Safety and Immunogenicity of Glycoprotein D–Adjuvant Genital Herpes Vaccine

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Background. Two previous trials have suggested that a herpes simplex virus (HSV) type 2 glycoprotein D (gD) vaccine combined with the adjuvants alum and 3′-O-deacylated-monophosphoryl lipid A (MPL) is well tolerated and provides protection against genital herpes disease in women with no preexisting HSV antibody.

Methods. The safety and immunogenicity of this vaccine were evaluated in a large, multicenter, double-blind, randomized, placebo-controlled trial. The effects of sex and preexisting HSV immunity were sought.

Results. When solicited symptoms that continued after the initial 4 days of observation were excluded, the incidence of unsolicited symptoms occurring during the 7 months after vaccination (the primary analysis period) was 22.1% in vaccine recipients and 21.9% in placebo recipients. Significant increases in the number of local and systemic symptoms were found in vaccine recipients within 4 days after vaccination. However, most symptoms were mild to moderate in severity and were short lived. Women reported symptoms more frequently than did men, but preexisting immunity had little effect. The vaccine induced higher titers of HSV gD antibody on enzyme-linked immunosorbent assays than did natural infection with HSV.

Conclusion. The vaccine was generally safe, well tolerated, and immunogenic.
study was approved by the human investigations review committees at all study centers, and subjects provided written, informed consent.

**Study design.** The study was a double-blind, randomized, placebo-controlled, multicenter trial. Subjects received either vaccine or placebo (ratio of vaccine recipients to placebo recipients, 2:1) at 0, 1, and 6 months by intramuscular injection into the deltoid muscle. All subjects were scheduled to be observed for at least 13 months. Subjects enrolled outside of the United States were observed for an additional 6 months.

Data on local symptoms (i.e., soreness, redness, and swelling) and general symptoms (i.e., fatigue, malaise, fever, and headache) that occurred during the 4 days after each injection (days 0–3) were recorded on diary cards. Severity was determined on a scale of 1–3. Subjects also reported any unsolicited adverse events that occurred within 30 days after each injection, as well as serious adverse events that occurred at any time during the trial. Solicited symptoms that continued after day 3 after vaccination were reported as unsolicited symptoms. Unsolicited signs and symptoms were coded by use of the *World Health Organization Dictionary for Adverse Reactions Terminology*; every reported sign and symptom was matched to the appropriate *World Health Organization* (WHO)—preferred term. The occurrence of unsolicited symptoms during months 0–7 was the primary safety end point.

An additional safety analysis evaluated the effect of vaccination on the frequency of HSV episodes. Self-reported evaluations of recurrences of HSV episodes were used for persons with preexisting nongenital HSV disease, whereas cultures of samples obtained during the first episode of genital or nongenital HSV disease were evaluated for persons with no prior history of HSV disease.

Serious adverse events were defined as events that were life threatening, as events that began <1 h after vaccine administration (e.g., anaphylaxis, vasovagal reaction, and hyperventilation), as events that resulted in hospitalization, as new cases of cancer, or as events that resulted in severe or permanent disability or death. Also considered were laboratory test results suggesting a significant system dysfunction, congenital abnormalities, or any events that the investigator regarded as serious or that suggested any significant hazard that might have been associated with the use of the vaccine.

Blood samples were obtained for HSV antibody evaluation at the screening visit, 1 month after the receipt of the final vaccine or placebo dose (i.e., at month 7), and around month 13 at preselected centers. Blood samples were obtained for hematological and biochemical evaluations at months 7 and 13 at selected centers.

All subjects were advised about signs and symptoms of genital herpes and methods to reduce the risk of infection. Subjects who experienced a first episode of genital or nongenital herpes were requested to visit the clinic within 48 h after the onset of signs or symptoms. Swab specimens were obtained for HSV culture.

**Vaccine and placebo.** The gD-alum-MPL vaccine contained a truncated form of a recombinant HSV-2 gD molecule, purified from Chinese hamster ovary cells transfected with a plasmid containing a gD DNA fragment from the HSV-2 strain G. The antigen was adsorbed with 3-O-deacylated MPL onto alum [5]. Each vaccine dose contained 20 µg of gD, 50 µg of MPL, and 500 µg of alum. Placebo consisted of 500 µg of alum.

