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Should we target patients with autoimmune diseases for HPV vaccine uptake?

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Abstract

Human papillomavirus (HPV) is the cause of most cases of cervical cancer worldwide. Studies suggest that patients with autoimmune diseases (AD) may be at increased risk for persistent HPV infection, cervical dysplasia, and possibly, cervical cancer. Despite this heightened risk, and studies demonstrating the safety and efficacy of the HPV vaccine in this population, uptake among patients with AD, and in the population overall, remains low. A number of studies suggest that this may be attributed to lack of patient and provider awareness, no school-based requirement for vaccination, and a hesitancy to discuss sexually transmitted diseases with adolescents. Among patients with AD, access to preventive care in general may be reduced. Overall, heightened public health efforts are needed to improve HPV vaccination uptake in the entire population and among patients with AD who may be at increased risk for persistent infection and for cervical dysplasia.

Keywords

HPV vaccine; cervical dysplasia; autoimmune disease; systemic lupus erythematosus; rheumatoid arthritis

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted disease in the U.S. and the cause of most cases of cervical cancer worldwide.[1] Persistent infection with high-risk HPV subtypes is a key risk factor for the development of high-grade cervical dysplasia, a precursor to cervical cancer.[2] While there is debate in the literature as to the definition and biologicalmechanism of persistent HPV infection, risk factors appear to include older age, HPV genotype, infections, inflammatory states and immunosuppression.[2] Autoimmune diseases (AD), specifically systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), have been associated with persistent HPV infection and with an increased risk of high-grade cervical dysplasia and cervical cancer.[3] In 2006 and 2009, the U.S. Food and Drug Administration approved two HPV vaccines for children and young adults age 9-26

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years. Despite substantial evidence demonstrating HPV vaccine efficacy and safety, uptake in the U.S. has been slow. With the potentially increased risk of persistent HPV infection and high-grade cervical dysplasia among individuals with AD, the timely question of whether this population should be targeted to increase vaccine uptake is raised.

Autoimmune Diseases and HPV Infection

Patients with systemic inflammatory AD, including inflammatory bowel disease (IBD), RA and SLE have an increased risk of infection compared to the general population. This may be due to an immunocompromised state from the AD, the immunosuppressive medications used, or effects from both. Patients with AD who are infected with HPV may have an increased risk of cervical dysplasia.[3–6] The mechanism by which HPV infection progresses to cervical cancer among immunosuppressed patients has not been fully delineated; however, viral reactivation from a latent state has been suggested.[7] Impaired immune responses in AD patients may lead to an inability to clear HPV infection resulting in persistent infection and in turn, an increased risk of high-grade cervical dysplasia and cervical cancer.[3]

In SLE patients, studies have documented a higher risk of abnormal Papanicolaou (Pap) smears compared to healthy controls, and an association between degree of immunosuppression and increased susceptibility to persistent high-risk HPV infection.[4,6] Most studies to date have been small and cross-sectional and have not consistently demonstrated a statistically significant increased risk of cervical cancer in SLE patients.[8] In a study of RA patients in Mexico, researchers observed an association between methotrexate use, longer duration of steroid therapy and HPV positivity.[6] A small study of patients with IBD reported an increased risk of an abnormal Pap smear and of high-grade lesions compared to healthy controls, particularly among patients receiving immunosuppressive medications.[5]

A large, recently published cohort study using U.S. insurance data from 2001-2012 demonstrated a 1.5 times higher risk of high-grade cervical dysplasia or cervical cancer among patients with RA and SLE compared to those without systemic inflammatory diseases.[3] This effect was seen after adjusting for many potential confounders. Among IBD patients there appeared to be an increased risk of high-grade cervical dysplasia or cervical cancer with the use of immunosuppressive medications, albeit not statistically significant in a fully adjusted model.[3] Psoriasis was also studied here and these patients did not have an increased risk of high-grade cervical dysplasia or cervical cancer. The use of a large database enabled the researchers to examine associations between these relatively uncommon exposures and outcomes, which prior smaller studies may not have been powered to do. In addition, multiple sensitivity analyses demonstrated that the effect from residual confounding would be unlikely to explain the increased risk of high-grade cervical dysplasia or cervical cancer observed in RA and SLE patients compared to those without systemic inflammatory diseases.

HPV Vaccine Safety and Efficacy in Patients in Autoimmune Diseases

The HPV vaccine has been shown to be safe and efficacious in the general population and a few studies have specifically examined the vaccine's safety in patients with AD. One such study compared the safety and immunogenicity of the bivalent vaccine in females with juvenile idiopathic arthritis (JIA) to healthy female adolescents.[9] Although HPV antibody concentrations were lower in JIA patients and the magnitude of the B cell response was lower compared to healthy adolescents, there were no statistically significant differences observed. Furthermore, there were no increases in flares or adverse events among JIA patients. A second study evaluated the immunogenicity and safety of the quadrivalent vaccine in patients with SLE and found that the vaccine was well tolerated, did not increase disease activity and was reasonably effective.[10] A small study of vaccinated IBD patients similarly indicated similar mean HPV antibody titres for patients compared to controls and no increase in adverse events.[11]

