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The effect of history of abnormal pap smear or preceding HPV infection on the humoral immune response to Quadrivalent Human Papilloma virus (qHPV) vaccine in women with systemic lupus erythematosus

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ABSTRACT

Objective: To determine if natural human papillomavirus (HPV) infection would induce an anamnestic response to quadrivalent (qHPV) vaccine in women with Systemic Lupus Erythematosus (SLE).

Methods: Thirty four women (19-50 years) with mild to moderate and minimally active or inactive SLE received standard qHPV vaccine. Neutralizing antibody titers to HPV 6, 11, 16 and18 were evaluated pre- and post- vaccine using HPV competitive Luminex Immunoassay. For each HPV type, logistic regressions were performed to explore the relationship between a positive titer at baseline with their final geometric mean titer and with the rise in titer. Fisher's Exact Test was used to assess the association of at least one positive HPV antibody test at baseline and history of abnormal pap.

Results: History of abnormal pap smear/cervical neoplasia occurred in 52.9%. Baseline anti HPV antibody titers: 21% = negative for all 4 HPV types, 79% = positive for ≥1 of the HPV types. Statistical analysis showed: those with a history of abnormal pap smear/cervical neoplasia were likely to have a positive anti-HPV antibody result pre-vaccine to ≥ 1 of the 4 types, $p = 0.035$ Fisher's Exact Test. In general, HPV exposed women showed higher post vaccine GMTs than HPV unexposed women with higher point estimates. However, when examining the rise in titers using logistic regression, there was no evidence of an anamnestic response.

Conclusion: Prior HPV infection and cervical neoplasia in SLE are linked with no anamnestic response to HPV vaccine. This supports not checking HPV-antibodies pre-vaccine. Women with SLE should be vaccinated for HPV.

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SLE; HPV; autoimmunity; cervical cancer; vaccine

Introduction

Systemic lupus erythematosus is a multisystem autoimmune disease of female preponderance characterized by impaired immunity which makes these women more susceptible to acquire persistent HPV cervical infection.[1-4] Women with SLE have a predilection for cervical dysplasia, which leads to cervical cancer and although the mechanism is poorly understood, it is likely due to increased rates of persistent infection with high risk human papillomavirus (HPV).[5-9] Black women have a higher disease burden (incidence and mortality) for both systemic lupus erythematosus and cervical cancer compared to whites.[10-12] Human papillomavirus infection is the most common sexually transmitted infection in the US and usually clears spontaneously within 2 years via local cell mediated immunity in the cervix.[13,14] High risk HPV types have a tendency to persist in cervical tissue and integrate into host DNA which leads to oncogene overexpression and neoplastic transformation.[15] There are several high risk HPV types, of which types 16 and 18 account for approximately 70% of all cervical cancer cases in the general population.[16] HPV vaccination is the most effective way to prevent cervical infection and HPV related neoplasia. We recently published results from a clinical trial which showed that the quadrivalent HPV vaccine was safe and immunogenic in women with SLE.[17] High-risk groups, such as Blacks, who are already disproportionately affected by both SLE and cervical cancer may benefit from HPV vaccines (even after being exposed to different oncologic strains) which prevent cervical cancer, a cancer that kills Black women more than any other racial group in America.

Little is known about the immune response to HPV infection and vaccination in women with SLE, and if HPV exposed women with SLE can mount an anamnestic response to the vaccine. Although seroconversion and rise in geometric mean titers (GMTs) are used to define immunogenicity, no minimum threshold level of neutralizing antibody titer has been established as protective for HPV cervical disease. In addition, few studies have assessed whether previous HPV exposure by natural infection causes an anamnestic response to the vaccine in normal individuals. Immunosuppressed populations that have decreased humoral immune response to vaccine may not be

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able to mount an anamnestic response. An anamnestic response may be helpful in to improve vaccine immunogenicity as well as vaccine efficacy in preventing re-infection. For this study, we sought explore if natural HPV infection would induce an anamnestic response to qHPV vaccine in women with SLE. To answer this question, we did a secondary analysis of data from our previously completed clinical trial to assess for any difference in immune response to vaccine between HPV exposed and unexposed women with SLE.