**Data and safety monitoring board.** A data and safety monitoring board was responsible for oversight of the study, including review of safety data prior to unblinding.

**HSV ELISAs.** Humoral responses to the vaccine were determined with use of an anti–HSV-2 glycoprotein D (gD2) ELISA [5]. The titers were determined from a reference standard curve expressed as anti-gD2t ELISA units (EU)/mL by a 4-parameter interpolation method. Geometric mean levels were compared after conversion to log10.

The presence of HSV-1 and/or HSV-2 antibodies was determined with use of a gG1 and gG2 ELISA assay validated against Western blot assay [5]. The cutoff for the gG1 was 6 EU/mL, and the cutoff for gG2 was 30 EU/mL.

**Statistical methods.** The analyses for the primary safety end point “unsolicited symptoms during the 7 month vaccination period” were limited to descriptive statistics. Overall incidences and 2-sided 95% CIs were calculated by preferred term. Overall incidence rates with 2-sided 95% CIs were calculated for serious adverse events. The incidence among groups of solicited local and general symptoms was calculated on the basis of the number of forms used to collect safety data from the diary card or from the subject visit interview (i.e., “symptom sheets”), and comparisons were made using Fisher’s exact test. Geometric mean titers with 2-sided 95% CIs were determined, as were seropositivity rates (anti-gD2t ELISA result, ≥40 EU/mL) with 95% CI. Geometric mean titers were compared using Kruskal-Wallis tests. Postvaccination seropositivity rates were compared by a Fisher’s exact test. Differences with a P value of ≤.05 for 2-sided tests were considered to be statistically significant.

**RESULTS**

**Study subjects.** A total of 8202 subjects were screened, and 7460 were enrolled in the study (4968 in the vaccine group and 2492 in the placebo group) (figure 1). The intention to treat analysis (ITT) population included 4811 vaccine recipients and 2412 placebo recipients. Subjects not included in the ITT population included 742 subjects who never received vaccine or placebo because they did not meet eligibility criteria and 237 from 1 site who were excluded because of concerns about data integrity that arose after study completion. Of the 7223 subjects in the ITT population, 7074 (97.9%) were included in
Figure 1. Flow diagram of the eligibility of subjects for the according-to-protocol (ATP) analysis used in this article. ITT, intention-to-treat.

The according-to-protocol (ATP) analysis, and 6370 (88.2%) completed the study. The analysis presented is the ATP analysis, which included all subjects who were enrolled, received ≥1 dose of the correct vaccine or placebo, and had ≥1 solicited or unsolicited symptom sheet available for analysis. Solicited and unsolicited signs and symptoms that occurred after receipt of 13,796 vaccine doses and 6975 placebo doses were examined for the ATP analysis. At least 97% of the data were available following each dose.

The most common reasons that the 586 vaccinees and 267 placebo recipients (P = not significant) did not complete the study were loss to follow-up (566 subjects [391 vaccine recipients and 175 placebo recipients]), withdrawal of consent during the trial (128 subjects [92 vaccine recipients and 36 placebo recipients]), and protocol violations (74 subjects [46 vaccine recipients and 28 placebo recipients]). Fifty-three subjects (40 vaccine recipients and 13 placebo recipient) dropped out of the study because of adverse events. Twenty-three of these events (17 in the vaccine group and 6 in the placebo group) were believed by the investigator to be definitely, probably, or possibly related to receipt of the vaccine. Withdrawal associated with either solicited local or general symptoms accounted for 9 of the withdrawals from the vaccine group and 5 from the placebo group. Pregnancy accounted for 31 dropouts (16 in the vaccine group and 15 in the placebo group). One vaccinee was withdrawn from the study by the sponsor; this withdrawal was not associated with an adverse event.

