GEN-003 HSV-2 Immunotherapy Reduces HSV-2 Shedding Equivalently in HSV-1 Seropositive and Seronegative Individuals

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Abstract

GEN-003 is a candidate protein subunit immunotherapy under development for the treatment of genital HSV-2 infection. As reported in a clinical trial, subjects receiving the adjuvanted GEN-003 vaccine demonstrated reductions in the frequency of viral shedding (up to 52%) and lesion rate (up to 65%)[1]. The vaccine was immunogenic, eliciting T cell, IgG and neutralizing antibody responses. We previously reported that subjects seronegative for HSV-1 (HSV-1$^-$), as determined by HerpeSelect ELISA, had higher and more persistent fold changes in IgG titers to gD2, compared to those who were seropositive (HSV-1$^+$)[2]. As a result of this observation, we performed a retrospective analysis to determine if HSV-1 serostatus affects the virologic response to GEN-003 as measured by viral shedding. For this analysis we included data from the 56 subjects that received the two effective dose levels of vaccine (30 or 100 µg). By HSV-1 serostatus, 28 were negative, 19 were positive, and 9 were undetermined. Shedding rates were measured for all at baseline and for 53 immediately after immunization. Mean baseline shedding rates were similar for each serostatus: 14.3% (HSV-1$^-$) and 15.5% (HSV-1$^+$). Following immunization, shedding rates were lower for both (HSV-1$^-$, 8.3%; HSV-1$^+$, 6.8%) and not statistically different. There were also no differences in DNA copy number patterns. We next determined if HSV-1 serostatus impacted asymptomatic shedding. 14 of 28 (50%) HSV-1$^-$ subjects and 12 of 19 (63%) of HSV-1$^+$ subjects showed a decrease from their own baseline shedding after vaccination, with a mean rate for the HSV-1$^-$ subjects of 11.2% at baseline and 6.9% after immunization. By comparison, shedding among HSV-1$^+$ subjects decreased from 12.7% to 8.8%. The changes were not significantly different between serogroups. Taken together, these data indicate that GEN-003 immunotherapy results in a similar antiviral benefit to HSV-2-infected subjects who are seropositive or seronegative for HSV-1.

Background

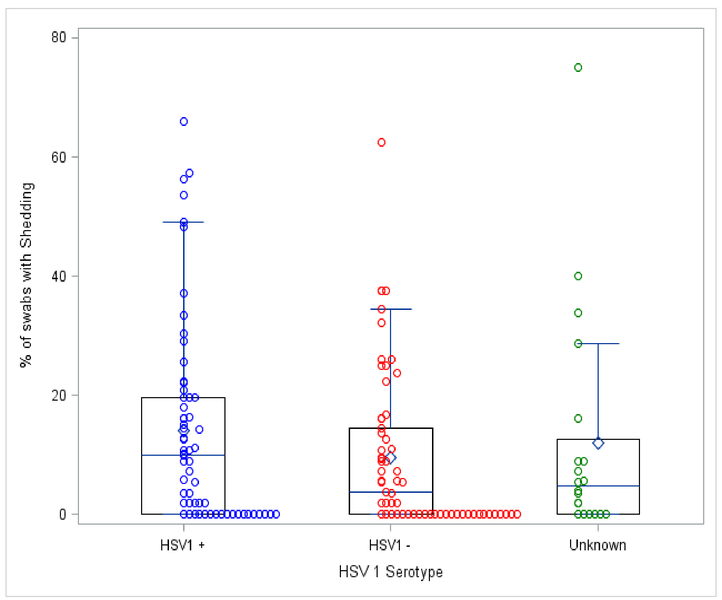
GEN-003 is a candidate therapeutic HSV-2 vaccine containing a fragment of infected cell protein 4 (ICP4.2), a deletion mutant of glycoprotein D2 (gD2ΔTMR), and Matrix-M2 adjuvant. In study GEN-003-001 (ClinicalTrials.gov NCT01667341), there were two dose levels of vaccine that resulted in reduced shedding among HSV-2 infected subjects, 30 and 100µg of each antigen adjuvanted with 50µg of Matrix-M2. Immediately post-vaccination, participants receiving the 30µg dose level of vaccine had a 52% reduction in viral shedding that persisted for six months. Similarly, subjects receiving 100µg of GEN-003 had a reduction of 31% immediately post-vaccination. For the purposes of this evaluation, data from subjects in both of these dose levels (N = 56) were pooled. To determine HSV-1 serostatus, serum from trial participants was evaluated at Genocea using the HerpeSelect ELISA (Focus Diagnostics, Cypress CA). Subject demographics and HSV-1 status are indicated in **Table 1**. The viral shedding assay methods are described in **Poster 1.51**.