Results

The 34 women who completed the study were predominantly African-American (79%), with a mean age of 38.1 years and a mean age at diagnosis of SLE at 28.6 years. Risk factor assessment for HPV in these women showed that 35.3% had a history of smoking, 91% reported 4 or more sexual partners, 50% had a history of sexually transmitted diseases, and only 27.3% used condoms on a regular basis. Most of the women (52.9%) had abnormal pap smears ranging from ASCUS (atypical glandular cells of undetermined significance) to CIN 3 (cervical intraepithelial neoplasia grade 3) Table 2. Those with a history of abnormal pap smear/cervical neoplasia were more likely to have a positive neutralizing anti-HPV antibody result pre-vaccine compared to those who didn't (94% versus 63%), p = 0.035, Fisher's Exact Test.

At baseline, most of the of the women had positive neutralizing anti-HPV antibody titers to one or more of the HPV types in the qHPV vaccine, indicating previous infection Table 3. Only 21% (7/34) of the women were naïve to all 4 HPV types, with 79% (27/34) being positive for ≥1 HPV type and 35% (12/34) being positive for ≥ 2 or HPV types at baseline. Highly immunogenic responses were seen in all patients with rise in mean geometric titers (GMTs) post vaccine for both HPV naïve (seronegative at baseline) and HPV exposed (seropositive at baseline) women for all 4 HPV types, with a seroconversion rate of 100% in HPV naïve women.

In general, HPV exposed women showed higher post vaccine GMTs than HPV unexposed women with higher point estimates Table 4. Logistic regression analysis results are shown in Table 5. Results indicate that the final titers were statistically significantly higher when antibodies were positive at baseline for HPV types 6, 11, and 16. However, when examining the rise in titers, there was no evidence of an anamnestic response. In fact, we found the opposite response in HPV types 16 and 18. We also explored the idea of controlling for demographic variables such as age, race, and age at lupus diagnosis. However with the low number in our sample and high collinearity, results were not reliable.

Discussion

The key finding of our study is that in women with SLE, those with prior natural infection with HPV did not show an anamnestic response to the qHPV vaccine. Despite the fact that the post vaccine GMT point estimates in HPV exposed women

Table 1. Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
Diagnosis of SLE by ACR criteria	History of severe SLE (major organ involvement such as renal or central nervous system)
History of + ANA test	History of prior use of cyclophosphamide, rituximab, mycophenolate mofetil, azathioprine, methotrexate, cyclosporine or any other cytotoxic drug.
SELENA/SLEDAI ≤ 2	SELENA/SLEDAI>2
Age ≥ 18 and ≤ 50 years	End stage renal disease requiring dialysis
Female gender	Were a renal transplant recipient
Ability to provide informed consent	Inability to provide consent
Prednisone dose ≤15 mg/day	Prednisone dose >15 mg/day
Hydroxychloroquine dose ≤ 400 mg/day	Hydroxychloroquine dose >400 mg/d
	Hypersensitivity to any vaccine component
	Active chronic infections including but not limited to HIV (human immune deficiency), chronic hepatitis B or C, tuberculosis
	Positive purified protein derivative (PPD) test for tuberculosis
	Pregnancy
	Desire to become pregnant
	Were breast feeding
	Inability to complete vaccine series
	Received any blood product or component in the previous 6 months
	Received any inactivated vaccine product within the past 14 days
	Received any live vaccine product within the past 21 days
	Fever (T>100.4F)
	Current substance abuse
	Under treatment for anti-phospholipid antibody syndrome
	History of deep venous thrombosis
	Lab tests positive in the last 6 months for: Lupus anticoagulant, anti-cardiolipin antibody titers at moderate to high titers (IgG AclAb>40 GPL< IgM AclAb>20MPL)
	Treatment with any experimental drug in the past 6 months
	High probability of poor compliance with study procedures
	Received prior HPV vaccinations

Table 2. Demographics and Cervical Neoplasia (n = 34).

Variable	Measurement
Race	79% African American
Mean age at enrollment	38.1 years
Mean age at time of SLE diagnosis	28.6 years
4 or more ACR criteria for SLE	100%
Sexual history: ≥4 sexual partners	91%
≥ 1 sexually transmitted infection	50%
History of Smoking (tobacco)	35.3%
Condom use	27.3%
History of abnormal pap smear	52.9%
Cervical Neoplasia/pap smear history	Number (n = 34)
Normal	19
Cervical dysplasia, unspecified	4
ASCUS*	4
LGSIL*	2
HGSIL* or CIN 3*	3
Cervical Cancer	2

*ASCUS = atypical squamous cells of undetermined significance
*LGSIL = low grade squamous intraepithelial lesion
*HGSIL-high grade squamous intraepithelial lesion
*CIN 3 = cervical squamous intraepithelial neoplasia, grade 3

Table 3. Baseline anti-HPV antibody seropositivity status (n = 34).