The demographic characteristics of the subjects evaluated in the ATP analysis are presented in table 1. The majority of subjects were female (54.7%) and white (91.1%). The proportion of women differed by serostatus, ranging from 64.2% of dual-seropositive subjects to 46.3% of HSV-1– and HSV-2–seronegative subjects (i.e., “dual-seronegative subjects”). A history of nongenital herpes was reported by 43.3% of subjects, with most reporting orolabial herpes. Of those with HSV-1 antibody, 54.3% reported a history of orolabial disease. No major differences were noted between treatment groups.

Safety. The incidence of any solicited local symptoms occurring within the 4 days after receipt of each vaccination dose was significantly higher among vaccine recipients (81.7%) than among placebo recipients (58.0%) (figure 2, top). Similarly, each local symptom was also more common among vaccine recipients (P < .001 for each). The incidence of local, grade 3, solicited symptoms was relatively low in both groups but was significantly higher in the vaccine group than in the placebo group (7.0% vs. 1.2%; overall/dose). Almost all solicited local
When analyzed by serostatus (figure 3, top), no significant differences were found between groups, although grade 3 reactions were least common in the dual-seronegative group (4.3%) and were most common in the dual-seropositive group (10.4%). It is possible that this difference reflects the higher proportion of women in the latter group, as discussed above.

Solicited systemic symptoms occurring within 4 days of vaccination were found in 14.7%–26.8% of the vaccinees and 10.4%–22.6% of placebo recipients after any dose (figure 2, bottom). Vaccinees had significantly increased rates overall and for each symptom (P < .001). Fatigue was the most common symptom, and fever was uncommon but significantly more likely in vaccinees than in placebo recipients (2.6% vs. 1.8%). Severe systemic symptoms were rare, occurring after 2.5% of vaccine and 1.9% of placebo doses (P = not significant). The incidence of solicited systemic symptoms did not increase with the number of doses (figure 2, bottom) or differ by serostatus (figure 3, bottom).

When analyzed by sex, each systemic symptom was more common among female vaccine recipients and female placebo recipients than among their male counterparts (data not shown). Differences between the men and women were significant for fatigue, headache, and malaise for both vaccine recipients and placebo recipients.

As seen in table 2, the overall incidence of unsolicited symptoms reported between month 0 and month 7 was slightly higher in the vaccine group (27.6%, overall/dose) than in the placebo group (23.1%). The 95% CIs did not overlap. The difference in symptoms was mainly due to injection site symptoms in vaccinees (8.4%) and placebo recipients (1.5%) that continued after the 4 day observation period. None of the other comparisons of unsolicited symptoms for the WHO body systems displayed a significant difference (i.e., the 95% CIs were overlapping). The incidence of grade 3 unsolicited symptoms occurring between month 0 and month 7 was 2.3% in vaccinees and 2.4% in placebo recipients. Only 0.4% and 0.2% of these grade 3 symptoms, respectively, were assessed as probably or possibly related to vaccine by the investigators. Overall, no clinically relevant differences or changes in biochemical or hematological indices were noted.

Between month 0 and month 7, serious adverse events were reported in 2.1% of vaccine recipients and 2.2% of placebo recipients. Between month 7 and the end of the study (month 13 at US centers and month 19 in non-US centers), the corresponding values were 2.0% and 2.4%. Serious adverse events assessed by the investigator as probably or possibly related to injection were reported in 4 subjects in the vaccine group (diplopia, vasovagal syncope, metallic taste in the mouth and fever <1 h after vaccination, and tongue tingling and throat tightness <1 h after vaccination) and 1 subject in the placebo group (metallic taste in the mouth <1 h after receipt of placebo).
During the study, 91 pregnancies were reported (62 in vaccine recipients and 29 in placebo recipients) among 89 subjects. No major differences were observed between vaccine recipients (11.3%) and placebo recipients (6.9%) with regard to the number of miscarriages, spontaneous abortions, or fetal deaths.

