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Long-term immunogenicity of a quadrivalent human papillomavirus vaccine in systemic lupus erythematosus

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ABSTRACT

Objectives: To evaluate the 5-year immunogenicity of a quadrivalent human papillomavirus (HPV) vaccine (GARDASIL) in patients with systemic lupus erythematosus (SLE).
Methods: Female SLE patients and controls, aged 18–35 years, who received GARDASIL in 2011 and sero-converted 12 months post-vaccination were followed for persistence of immunogenicity. Antibody measurement to HPV serotypes 6, 11, 16, 18 was repeated at 5 years. The rate of sero-reversion was compared between patients and controls, and factors associated with sero-reversion of the anti-HPV antibodies were studied.
Results: 50 SLE patients and 50 controls were vaccinated with GARDASIL. Among subjects who sero-converted at 1 year and consented for this study, antibodies to HPV serotypes 6, 11, 16 and 18 at 5 years were persistent in 24/27 (89%), 26/31 (84%), 32/34 (94%) and 24/25 (96%) of the SLE patients; and 32/33 (97%), 32/33 (97%), 32/32 (100%) and 23/24 (96%) of the controls, respectively. Antibody titers to HPV-6 and 16 were significantly lower in patients than controls. Seven (21%) SLE patients had sero-reversion of ≥1 anti-HPV antibodies. Sero-reverted patients experienced significantly more SLE flares, particularly renal, and had received significantly higher cumulative doses of prednisolone, mycophenolate mofetil and tacrolimus than those with persistent immunogenicity. The cumulative doses of prednisolone correlated inversely and significantly with the anti-HPV 6, 11, and 16 titers at 5 years.
Conclusions: Immunogenicity of the quadrivalent HPV vaccine was retained in a high proportion of SLE patients at 5 year. Patients with more SLE renal flares and had received more immunosuppression were more likely to have sero-reversion of the anti-HPV antibodies.
Clinical trial registration number: US ClinicalTrials.gov (NCT00911521 & NCT02477254).

1. Introduction

Human papillomavirus (HPV) is a small double-stranded DNA virus that commonly infects humans [1]. Of the more than 200 genotypes of HPV, more than 40 are able to specifically infect the anogenital tract [2]. Genital infection with HPV is one of the commonest sexually transmitted infections worldwide [3]. The majority of HPV infections is asymptomatic and cleared within 1–2 years post-infection [1]. However, in some individuals, particularly those with impaired immunity, HPV infection is persistent and results in genital warts, cervical smear abnormalities, cervical intraepithelial lesions and cervical cancer. The HPV-16 and HPV-18 serotypes account for 70% of all cervical cancers, around 50% of high-grade and 30–50% of low-grade cervical intraepithelial lesions [4].

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease that predominantly affects young women of the childbearing age. As a result of intrinsic immunological aberrations and immunosuppressive therapies, SLE patients are more susceptible to HPV infection than healthy subjects. Moreover, HPV infection in SLE patients is more likely to involve multiple serotypes and persist over time [5,6]. In a systematic review, an increased prevalence of latent HPV infection and cervical dysplasia in patients with SLE as compared to controls was reported [7]. A meta-analysis also revealed that the pooled risk of high-grade cervical intraepithelial lesions was increased by 7–8 folds in SLE patients with reference to healthy women [8].

Randomized controlled trials and meta-analysis have shown that the HPV vaccines are safe and highly efficacious in reducing the occurrence of high-grade cervical intraepithelial lesions and anogenital disease in women [9–11]. Vaccination of young women aged 16 to 23 years with the quadrivalent HPV vaccine, GARDASIL, resulted in very high sero-conversion rates for the all the HPV ser-

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otypes [6,11,16,18], and was well tolerated [12]. The quadrivalent HPV vaccine was also shown to be efficacious in reducing HPV-related diseases in older women aged 24–45 years [13].

The long-term immune response to GARDASIL in adult women, adolescents and pre-adolescents has just been released [14–16]. Sero-positivity of the antibodies to the four HPV serotypes persisted in 81.5%-96% in these subjects 6–10 years after vaccination. However, there is little information regarding the long-term immunogenicity of the quadrivalent HPV vaccine in patients with autoimmune diseases. We have previously reported high rates of sero-conversion of the anti-HPV antibodies at 1 year post-vaccination in 50 SLE patients with inactive disease [17]. There was no increase in SLE flares or adverse events as compared to non-vaccinated SLE patients and controls, respectively. However, antibody titers to certain HPV serotypes were lower in users of mycophenolate mofetil (MMF) and prednisolone. We hereby reported the 5-year immunogenicity of the quadrivalent HPV vaccine in the same cohort of SLE patients and factors associated with sero-reversion of the anti-HPV antibodies.