HPV type	Positive (n)	Negative (n)
HPV 6	18	16
HPV 11	7	27
HPV 16	15	19
HPV 18	7	27

with SLE were higher, the magnitude of rise was not increased in HPV exposed women as would be expected for an anamnestic immune response. This was an unexpected finding and likely due to HPV exposed women having higher antibody titers at baseline. There was however, an association of seropositivity at baseline with history of abnormal pap smear/cervical neoplasia, which supports the supposition that increased cervical neoplasia in women with SLE is causally related to HPV infection.

Immunogenicity to HPV vaccination is influenced by several factors, including age, immunosuppressed state and possibly previous HPV exposure. Younger individuals have higher GMTs induced by the vaccine, which is why we used the 35–45 year old age group to compare point estimates of post vaccine GMTs since our cohort mean age was 38.1 years.[18-21] The kinetics of antibody response to qHPV vaccine show a peak one month after the third vaccine shot and a decrease in level to a plateau at 18 months, with high GMTs maintained at 5 years post vaccine.[18,20-22] There are some studies assessing immunogenicity in immunosuppressed populations with most showing immunogenicity with slightly lower GMTs post vaccine than in normal individuals. In those infected with human immunodeficiency virus (HIV), qHPV vaccine is highly immunogenic but induces lower GMTs which correlates with lower CD4 counts (<200) and with highly active anti-retroviral therapy (HAART) therapy improving response.[23-26] A suboptimal vaccine response to HPV vaccination was seen in kidney and other solid organ transplant recipients.[27,28] In children with a variety of immunosuppressive disorders, adequate immune response to vaccine was reported, but with lower GMT titers induced than in normal children.[29] In autoimmune diseases, including SLE, similar findings were noted with HPV vaccine being immunogenic but inducing lower GMTs than seen in the normal population.[30-32]

Little is known about the anamnestic response to qHPV vaccine, and there is no defined antibody level to guide clinicians about the indications and utility for pre-vaccine antibody testing and booster vaccination. Data from studies assessing booster vaccination for HPV show an anamnestic response to booster doses of HPV vaccine with immune memory anamnestic response to antigen challenge also reported.[33-35] However, there is a paucity of information on the anamnestic response to vaccine after natural infection with HPV. Data from a large study in normal subjects age 9–26 years (n = 12,343 males and females) showed a more robust anti HPV response to qHPV vaccine in those who were seropositive at baseline.[36] This was confirmed in a subsequent study showing an anamnestic antibody response in men (age 16–26 years) who were seropositive before HPV vaccination.[37] Both of these studies suggest that in normal individuals of young age, there is an anamnestic response to HPV vaccine after natural infection. Our data suggests that although women with SLE have an adequate immunogenic response, there is no anamnestic response to qHPV vaccine in those who had a prior history of HPV infection. This is likely related to impaired immune function in SLE preventing the development of an anamnestic response to a previously exposed pathogen.

Limitations of our study our study include small sample size and a low risk SLE population (mild disease, little immunosuppression). A low risk sample was used as an initial step in evaluating qHPV vaccine in SLE to decrease the risk for safety issues related to vaccine. The small sample size made appropriate control for age, age at SLE diagnosis, smoking and race of the logistic regression impossible, as noted above. Another limitation was the lack of a placebo group with randomization to reduce bias. Since this was a phase I study in SLE to look at safety and immunogenicity, a small sample was selected as the initial study to identify any safety signals using the large population data published in package insert for Gardasil® for comparison to normals (controls). One potential bias includes selection bias, since these women were recruited from one site and geographic area so results may not be generalizable to all lupus populations. In addition, this cohort of women agreed to receive this vaccine as part of the study (since there was no placebo), indicating that perhaps these subjects may have felt they had increased risk for acquiring HPV infection due to known risk factors such as unprotected sex and multiple partners. The main strength of our study was that this was a closely monitored and rigorous trial with successful completion of the vaccine series in our subjects.