Immunogenicity. Data from 380 vaccine recipients and 176 placebo recipients were included in the ATP analysis of antibody responses. At month 7, all vaccine recipients were gD2 seropositive, regardless of initial serostatus (data not shown). At month 13, a total of 99.1% of initially HSV-seronegative vaccine recipients remained gD2 seropositive. Examination of the magnitude of the response revealed that, at month 7, the anti-gD2
Figure 3. Effect of herpes simplex virus (HSV) serostatus on incidence of solicited local (top) and systemic (bottom) symptoms for the 4 days after receipt of each vaccine dose. The HSV serostatus of the subjects was determined before immunization using a gG1 and gG2 ELISA that measures type-specific HSV antibody levels. Neg, negative; Pos, positive.

geometric mean titer was higher in patients in the initially HSV-seronegative group vaccinated with gD (4726 EU/mL) than either the prevaccination levels in the HSV-seropositive vaccinees (786–3326 EU/mL) or the levels in the HSV seropositive placebo recipients at any time (1777–2158 EU/mL) (all with nonoverlapping 95% CIs). After vaccination, levels in persons who were initially HSV seropositive increased from 2.4-fold (dual-seropositive persons) to 11.1-fold (HSV-2–seropositive persons) and were higher than in initially HSV-seronegative vaccinees (with nonoverlapping 95% CIs). By month 13, the levels had decreased in vaccine recipients, although the level in the HSV-seronegative subjects (1309 EU/mL) remained higher than in the HSV-2–seropositive subjects before immunization (786–802 EU/mL; P = not significant). Levels in those HSV-seropositive persons before receipt of vaccine remained 1.6-fold (for dual-seropositive persons) to 5.0-fold (for HSV-2–seropositive persons) greater than levels before receipt of vaccine.

Women developed higher levels of antibody than did men
Table 2. Incidence of unsolicited symptoms between months 0 and 7 in a study of genital herpes vaccine.

<table>
<thead>
<tr>
<th>Patient group, symptom category</th>
<th>No. of doses with reports available</th>
<th>Incidence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine recipients</td>
<td>13,796</td>
<td>...</td>
</tr>
<tr>
<td>Unsolicited, with ongoing solicited symptoms</td>
<td>...</td>
<td>27.6 (26.9–28.3)</td>
</tr>
<tr>
<td>Unsolicited, without ongoing solicited symptoms*</td>
<td>...</td>
<td>22.1 (21.4–22.8)</td>
</tr>
<tr>
<td>Placebo recipients</td>
<td>6975</td>
<td>...</td>
</tr>
<tr>
<td>Unsolicited, with ongoing solicited symptoms</td>
<td>...</td>
<td>23.1 (22.1–24.1)</td>
</tr>
<tr>
<td>Unsolicited, without ongoing solicited symptoms*</td>
<td>...</td>
<td>21.9 (20.9–22.9)</td>
</tr>
</tbody>
</table>

* The difference between treatment groups was largely due to solicited symptoms that were ongoing after day 3 and therefore reported as unsolicited symptoms. The results in this row eliminate these symptoms.

Table 3. Positive herpes simplex virus (HSV) culture results in subjects without preexisting HSV serotype-specific antibody in a study of genital herpes vaccine.

<table>
<thead>
<tr>
<th>Subject group, serostatus</th>
<th>Vaccine recipients</th>
<th>Placebo recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects</td>
<td>Subjects with genital herpes</td>
</tr>
<tr>
<td>Subjects without preexisting HSV serotype-specific antibody</td>
<td>1126</td>
<td>8 (5)</td>
</tr>
<tr>
<td>HSV-1 and HSV-2 negative</td>
<td>181</td>
<td>1</td>
</tr>
<tr>
<td>HSV-1 positive, HSV-2 negative</td>
<td>2721</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Subjects with preexisting antibody to same HSV serotype as isolate</td>
<td>181</td>
<td>1 (1)</td>
</tr>
<tr>
<td>HSV-1 negative, HSV-2 positive</td>
<td>2721</td>
<td>0</td>
</tr>
<tr>
<td>HSV-1 positive, HSV-2 negative</td>
<td>515</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

* All nongenital isolates were HSV-1.

