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Effect of an immune enhancer, GPI-0100, on vaccination with live attenuated herpes simplex virus (HSV) type 2 or glycoprotein D on genital HSV-2 infections of guinea pigs

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Abstract

These studies were performed to determine the effect of AD-472, an attenuated human herpes simplex virus (HSV) type 2 or HSV-2 glycoprotein D (gD) when combined with an adjuvant, GPI-0100, a semi-synthetic Quillaja Saponin analog in a genital HSV-2 infection in guinea pigs. While animals immunized with either vaccine had reduced clinical disease, GPI-0100 only improved the efficacy of gD and did not affect the efficacy of the live vaccine. Neither vaccine had any therapeutic effect if administered 24h after viral infection.

Keywords

Herpes; Vaccine; HSV-2; gD2; AD-472; Guinea pigs; GPI-0100

As previously reported, successful immunization using GPI-0100, a semi-synthetic Quillaja Saponin analog, as an adjuvant, with HSV-1 glycoprotein D (gD) protected against lethal systemic infections of HSV-1 in SKH-1 mice and against clinical disease in a genital HSV-2 infection in guinea pigs (Quenelle et al., 2006). In addition, a report of the successful immunization using AD-472, a modified live HSV-2 vaccine has shown that guinea pigs had significant improvement in clinical disease when immunized prior to vaginal viral challenge with HSV-2 (Prichard et al., 2005). Studies presented here investigated the potential of enhanced protection using the adjuvant GPI-0100 with the live vaccine virus, AD-472, in an HSV-2 genital disease in guinea pigs.

Female Hartley guinea pigs were infected intravaginally with HSV-2 strain G as described previously (Prichard et al., 2005; Quenelle et al., 2006). For the prophylactic study, guinea pigs were immunized every other week for a total of three intramuscular injections at 65, 45 and 24 days prior to challenge. For the therapeutic study, guinea pigs were infected and then vaccinated intramuscularly once at 24h post-viral inoculation. Viral titers and external genital lesions scores were recorded as described previously (Prichard et al., 2005; Quenelle et al., 2006). A *P*-value of 0.05 or less was considered to be statistically significant.

Lesion-day area under the curve (AUC) values and mean peak lesion scores were reduced significantly ($P = 0.001$) for guinea pigs which received AD-472 alone, AD-472 with GPI-0100, HSV-2 gD with GPI-0100 or HSV-2 gD alone prophylactically (Table 1). The AUC values for those groups ranged from 2.3 to 6.5, whereas the vehicle control group had a value of 25. The guinea pigs that received AD-472 alone, AD-472 with GPI-0100, HSV-2 gD with GPI-0100 or HSV-2 gD alone had mean peak lesion scores of 0.3 to 1.0, while the vehicle control had a mean peak lesion score of 3.9. The lesion virus titers were reduced significantly in animals immunized with AD-472 only or HSV-2 gD with GPI-0100 with titer-day AUC values of 6.7 or 5.2, respectively ($P = 0.05$) and mean peak titers of 2.0 or 1.3 ($P = 0.05$, Table 2). Also, the mean peak titer of 1.9 for guinea pigs immunized with HSV-2 gD alone was reduced significantly ($P < 0.05$) when compared to vehicle controls.

In order to determine if infected animals could benefit from therapeutic immunization, animals were vaccinated 24 h following infection with the same regimens used above. Unfortunately, there was no therapeutic effect from post-infection immunization with AD-472, HSV-2 gD with or without GPI-0100 on clinical disease or virus titers in guinea pigs infected vaginally with HSV-2 (data not shown).

When administered prior to vaginal infections, AD-472 alone proved effective in reducing clinical disease, genital virus shedding and virus shedding from genital lesions, but not in reducing infection rates or in eliminating latency or recurrent disease. These results confirm that AD-472 is capable of reducing the disease burden, but GPI-0100 did not appear to enhance its efficacy. It is possible that other vaccination strategies involving GPI-0100 and live virus vaccine could be developed, although the replication of the attenuated virus may be sufficient to elicit a Th-1 response without the use of adjuvant.

By contrast, GPI-0100 did improve the efficacy of the gD vaccine and was expected given its previously reported activity as an adjuvant (Quenelle et al., 2006). Although animals remained susceptible to infection, yet clinical disease was significantly reduced and virus titers recovered from lesions were also significantly lower. While this effect was most apparent in reducing lesion virus titers, it also reduced the lesion-day AUC and mean peak lesion score to levels that were similar to the live virus vaccine, without the potential safety concerns.

