SAFETY OF GARDASIL® VACCINE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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PRIOR STUDIES-EVIDENCE BASED REFS.


WHY DO THIS STUDY?

Gardasil is a vaccine that immunizes for Human papilloma virus (HPV) types 16, 18, 6, 11
Women with SLE are at increased risk for cervical cancer/dysplasia
70% of cervical cancer is caused by HPV 16/18
90% of genital warts is caused by HPV 6/11
We believe that the increased risk of cervical cancer/dysplasia in women with SLE is due to failure to clear HPV due to immunosuppression
Women with SLE should be immunized for HPV

STUDY SYNOPSIS AND ORIGINATION

This is a phase I, investigator initiated study in progress
Primary endpoint is the safety of Gardasil® vaccine in SLE
Secondary endpoint is immunogenicity of this vaccine
Target enrollment is 40 women with SLE, ages 18-50 yrs.
Reporting on the first 20 enrolled
Gardasil is approved for use in women ages 9-26 yrs.
Since we planned to include women older than age 26 yrs., I was required to get my own IND from the FDA for Gardasil® vaccine

STUDY SYNOPSIS AND ORIGINATION

Originally we were looking at SLE patients on immunosuppression with major organ involvement and looking at immunogenicity
The FDA modified the protocol to: SLE patients on little or no immunosuppression and with no/minimal disease activity and excluded any patient with major visceral organ involvement such as renal and CNS
Working with the FDA was a great learning experience as well as a challenge
The scientific director at Merck, Inc. Dr. Al Saah was extremely helpful, supportive and great to work with

DISCLOSURES

• Merck, Inc.
• Glaxo Smith Kline (GSK)
• Merck, Serono, Inc.
**STUDY DESIGN (CLINICAL TRIALS.GOV)**

- Women with SLE age 18-50 yrs. with h/o mild to moderate SLE and minimally active or inactive disease (SELENA/SLEDAI < or = to 2)
- Only immunosuppressive meds allowed: Prednisone at \(<\) 15 mg and Hydroxychloroquine \(<\) 400 mg/d
- Subjects had to meet inclusion and exclusion criteria prior to each vaccine shot
- Gardasil was given at the standard dosing schedule of 0, 2, 6 months
- Narrow window for each vaccine shot (+/- 7 days) for the schedule stricter than used in practice
- Patients excluded if prior h/o DV T, severe disease, on IS drugs other than above, active disease or had chronic active infections
- Halting criteria developed for the study and the patient (DV T, demyelination, flare of SLE requiring hospitalization)
- We have a local DSMB to review the data and make sure the study was safe to continue every 3 months

**STUDY DESIGN, ADVERSE EVENTS**

- Adverse events were collected by the following methods:
  - 30 min. nurse observed AEs after vaccine given
  - 7 day solicited AEs collected by a memory sheet given to the patient
  - 30 day unsolicited AEs collected by a 30 day diary that the patient fills out
  - Weekly phone calls until visit 7 then monthly phone calls for 4 months
  - An adverse event is any new condition or lab abnormality or any change from baseline of a existing condition
  - Graded and terminology using NCI-CTC AE v4.0 (Common Terminology Criteria for Adverse Events (CTCAE))
  - Entered into the Oncore Database system which was very useful and meets FDA requirements.
  - Collecting these adverse events was daunting and there was a lot of background noise due to multiple co-morbidities in these patients

**HISTORY**

<table>
<thead>
<tr>
<th>N=20 women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>75% African American</td>
</tr>
<tr>
<td>Mean Age at enrollment</td>
<td>39.0</td>
</tr>
<tr>
<td>Mean Age at time of SLE diagnosis</td>
<td>29.8</td>
</tr>
<tr>
<td>4 or more ACR Criteria for SLE</td>
<td>100%</td>
</tr>
<tr>
<td>Sexual History: 4 or more sexual partners</td>
<td>95%</td>
</tr>
<tr>
<td>STI History: h/o 1 or more STIs</td>
<td>35%</td>
</tr>
<tr>
<td>Condom Use:</td>
<td>21%</td>
</tr>
</tbody>
</table>