NOTE. Data are total no. of HSV isolates with HSV type 2 (HSV-2) isolates in parentheses, unless otherwise indicated. There were 160 subjects with indeterminate serologic results in the vaccine group and 98 with indeterminate serologic results in the placebo group that were excluded from the analysis. This excluded 3 isolates (2 from the vaccine group and 1 from the placebo group) from analysis. In addition, 3 subjects in the vaccine group had HSV isolates that could not be typed and were excluded from the analysis, whereas 1 culture for an HSV-2–seropositive vaccinee was positive for both HSV type 1 (HSV-1) and HSV-2.

for each serostatus at month 7 and month 13, but none of the differences were statistically significant.

Effects of vaccine receipt on new episodes and recurrent episodes of HSV. Positive results of HSV cultures of samples from genital or nongenital sites were uncommon. Positive culture results occurred for 39 subjects (25 in the vaccine group and 14 in the placebo group) (table 3). HSV-2 was isolated from 32 of the 39 subjects. For 15 vaccine recipients and 6 placebo recipients for whom the antibody and viral type could be assessed, the result was found to represent a newly acquired infection, because antibody to the HSV type isolated was not present before vaccination. Nongenital isolates were all HSV-1. Thus, overall, vaccination did not appear to prevent the acquisition of genital or nongenital HSV disease or HSV-2 genital disease. In the group of subjects for whom the vaccine has previously shown efficacy—HSV seronegative women—the attack rate was 0.6% (3 subjects) among vaccine recipients, compared with 1.6% (4 subjects) among placebo recipients.

Clinical recurrences of nongenital disease occurred at nearly identical rates and frequencies in vaccine and placebo recipients (table 4). Thus, there was no evidence that vaccination exacerbated the recurrence rate of nongenital disease. Conversely, there was no evidence that vaccine reduced the frequency of recurrences.

DISCUSSION

In 2 previous studies, the rates of efficacy of an HSV-2 gD alum/MPL vaccine for prevention of genital herpes disease were 73% and 74% for HSV-seronegative female subjects whose reg-
ular sexual partner had a history of genital herpes [5]. The vaccine was not effective in men or in women with a previous HSV-1 infection. Limited safety data suggested that the vaccine was well tolerated.

In the large, multicenter study described here, we show that the vaccine is generally safe but did produce a significant increase in local reactions, especially soreness, when compared with those found in the placebo control group (figure 2, top). The reactions, however, were generally mild to moderate in severity and lasted ≤3 days. Severe local reactions occurred after receipt of 7.0% of vaccine doses and 1.2% of placebo doses (P < .001). The rate of local reactions did not increase in subjects after receipt of the second or third vaccine dose, compared with after the first (figure 2, top), or in subjects with prior HSV infections (figure 3, top), indicating that preexisting immunity did not increase the local reactogenicity of this vaccine.

Systemic reactions were less common than local reactions. Fatigue, headache, and malaise were reported after receipt of 16.2%–23.8% of vaccine doses and 1.2% of placebo doses (P < .001). The rate of local reactions did not increase in subjects after receipt of the second or third vaccine dose, compared with after the first (figure 2, top), or in subjects with prior HSV infections (figure 3, top), indicating that preexisting immunity did not increase the local reactogenicity of this vaccine.

Of interest, both local and systemic adverse reactions were reported more frequently in female vaccinees than male vaccinees. This difference was significant for all local reactions and for fatigue, headache, and malaise. Curiously, this increase in reported adverse events in females was also seen in placebo recipients. Differences for soreness, fatigue, headache, and malaise were all significant. The earliest report of increased reactions in female subjects that we identified was in 1975 [6]. In this report, the rate of subjective local reactions after influenza immunization was 8% higher among women than among men. Increased reported side effects in female subjects have also been seen in other evaluations of influenza vaccine [7, 8], hepatitis [9], and anthrax vaccine [10–12]. We could find no studies reporting an increase of reactions in placebo recipients. In the study reported here, this may have been due to the alum contained in the placebo, as other alum containing vaccines induce side effects more frequently in women than in men [11].

