

Episodic Treatment with Topical ACV/Hydrocortisone Prevents Cold Sores: A Randomized, Double-Blind, Patient-Initiated Clinical Trial

C. HULL¹, J. HARMENBERG², E. ARLANDER³, F. AOKI⁴, B. DARPO³, M. LEVIN⁵, S. TYRING⁶, S. L. SPRUANCE¹

¹Univ. of Utah Sch. of Med., Salt Lake City, UT, ²Karolinska Inst., Stockholm, Sweden, ³Medivir, Huddinge, Sweden, ⁴Univ. of Manitoba, Winnipeg, Canada, ⁵Univ. of Colorado Sch. of Med., Aurora, CO, ⁶Univ. of Texas Health.Sci. Ctr., Houston, TX

Background

The pathogenesis of recurrent herpes simplex labialis (HSL) involves both the destruction of cells by the virus, and the host immune response. Current approved antiviral medications provide modest reduction of lesion healing time through limitation of the virus replication, but has little impact on the associated inflammatory cascade (1-4).

The objective of the present Phase 3 clinical trial was to evaluate the efficacy and safety of ME-609, which contains 5% acyclovir and 1% hydrocortisone in a proprietary formulation in patients with recurrent HSL.

Materials and Methods

This randomized, double blinded study was conducted at 51 sites in US and 4 sites in Canada from July 2006 to December 2007. Written informed consent was obtained from all study subjects and an Institutional Review Board approved the study protocol. Subjects at least 18 years of age with a history of at least 3 HSL episodes in the past year were randomized to ME-609 (n=1018), acyclovir in the ME-609 vehicle (n=1033) or placebo (the vehicle; n=386).

Subjects were asked to start treatment at home 5 times daily for 5 days at the earliest sign/symptoms of their next HSL recurrence. Subject diary and daily clinical visits were used for safety and efficacy data collection. Secondary herpes recurrences were recorded and viral swabs collected.

The primary study endpoint was prevention of ulcerative lesions (aborted episodes that did not progress beyond the papule stage).

Secondary endpoints included ulcerative lesion:

- i) episode duration to loss of hard crust
- ii) lesion healing time to normal skin
- iii) lesion area

iii) cumulative lesion area, a global endpoint that combines drug effects on lesion type, lesion duration and lesion area and for which non-ulcerative (aborted) lesions were assigned a value of zero (5).

Results

The proportion of subjects with **non-ulcerative recurrences (aborted lesions)** was higher in the ME-609 group (254/601 = 42%) compared to the acyclovir (216/610 = 35%; p=0.014) and the placebo groups (60/232 = 26%; p<0.0001), independent of at what treatment stage subjects started treatment (Figure 1).

In subjects who developed an ulcerative lesion despite treatment, the mean **episode duration** and **lesion healing time** were significantly shorter in ME-609 treated subjects than in placebo subjects (Table 1).

The **maximum lesion area** was smallest in the ME-609 group but the differences were not statistically significant (Table 1). For the **cumulative lesion area** was reduced by half in the ME-609 group compared to placebo and was significantly smaller than in both the acyclovir and placebo groups (Table 1 and Figure 2).

Table 1.

| | ME-609 n=601 | Acyclovir in ME-609 vehicle n=610 | Placebo n=232 |
|--|-----------------|--|-----------------------|
| Subjects with non-ulcerative recurrences (%) p-value vs. ME-609 | 254 (42%) | 216 (35%) p=0.014 | 60 (26%) p<0.0001 |
| Ulcerative lesion episode duration, days, mean (SD) | 5.7 (2.8) | 5.9 (2.6) p=0.365 | 6.5 (3.3) p=0.008 |
| Ulcerative lesion time to lesion healing, days, mean (SD) | 9.6 (3.7) | 9.9 (4.3) p=0.297 | 11.0 (5.7) p<0.001 |
| Ulcerative lesion Max. lesion area mm ² , mean | 41 | 42 p=0.75 | 50 p=0.22 |
| Cumulative lesion area, mm ² , mean | 78 | 105 p=0.014 | 155 p<0.001 |

Results

Figure 1. The frequency of aborted lesions in relation to stage at start of treatment.

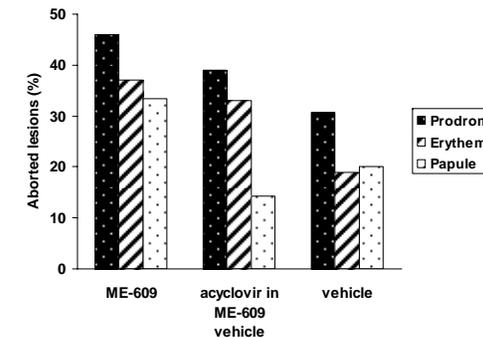
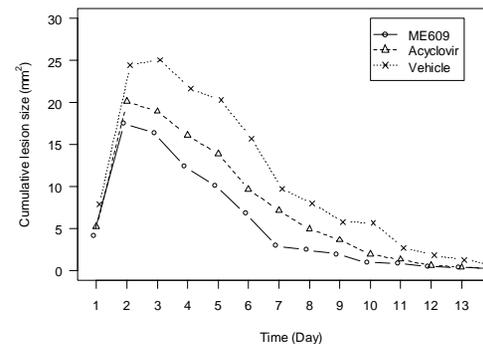


Figure 2. The mean cumulative lesion size.



The frequency of secondary herpes recurrences were 5%, 7% and 7% in ME-609, acyclovir and placebo groups. 22%, 24% and 40% of subjects had positive viral cultures in ME-609, acyclovir and placebo groups. The frequency and nature of adverse events were similar between the treatments.

Conclusions

- ME-609 prevented ulcerated lesions in subjects with recurrent HSL compared to both topical acyclovir and placebo.
- In subjects who developed an ulcerative lesion despite treatment, the healing time was reduced by ME-609 to the same extent as acyclovir alone.
- The cumulative lesion area, a global endpoint that also incorporates the preventive effect on ulcerative lesions, was reduced by half in the ME-609 group compared to placebo and was significantly smaller than in both the acyclovir and placebo groups.

ME-609 was approved for marketing in United States on July 31, 2009 with the following indication:

"ME-609 is indicated for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time"

References

1. Spruance SL. The natural history of recurrent oral-facial herpes simplex virus infection. *Seminars Dermatology* 1992;11:200-20
2. Spruance SL and McKeough MB. Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet radiation-induced herpes simplex labialis. A pilot study. *J Infect Dis* 2000;181:1906-1910.
3. Evans TG, Bernstein DI, Raborn GW, Harmenberg J, Kowalski J, and Spruance SL. Double-blind, randomized, placebo controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced herpes simplex labialis. *Antimicrob Agts Chemother* 2002;46:1870-1874
4. Spruance SL, Kriesel JD. Treatment of herpes simplex labialis. *Herpes*. 2002;9:64-69.
5. Hull C, McKeough M, Sebastian K, Kriesel J, Spruance S. Valacyclovir and topical clobetasol gel for the episodic treatment of herpes labialis: a patient-initiated, double-blind, placebo-controlled pilot trial. *J Eur Acad Dermatol Venereol*. 2009 Mar;23(3):263-7.