Immunogenicity of the Bivalent Human Papillomavirus Vaccine in Adolescents with Juvenile Systemic Lupus Erythematosus or Juvenile Dermatomyositis

To the Editor:

In healthy females, human papillomavirus (HPV) vaccines are safe, immunogenic, and effective in inducing protection against HPV16/18 infections and their associated premalignant lesions, especially when administered to girls before they become sexually active^{1,2}. Juvenile patients with rheumatic diseases such as systemic lupus erythematosus (SLE) or juvenile dermatomyositis (JDM) are at increased risk of infections due to the disease itself or its treatment³. This applies particularly to HPV infections in patients with SLE, because persistent HPV infections and cervical intraepithelial neoplasia (CIN) lesions are more prevalent in patients with SLE⁴. Interestingly, the immunogenicity of the quadrivalent HPV vaccine in adult SLE patients is lower than that in healthy controls⁵. However, the immunogenicity of the more immunogenic bivalent HPV16/18 vaccine in the target population, namely HPV-naïve adolescent patients with rheumatic diseases, remains unknown. We describe the immunogenicity of the bivalent HPV16/18 vaccine in a small group of patients with juvenile SLE or JDM compared to healthy female adolescents.

The bivalent HPV16/18 vaccine was introduced in the Dutch national immunization program in 2010 for girls aged 12 years, preceded by a catch-up campaign. From March 2009 until May 2011, female patients with SLE⁶ or JDM⁷ and healthy controls aged 12–18 years who voluntarily chose HPV vaccination were enrolled in a prospective controlled observational study (ClinicalTrials.gov; NCT00815282). Patients were recruited from the pediatric rheumatology unit of University Medical Center Utrecht; controls were recruited from 2 secondary schools. Written informed consent was obtained. The ethics committee of the Central

Committee on Research Involving Human Subjects approved the study.

Six patients with SLE were studied. They were aged 15.0 years (± 1.5) with mean disease duration 3.5 years (± 2.2). Six patients with JDM were also included, aged 15.3 years (± 2.3) and with disease duration 7.0 years (± 3.7). The mean age of 49 healthy controls, 14.3 years (± 1.2), was similar to that of patients ($p = 0.16$) at baseline. Participants received 3 doses of the HPV vaccine (Cervarix, GlaxoSmithKline Biologicals) in a 0, 1, 6 month schedule. HPV16/18-specific IgG antibodies were measured before vaccination and at 3, 7, and 12 months using a virus-like particle-based multiplex immunoassay⁸. Sera were considered HPV antibody-seropositive at a cutoff of 9 Luminex units/ml (LU/ml) for HPV16, and at 13 LU/ml for HPV18⁸. Post-vaccination, 12 serum samples from patients with SLE, 13 from patients with JDM, and 128 from controls were available.

SLE Disease Activity Index (SLEDAI) was low at baseline (range 0–8) and during followup (range 0–12). One patient experienced a mild/moderate flare at 7 months. SLEDAI scores decreased in 2 patients. All patients with JDM were in remission before and after vaccination. Treatment at baseline included glucocorticosteroids ($n = 6$), hydroxychloroquine ($n = 2$), azathioprine ($n = 1$), mycophenolate mofetil ($n = 1$), and methotrexate ($n = 2$). Four patients with JDM and 1 patient with SLE used no immunosuppressive drugs. During followup, immunosuppressive drugs were tapered in all patients, except for 1 patient in whom the hydroxychloroquine dose was increased at 7 months.

All patients and controls were seropositive for HPV16 and 18 after the third vaccine dose, except for 1 patient with JDM who was seronegative for HPV18 after initial low HPV18-specific antibody concentrations (20.5 LU/ml) at 3 months. In this patient, HPV16-specific antibody concentrations were also low after 3 vaccine doses (9.1 LU/ml). This patient did not use immunosuppressive drugs. HPV16/18-specific antibody concentrations were lower in patients compared to controls (Figure 1), reaching

Figure 1. Geometric mean antibody concentrations (GMC) against HPV16 (A, C) and HPV18 (B, D) at baseline and during followup in healthy controls (HC), patients with systemic lupus erythematosus (SLE; A, B), and patients with juvenile dermatomyositis (JDM; C, D). HPV vaccinations were given at 0, 1, and 6 months. Serum samples were taken at baseline, 3, 7, and 12 months. HPV: human papillomavirus.

statistical significance in patients with JDM at 7 months. At 12 months, no statistically significant differences were detected. The kinetics of the antibody response differed from controls, with no responses after the first 2 vaccine doses in patients with SLE and low responses after the third dose in patients with JDM.

The immunogenicity of the HPV vaccine in patients with rheumatic diseases may depend on the use of immunosuppressive drugs and on the underlying disease. For example, the HPV vaccine was shown to be immunogenic in 37 patients with inflammatory bowel disease, including 19 patients using a tumor necrosis factor- inhibitor⁹, whereas lower seropositivity rates were detected in 50 adult patients with SLE using various immunosuppressive drugs⁵.

Although our pilot study was limited by its small and heterogeneous sample size, it may indicate that the bivalent HPV16/18 vaccine induces seropositivity in a high proportion of female adolescents with SLE and JDM. However, vaccination-induced HPV16/18-specific antibody concentrations seemed lower, even in patients with rheumatic diseases who were not receiving immunosuppressive drugs. Because vaccine-derived HPV-specific antibodies are considered largely responsible for protection against persistent HPV infections and cervical intraepithelial neoplasia², protective immunity against HPV might not be guaranteed in these patients over time. A larger prospective trial is required to establish the safety and efficacy of HPV vaccination in these patients, and to determine the mechanisms behind the reduced immune responses against HPV. Until these data are available, immunosurveillance post-vaccination and continued secondary prevention through cervical smears may be prudent in patients with SLE or JDM.

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