In conclusion, our study showed that in women with SLE, qHPV vaccine was immunogenic with no evidence of an anamnestic response to vaccine after having a natural infection. This supports not checking for HPV antibodies or prior exposure before administering the HPV vaccine. The health disparity in Blacks for both cervical cancer and SLE highlights the importance of prevention and monitoring in this population. It may be that the next frontier in HPV vaccine may be off-label use

Table 4. Geometric Mean Titers post vaccine.

HPV type	Geometric mean titers SLE women seronegative at baseline for anti HPV ab(95% CI) milliMerck Units/ml	Geometric mean titers SLE women seropositive at baseline for anti HPV ab(95% CI) milliMerck Units/ml	*Package insert Gardasil® Geometric mean titers women ages 35–45 yrs(95% CI) milliMerck Units/ml
HPV 6	677.3 (440.4, 1,041.8), n = 16	2,769.49 (1,384.84, 5,538.60), n = 18	397.3 (397.3, 432.2)
HPV 11	827.6 (598.8, 1,143.4), n = 27	3,404.08 (2,005.40, 5,778.30), n = 7	512.8 (472.9, 556.1)
HPV 16	3,052.1 (2,186.8, 4259.9), n = 19	7,888.60 (3,992.09, 15,588.34), n = 15	2129.5 (1962.7, 2310.5)
HPV 18	567.7 (404.2, 797.4), n = 27	856.84 (375.41, 1955.24), n = 7	324.6 (297.6, 354.0)

*Gardasil® Full prescribing information (Package insert), Merck & Co. http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf.

Table 5. Logistic Regressions: Positive Baseline Results relationship with 1) Final geometric mean titer and 2) rise in geometric titer

	final geometric mean titer	rise in geometric mean titer
	OR (95% CI)/p	OR (95% CI)/p
HPV 06	10.760 (1.945 – 59.519)/p = 0.006	0.200 (0.034 – 1.180)/ p = 0.076
HPV 11	21,603.483 (3.213 – 145,266,895.5)/ p = 0.026	0.166 (0.016 – 2.035)/ p = 0.166
HPV 16	11.195 (1.511 – 82.941)/p = 0.018	0.008 (0.000 – 0.286)/ p = 0.008
HPV 18	3.896 (0.354 – 42.914)/p = 0.267	0.011 (0.000 – 0.356)/ p = 0.011

for specific, high-risk populations, such as Blacks with SLE. Studies with larger sample sizes are needed evaluate this health disparity further and determine best practices decreasing disease burden in high risk groups. As a general recommendation, women with SLE should be vaccinated for HPV as part of their overall health care.

Materials and methods

We analyzed immunogenicity data along with history of HPV exposure and abnormal pap smears from a previously completed phase I clinical trial conducted to assess the safety and immunogenicity of qHPV vaccine in SLE.[17] The subjects included in this trial consisted of 34 women ages 18–50 years with a history of mild to moderate SLE (fulfilling American College of Rheumatology (ACR) criteria for SLE) with minimally active or inactive disease who consented and completed the study.[38-40] This phase I study was approved by the Human Investigation Committee and Institutional Review Board (IRB #051012PH1F) at Wayne State University and the U.S. Food & Drug Administration (FDA) under investigational new drug (IND) application BB14113 for Gardasil® (Merck & Co., Inc.) with a local Data Safety Monitoring Board (DSMB) to monitor the study. This small sample size was determined as adequate by the FDA and Merck scientific team as an initial study to assess safety and immunogenicity in this high risk autoimmune population. Women outside of this recommended age group were included (and approved by the FDA under the IND specified above) since this population is high risk for cervical neoplasia and HPV infection throughout their lifetime if they are sexually active. Inclusion and exclusion criteria are included in Table 1.

Neutralizing anti-HPV antibody titers for HPV types 6, 11, 16 and 18 were drawn at baseline and one month after the third and last vaccine shot. Samples collected at baseline and one month post third vaccine shot were frozen at −70 degrees C and sent out to a Merck contracted laboratory at the end of the study. Neutralizing anti-HPV antibody levels were measured by HPV competitive Luminex Immunoassay.[41] Immune response to vaccine was quantitated by measuring the geometric mean titers (GMTs) for each HPV type with seroconversion assessed for those seronegative at baseline. For each HPV type, logistic regressions were performed to explore the point-biserial relationship between the independent variable of either the final geometric mean titer or the rise in geometric mean titer and the explanatory variable of previous exposure to HPV. Fisher's Exact Test was used to assess the association of at least one positive HPV antibody test at baseline and history of abnormal pap.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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