**HISTORY OF ABNORMAL PAP SMEARS**

- 40% of women in this study had a h/o of abnormal pap smears
- Histology type ranged from ASCUS to CIN 3
- This is consistent with our observation that women with SLE have increased risk for cervical dysplasia

**VACCINE SITE REACTIONS**

- VSRs occurred in 50%, with 90% being mild in our study
- Normal women given this vaccine from the label for Gardasil® is 83.9% for those given the vaccine vs. 75.4% for placebos
- Our data showed no increase in VSRs in women with SLE given this vaccine

**ADVERSE EVENTS**

<table>
<thead>
<tr>
<th>Organ system</th>
<th>AE type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Aching</td>
<td>9</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Back pain</td>
<td>7</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Leg pain</td>
<td>5</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle spasm</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Injury</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Tendon issue</td>
<td>1</td>
</tr>
<tr>
<td>Cardio-pulmonary</td>
<td>Chest pain</td>
<td>15</td>
</tr>
<tr>
<td>Cardio-pulmonary</td>
<td>Shortness of breath</td>
<td>5</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Cough</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Upper respiratory infection/avirus</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>Headache</td>
<td>25</td>
</tr>
<tr>
<td>Headache</td>
<td>Migraine</td>
<td>7</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Nonspecific rash (not SLE)</td>
<td>19</td>
</tr>
<tr>
<td>Neurology</td>
<td>Vhiigo</td>
<td>17</td>
</tr>
<tr>
<td>Neurology</td>
<td>Traumatic ulcers</td>
<td>1</td>
</tr>
</tbody>
</table>
NON VACCINE SITE ADVERSE EVENTS

- 90% of our cohort experienced at least one nvAE
- There were 105 nvAEs reported from 18 patients, 90% of these were mild or NOT related to vaccine
- One serious AE reported due to underlying osteoarthritis and cervical disc disease - patient was hospitalized
- Most common nvAEs were musculoskeletal (28) followed by cardiopulmonary (n=25), headache (n=21) and dermatologic (n=19)
- None of the nvAEs were related to SLE flare or vaccine
- There was no flare of SLE, thrombosis, or generation of thrombogenic antibodies in any patient

PROTOCOL DEVIATIONS AND OTHER ISSUES

- 7 protocol deviations – minor and did not affect safety or the study data
- 1 SAE due to hospitalization for pain related to osteoarthritis
- One patient developed swelling of about 4 cm after the first vaccine and did not get the second or third shot due to risk of worsened swelling with subsequent shots. She later told us she had exaggerated responses to vaccines in the past. She remains in the study to get her anti HPV antibody titer

CONCLUSIONS

- It is better to work without an IND if the proposal can be modified to fit already existing FDA approved criteria for a vaccine. Working with the FDA is a challenge
- Working in an environment with infrastructure (Oncore database system, Clinical research center with coordinators and study monitors) is essential to manage IND studies due to strict FDA requirements and reporting.
- Looking at all AEs is not really necessary or effective since there is a lot of background noise due to multiple comorbidities (some of our patients were journaling)
- It is better to look only at VSRs, SAEs and AEs of special interest when doing this type of study in SLE.
- The company was very supportive and helpful

CONCLUSIONS

- So far, Gardasil® vaccine in SLE does not appear to be associated with any increase in adverse events.
THANK YOU!
ANY QUESTIONS?

- Thanks to my research team
- Dr. Robert J Sokol, MD-mentor, co-inv
- Ardeila Magee, RN-nurse coordinator
- Lynnette Essenmacher, MS data manager
- Sub-investigators: Renee Dhar, BS, Harpreet Sagar, MD Malini Venkatram MD
- Statistician: Joel Ager, PhD