The results of the primary end point evaluation (unsolicited symptoms reported between month 0 and month 7) revealed no significant differences when local reactions that continued beyond the 4 days of initial observation were removed from the analysis. Likewise, there was no difference in the frequency of unsolicited symptoms for any system when evaluated using the WHO body system or clinically relevant changes in biochemical or hematological indices. There was also no evidence that the vaccine recipients induced serious adverse events, because rates were similar in vaccine and placebo recipients. Serious adverse events assessed by the investigator as related or possibly related to vaccination were reported for 4 vaccine recipients and 1 placebo recipient.

This study was also designed to determine whether vaccination would affect the incidence of recurrences in persons with a past history of nongenital HSV disease (mostly HSV-1 oral labialis). We found that the proportions of vaccine recipients and placebo recipients with recurrences (59.4% and 60.2%, respectively) and the mean number of recurrences (3.5 and 3.3, respectively) were almost identical. In other studies that have evaluated the potential of similar HSV vaccines to reduce the number of genital HSV recurrences, the efficacy was low, but clearly the vaccines did not show any propensity to increase recurrences [13, 14]. Thus, it appears that vaccinating persons who have previously been infected with HSV-1 or HSV-2 will neither increase the reactogenicity of the vaccine nor increase recurrence frequencies.

The immunogenicity of the vaccine was also evaluated with regard to gD-binding antibody. Vaccination induced gD antibody in all HSV-seronegative subjects after 3 doses, and this response persisted in 99.1% of these vaccinees for at least 6 months. Peak antibody levels in HSV-naive subjects were higher than those induced by natural infection (figure 4). Thus, the geometric mean titer in HSV-seronegative subjects at month 7 was higher than titers in HSV-1–positive, HSV-2–positive, or dual-seropositive placebo recipients at any time. In vaccinees who were HSV seropositive before immunization, titers in-

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Table 4. Number of subjects with at least 1 clinical recurrence of nongenital herpes disease among subjects with a history of nongenital herpes disease at study entry.

<table>
<thead>
<tr>
<th>Vaccine group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient sex</strong></td>
<td><strong>Vaccine group</strong></td>
</tr>
<tr>
<td></td>
<td><strong>No. (%) of subjects with ≥1 recurrence</strong></td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Female</td>
<td>1217</td>
</tr>
<tr>
<td>Male</td>
<td>815</td>
</tr>
<tr>
<td>All</td>
<td>2032</td>
</tr>
</tbody>
</table>

* Mean number of recurrences in subjects with ≥1 recurrence.
Figure 4. Geometric mean herpes simplex virus (HSV) glycoprotein D (gD) antibody levels before and after gD immunization. Levels are shown for female subjects, male subjects, and all study subjects and are grouped by initial HSV serostatus. M7, 7 months after the first immunization (i.e., 1 month after the third and final immunization); M13, 13 months after the first immunization; Pre, before immunization; +, positive, −, negative.

Increased 2.4–11.1-fold after immunization and were higher than those achieved after immunization of HSV-naive subjects. Thus, priming of the immune response to gD by natural infection contributed to an increase in peak and sustained gD titers.

By month 13, antibody levels had decreased substantially in vaccinees but still remained higher than those detected in HSV-2–infected placebo recipients. Titers were higher in female vaccine recipients than in male vaccine recipients, but these differences were not significant, and it is unlikely that these differences accounted for the sex-specific efficacy. However, it is still possible that differences in the cell-mediated immune response could account for the differences in protection.
Although this trial did not attempt to evaluate efficacy of the vaccine, information on new episodes of HSV disease was collected. New, symptomatic genital herpes infections were detected in 15 vaccinees (11 of whom were infected with HSV-2 and 4 of whom were infected with HSV-1) and 6 placebo recipients (6 of whom were infected with HSV-2). Because this vaccine reportedly decreased the rate of genital herpes disease only in female subjects [5], we also evaluated genital disease in this group. New, symptomatic genital HSV infections were detected in 3 female vaccine recipients (0.6%) and in 4 female placebo recipients (1.6%).

In summary, this large study provided further evidence for the safety and immunogenicity of this vaccine. Ongoing trials will determine the effect of vaccine on genital herpes disease and infection in HSV-seronegative women and the safety and immunogenicity of the vaccine in adolescent and preadolescent female subjects, the target population for immunization.

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