In these studies, therapeutic immunizations given 24 h after vaginal virus infections were unsuccessful in reducing clinical disease regardless of antigen or adjuvant given, although this may be a difficult goal to achieve. Even naturally acquired infection is incompletely protective against re-infection with either virus type. To date, one subunit vaccine has shown a slight reduction in the number of episodes of recurrent clinical disease in those persons already infected with HSV-2 (Straus et al., 1994). Another study has documented some protection only for HSV seronegative women regarding protection from infection; however neither men nor HSV-1 seropositive women were protected (Stanberry et al., 2002). It is plausible that high levels of HSV-2 antigen specific secretory antibody and T-cells in the female genital mucosal secretions conferred protection against infection. Abrasions in the stratified squamous epithelial surface of male genitalia are the primary means of infectious transmission of HSV-2, and non-mucosal surface may be more difficult to protect immunologically (Stanberry and Rosenthal, 2005). Clearly further work is needed to provide protective immunity for naïve individuals or to enhance immunity for those patients already infected.

The results from these studies suggest that both AD-472 and GPI-0100 hold promise as components of immunogenic preparations for use against human HSV-2 disease.

Specifically targeting mucosal surfaces with these agents may further enhance mucosal immunity, particularly for women.

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Table 1
Effect of prophylactic immunization with AD-472 or HSV-2 gD combined with GPI-0100 on lesion scores in an HSV-2 genital herpes infection of guinea pigs

Immunization ^a	# With lesions/#inoculated	Lesion-day AUC	P-Value	Mean peak lesion score (±S.D.)	P-Value
Vehicle only	14/15	25.0	–	3.9 ± 1.5	–
GPI-0100 (200 µg) only	12/15	22.8	NS ^b	3.4 ± 1.9	NS
AD-472 (1×10^5 PFU/ml) ± GPI-0100 (200 µg)	11/15	3.6	<0.001	0.8 ± 0.65	<0.001
AD-472 (1×10^5 PFU/ml) only	6/15	2.3	<0.001	0.4 ± 0.51	<0.001
HSV-2 gD (20 µg) ± GPI-0100 (200 µg)	4/14	2.3	<0.001	0.3 ± 0.5	<0.001
HSV-2 gD (20 µg) only	12/15	6.5	<0.001	1.0 ± 0.58	<0.001

^aImmunizations were delivered i.m. in 0.2ml doses on days 65, 45, and 24, then guinea pigs were challenged with 3×10^6 PFU/ml of HSV-2 (G strain) on day 0.

^bNS = not significant when compared to the vehicle using Mann-Whitney U/Rank Sum Test with $P < 0.05$ considered significant.

Table 2
Effect of prophylactic immunization with AD-472 or HSV-2 gD combined with GPI-0100 on lesion virus titers in an HSV-2 genital herpes infection of guinea pigs

Immunization ^a	#Virus positive/#inoculated	Titer-day AUC	P-Value	Mean peak titer $\pm$ S.D. ^b	P-Value
Vehicle only	14/15	14.5	–	3.4 $\pm$ 0.7	–
GPI-0100 (200 μ g) only	11/15	13.9	NS ^c	3.3 $\pm$ 0.3	NS
AD-472 (1×10^5 PFU/ml) $\pm$ GPI-0100 (200 μ g)	5/15	10.1	NS	2.3 $\pm$ 1.1	NS
AD-472 (1×10^5 PFU/ml) only	4/15	6.7	<0.05	2.0 $\pm$ 0.8	<0.05
HSV-2 gD (20 μ g) $\pm$ GPI-0100 (200 μ g)	3/14	5.2	<0.01	1.3 $\pm$ 0.1	<0.01
HSV-2 gD (20 μ g) only	10/15	6.9	NS	1.9 $\pm$ 1.0	<0.05

^aImmunizations were delivered i.m. in 0.2ml doses on days 65, 45, and 24, then guinea pigs were challenged with 3×10^6 PFU/ml of HSV-2, G on day 0.

^bTiter (Log₁₀ CCID₅₀/ml) $\pm$ standard deviation.

^cNS = not significant when compared to the vehicle using Mann–Whitney U/Rank Sum Test with $P < 0.05$ considered significant.