Table 1. Demographics Of Subjects in Analysis

	Placebo	GEN-003
N	28	56
No. of women (%)	17 (60.7)	33 (58.9)
Mean Age (Range)	37 (23-50)	38 (22–50)
Race n (%)		
White	17 (60.7)	33 (58.9)
Black	10 (25.7)	18 (32.1)
Asian	-	1 (1.8)
Multiracial	-	1 (1.8)
Other	1 (3.6)	2 (3.6)
Mean years since diagnosis (range)	8 (1-26)	10 (1-33)
Mean lesion episodes in last 12 months* (range)	5 (3-8)	5 (3-9)
No. HSV-1 positive (%)	11 (39.3)	19 (33.9)
No. HSV-1 seronegative (%)	14 (50.0)	28 (50.0)
No. HSV-1 undetermined (%)	3 (10.7)	9 (16.1)
No. reporting oral lesion Hx. (%)	5 (7.9)	9 (16.1)

Results

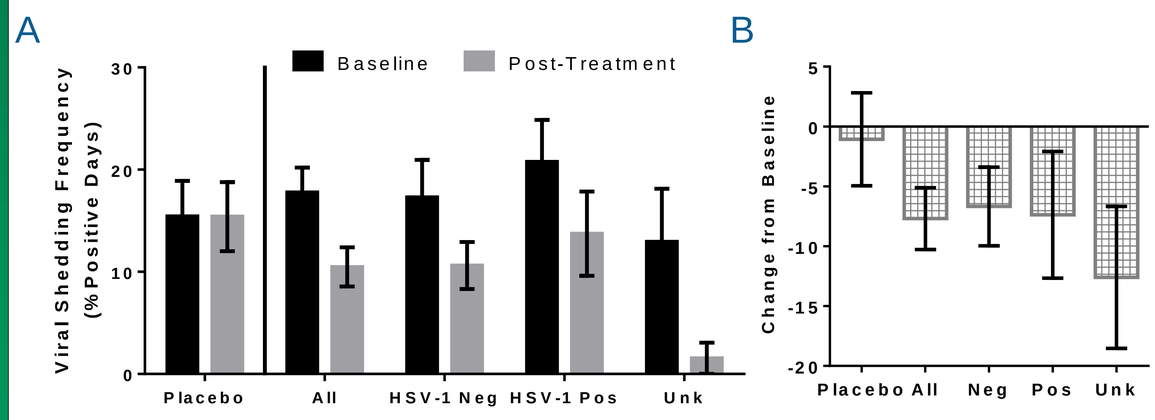
Figure 1. Mean Baseline HSV-2 Shedding Rates Are Similar Between HSV-1 Seropositive and Seronegative Subjects



Baseline viral shedding rates were determined for all subjects participating in the GEN-003-001 clinical trial by real-time quantitative PCR of genital swab samples collected from the anogenital region, twice a day for 28 days prior to immunization. The frequency was calculated as the number of swabs positive for HSV-2 DNA over the total number of swabs collected for each subject. Box and Whisker plots are presented. Each symbol represents the baseline shedding frequency for one subject. There were no significant differences in baseline shedding across the groups.

