menge et al. reported on four cases of Neuromyelitis optica having occurred after the administration of HPV vaccine [26]. This disease is rarely observed in adolescent, but the observed cases may reflect the natural disease prevalence considering the large population exposed