2. Patients and methods

2.1. Study design

This is a long-term follow-up study of the immunogenicity of a quadrivalent HPV vaccine, GARDASIL, at 5 years post-vaccination in a cohort of female Chinese patients with SLE. The study was approved by the Research and Ethics Committee of our hospital and registered in US ClinicalTrials.gov (NCT02477254). Written informed consent was obtained from all the participants (patients and controls).

2.2. Study population

Consecutive female patients who fulfilled ≥4 ACR criteria for SLE [18] were recruited in the year 2011 [17]. An equal number of age-matched healthy subjects were also recruited for the same vaccination protocol. The inclusion criteria for SLE patients were: [1] aged 18–35 years; and [2] those receiving a stable dose of immunosuppressive agents within 3 months of entry. The inclusion criteria for female controls were: [1] aged 18–35 years, matched that of recruited patients; [2] absence of any chronic medical illnesses; and [3] those not receiving any long-term medications including non-prescription drugs and herbs. Exclusion criteria for patients and controls were: [1] previous HPV vaccination; [2] history of allergy to HPV vaccines; and [3] history of documented HPV-related genital infections.

2.3. Study protocol

Fifty patients and fifty controls were given the quadrivalent HPV vaccine by intramuscular injection at baseline, month 2 and month 6. Immunogenicity of the HPV vaccine at month 7 and month 12 has been reported in our original study [17]. For those subjects who had sero-converted for at least one anti-HPV antibody at month 12 and consented for this follow-up study, a repeat assay of the antibodies to HPV serotypes 6, 11, 16, 18 were performed at 5 years post-vaccination using an IgG immunoassay developed on a Luminex microsphere platform (total IgG LIA; Merck Research Laboratory). Patients were followed regularly at an interval of 3–4 months in our clinic. More frequent follow-up visits would be arranged for those who experienced symptoms of disease flares or other complications.

The outcome of interest in this study was the rates of persistence of the anti-HPV serotypes at 5 years post-vaccination in both patients and controls. Factors associated with sero-reversion of the anti-HPV antibodies in SLE patients were also evaluated. These factors included age, SLE duration at study entry, the total number of SLE flares and the cumulative doses of various immunosuppressive agents used (prednisolone, cyclophosphamide [CYC], MMF, azathioprine [AZA], cyclosporin A [CSA], tacrolimus [TAC] and hydroxychloroquine [HCQ]) during the 5-year follow-up since HPV vaccination. Data were collected at 5 years post-vaccination by chart review.

2.4. Measurement of anti-HPV antibodies

The total IgG anti-HPV antibodies at 5 years post-vaccination were assayed by an immunoassay developed by Merck Research Laboratories on a Luminex microsphere platform as described elsewhere [19,20]. This assay measured a broader subset of the total antibody concentrations to HPV virus-like particles (VLPs) 6, 11, 16, and 18 and did not distinguish between neutralizing and non-neutralizing antibodies [19]. Positive results were defined by anti-HPV titers >9 milli Merck Units per mL (mMU/mL; arbitrary value for measuring HPV antibody responses in sera), >6 mMU/mL, >5 mMU/mL, and >5 mMU/mL for anti-HPV 6, 11, 16 and 18, respectively. Sero-reversion was defined as a transition from a positive to a negative result of the antibody test.

For comparison of the anti-HPV titers between 12 months and 5 years post-vaccination, the titers measured by the same multiplexed competitive Luminex immunoassay (cLIA) as adopted in our previous study [17] were used. This assay quantified antibodies to a single neutralizing epitope on four separately manufactured VLPs for HPV6, 11, 16, and 18.

2.5. Assessment of disease activity and flares of SLE

Disease activity of SLE was assessed by the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLE Disease Activity Index (SLEDAI), a validated instrument employed in the SELENA trials [21]. The physician's global assessment (PGA) of disease activity (score 0–3) was also performed by the attending rheumatologists to grade their impression on the disease activity of the patients [22]. Flares of SLE were assessed by the SELENA flare instrument [21] according to the clinical status of the patients with reference to that of the preceding clinic visit. Mild / moderate and severe flares were defined by different degrees of increment in SLEDAI, PGA score, nature of active manifestations and the intensity of immunosuppressive therapies.

2.6. Statistical analyses

Values in this study were expressed as mean ± standard deviation (SD). The median and quartiles were used for the anti-HPV titers because they did not follow a normal distribution. Continuous variables between two groups were compared by the non-parametric Mann Whitney U test. The rates of sero-conversion at 12 months and persistence of immunogenicity at 5 years of the anti-HPV serotypes of patients and controls were compared by the Chi-square test. When the frequency of any cell was less than 5, the Fisher's exact test was used instead. Spearman's rank correlation was used to study the bivariate relationship between anti-HPV titers and other variables such as age, SLE duration and the cumulative doses of immunosuppressive medications used. Linear regression models were established to study the contribution of a covariate to the anti-HPV titers adjusted for other confounding factors. The regression coefficients (Beta) and the P values were presented.

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