A few small case series have reported potential temporal relationships between HPV vaccination and the incidence of SLE.[12,13] However, a multi-centered case-control study found no evidence of increased risk of AD following quadrivalent HPV vaccination.[14] Similarly, an autoimmune surveillance study of nearly 200,000 women belonging to two California managed care organizations, demonstrated no autoimmune safety signal in women who received the quadrivalent HPV vaccine.[15] A large cohort study in Denmark and Sweden assessed nearly 300,000 girls who received at least one HPV vaccine and also found no evidence of an association between vaccine exposure and development of autoimmune events.[16] A comprehensive review that included case reports and series, case-control studies, post-marketing surveillance programs and analyses by the Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System, looked at the incidence of autoimmune conditions and concluded that the level of risk cannot be determined based on the data available.[17] These authors provided an appropriate warning against misinterpreting causal links when the target population for HPV vaccination is adolescent females- a group with a high overall incidence of AD. They note that the possibility of a genetic predisposition to vaccine-induced AD warrants further investigation.

HPV Vaccine Uptake in Children and Adolescents with Autoimmune Diseases

In general, uptake of the HPV vaccine in the U.S. has lagged behind other recommended vaccines and is lower than in other countries.[18] A prior study using managed care organization data demonstrated that females with a history of immune-related conditions had comparable rates of HPV vaccine initiation compared to those without.[19] With the potentially increased risk of cervical dysplasia and cervical cancer among patients with AD in mind, we investigated whether there is a difference in HPV vaccine uptake in this group compared to the healthy population since vaccine approval. Using claims data from a nationwide U.S. commercial insurance, we examined uptake among 9-26 year-olds with and without AD between 2006 and 2012. Among 5,643 patients with AD and 20,643 without, 21 percent of AD females, compared to 23 percent of non-AD females, received ≥1 HPV vaccine ($p < 0.01$) and of those, 53 percent with AD and 51 percent without ($p=0.45$)

completed the three dose series.[20] Overall, we found nearly comparable and strikingly low vaccine uptake among those with and without AD. A number of studies suggest that low uptake in the population in general may be attributed to lack of patient and provider awareness, lack of a national mandate for HPV vaccine administration, and a hesitancy to discuss sexually transmitted diseases with adolescents.[18] One study presented results of a survey administered to parents of 11 and 12 year-olds and demonstrated adequate awareness of the perceived risk of HPV and the potential for risk reduction with the vaccine.[21] However, the parents believed that adolescent sexual behavior would increase by a factor of 1.8 if vaccinated. The authors postulate that addressing concerns relating to sexual activity among adolescent vaccine recipients may improve uptake overall.[21] We concluded from our study that public health efforts are needed in the entire population to improve HPV vaccination rates and possibly, higher risk patients, such as those with AD or other inflammatory or immunocompromised states, should be targeted.

Barriers to HPV Vaccine Uptake in Autoimmune Disease Patients

It is possible that despite the increased risk of persistent HPV infection, cervical dysplasia and potentially of cervical cancer inpatients with AD, there maybe unique barriers to HPV vaccination. First, providers of patients with AD may be unaware of this heightened risk and therefore may not seek to preferentially vaccinate this population. Young patients with AD may similarly be uninformed as to their risk and may feel overwhelmed by their increased interaction with the healthcare system for their AD and therefore, avoid additional preventive care. A prior study suggests that younger patients with SLE may receive less preventative care services, including less cervical cancer screening, compared to the general population.[22] A study among patients with JIA also demonstrates relatively low vaccination coverage overall in this population, although HPV vaccination was excluded given the time frame of the study.[23] Rheumatologists often provide primary care services to patients with rheumatic diseases and may not routinely stock the HPV vaccine. The shortage of pediatric rheumatologists in the U.S. may limit the amount of clinic time available per patient and narrow the visit's focus to disease management rather than preventive care. With complex diseases, it is even possible that vaccinations may be forgotten given the time constraints placed on patient-physician encounters.[23] There may also be a tendency to avoid health care interventions, such as vaccines like HPV that are not mandated for school enrollment, among children who are chronically ill. Rare case reports that suggest a temporal relationship between vaccination and development of AD may further lead providers and parents to avoid administration in patients with known disease.

Recommendations and Future Directions

Recent studies suggest that patients with AD, notably RA and SLE, may have an increased risk of high-grade cervical dysplasia and cervical cancer. Two HPV vaccines are widely available, safe and largely efficacious among patients with AD; however to date, we have not observed increased uptake in this population. In general, HPV vaccine uptake has been significantly slower than other vaccines likely because there are no school-wide requirements for vaccination, patient, parental and provider education may be insufficient, and there is sensitivity around discussion of sexually transmitted diseases.[18] The HPV

vaccine provides our society with the unique opportunity to reduce the incidence of common STD and potentially lethal cervical cancer. Further research is necessary to better understand the pathophysiology of persistent HPV infection and the risk of cervical cancer among patients with various AD and other immunocompromised states, and among those receiving immunosuppressive medications. Based on our knowledge to date, we must enhance our public health efforts to improve HPV vaccine uptake in the entire population, with an eye towards ensuring that the vaccine is readily accessible and consistently offered to individuals with AD who may be at higher risk.

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