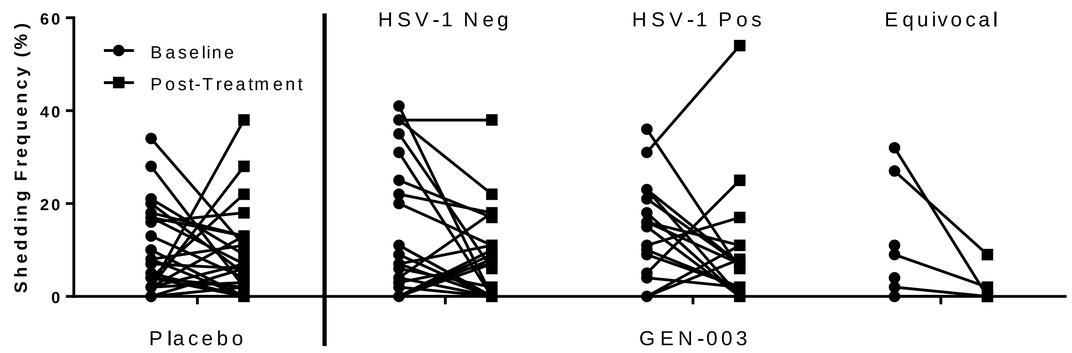
Results

Figure 2. GEN-003 Reduces HSV-2 Shedding Among Both HSV-1 Seropositive and Seronegative Subjects



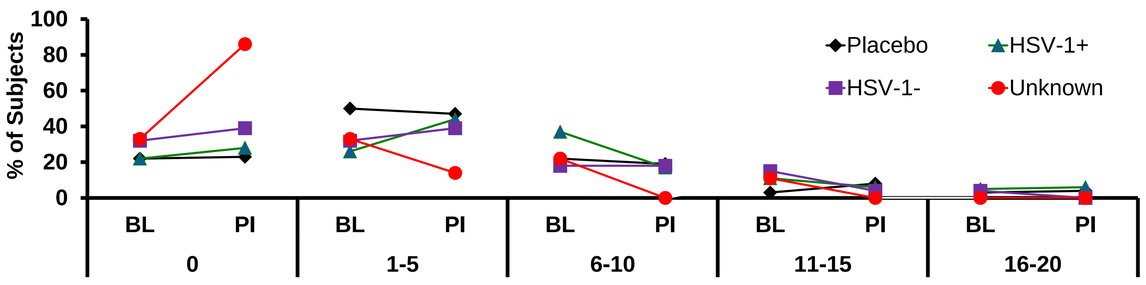
For methods see Figure 1. A) The frequency of days with swabs positive for HSV-2 DNA for placebo and subjects receiving active doses of GEN-003: either all subjects, or subjects categorized by HSV-1 serostatus (pos, neg, unk). B) The change from baseline calculated for the data set shown in Panel A. Data are shown as the mean ± SEM. The data were similar if analyzed by days (as shown) or by swabs (not shown).

Figure 3. Asymptomatic HSV-2 Shedding: Similar Reductions Were Achieved for Both HSV-1 Positive and Negative Subjects



Viral shedding in the absence of lesions is defined as asymptomatic shedding. To determine if the frequency of asymptomatic shedding was also reduced independently of HSV-1 serostatus, the frequency of viral shedding on days when lesions were not self-reported by the trial participant was calculated. Each symbol represents the viral shedding for an individual at baseline (circles) and post-immunization (squares). In the HSV-1 negative subjects, 14 of 28 (50%) had a reduction from baseline as compared to 12 of 19 (63%) in the HSV-1 positive cohort.

Figure 4. The Number of Days with HSV-2 DNA Present Were Changed Similarly Between HSV-1 Seropositive and Seronegative Subjects



Number of Days with Shedding Detected BL= Baseline PI= Post-immunization

To determine if vaccination with GEN-003 altered the number of days with HSV-2 DNA present on swabs,, the frequency of subjects with DNA detected on swabs between zero and 20 days were calculated (in increments of five). On average, the frequency of immunized subjects that had HSV-2 DNA present between zero and five days increased; and those with DNA present between 6 and 20 days decreased or remained constant.

Conclusions

- GEN-003 is an effective vaccine in both HSV-1 seronegative and seropositive HSV-2-infected individuals.
- There is a trend toward increased HSV-2 shedding at baseline in HSV-1 seropositive subjects, but it is not statistically different than in seronegative subjects.
- Both overall and asymptomatic HSV-2 shedding rates were reduced similarly in HSV-1 seropositive and seronegative subjects.
- The number of days shedding were consistently impacted by vaccination, irrespective of HSV-1 serostatus.