Double-Blind, Randomized, Placebo-Controlled Study of Topical 5% Acyclovir–1% Hydrocortisone Cream (ME-609) for Treatment of UV Radiation-Induced Herpes Labialis

T. G. Evans,^{1,*} D. I. Bernstein,² G. W. Raborn,³ J. Harmenberg,^{4,5} J. Kowalski,^{4,5} and S. L. Spruance⁶

University of Rochester, Rochester, New York¹; Children's Hospital Research Foundation, Cincinnati, Ohio²; University of Alberta, Edmonton, Alberta, Canada³; Medivir AB, Huddinge,⁴ and Karolinska Institute, Stockholm,⁵ Sweden; and University of Utah, Salt Lake City, Utah⁶

Received 12 November 2001/Returned for modification 4 January 2002/Accepted 14 March 2002

Immunopathology is recognized as an important component of infectious disease manifestations, and corticosteroids have been used as an adjunct to antimicrobial therapy for a variety of conditions. Antiviral therapy of herpes labialis has been shown to result in only a small reduction in the time to healing and the duration of pain. To determine if topical application of a combination product containing 5% acyclovir and 1% hydrocortisone (ME-609) could provide benefit to herpes labialis patients, 380 immunocompetent adults with a history of herpes labialis were exposed to experimental UV radiation (UVR) to induce a recurrence. On day 2, just before the appearance of the majority of lesions ("delayed" lesions), subjects were randomized to receive active medication or vehicle control six times per day for 5 days. Overall, 120 of 380 patients developed delayed classical lesions, of whom 50 of 190 (26%) had been treated with ME-609 and 70 of 190 (37%) had received placebo (a reduction of 29% [$P = 0.02$]). Healing time, measured as the time to normal skin, was reduced by treatment with ME-609 (9.0 days for treated patients versus 10.1 days for the controls [$P = 0.04$]). There was a trend toward a reduction in the maximum lesion size in the ME-609 recipients compared to that in the controls (43 versus 60 mm², respectively [$P = 0.07$]). The treatment had no effect on lesion pain, but ME-609 treatment reduced the number of patients with moderate or severe tenderness. Compared to treatment with a placebo, treatment with the combination antiviral-immunomodulatory cream provided benefit to patients with experimental UVR-induced herpes labialis, reducing classical lesion incidence, healing time, lesion size, and lesion tenderness. ME-609 is a novel product that merits further evaluation as a treatment for cold sores.

Treatment of herpes simplex virus (HSV) infections with antiviral drugs has been a major challenge for investigators for more than 30 years. The benefits of treatment of recurrent HSV infection have been modest in contrast to the benefits of treatment of primary infection. The main clinical benefit in the treatment of recurrences has been the modest reduction in lesion healing time of approximately 10 to 15% (5, 10). Recurrent disease differs from the primary episode in that the virus is cleared much more rapidly, usually within 3 days or less. Although the immune response is quicker and more effective in controlling recurrent disease, it also may be responsible for most of the clinical symptoms, which persist for up to a week after the virus can no longer be isolated (6, 9). Thus, a combined modality of therapy aimed at both an antiviral effect and an immunomodulatory effect has been proposed in a number of studies (1, 9).

The availability of a small-animal model for evaluation of the effects of treatment on the severity of recurrent lesions has been a limiting factor in evaluations of therapy. A novel animal model of recurrent HSV disease was recently developed by the use of zosteriform HSV infection in mice combined with adoptive transfer of immunity (1). This model mimics both the clinical parameters of reactivated HSV infection and the ef-

fects of antiviral treatment. Using this model, Awan et al. (1, 2) evaluated many combinations of antiviral agents and immunomodulators. In those studies, the combination of 5% acyclovir and 1% hydrocortisone in a topical cream (referred to as ME-609) was shown to be optimal.

Multiple parameters have been used to assess herpes labialis lesions (3, 5, 8, 9). These include the incidence of lesions, the proportion of aborted lesions (lesions that do not develop beyond the initial phase of a lesion with edema and redness, known as the papule stage), the maximal lesion area, the degree of pain, and the time to healing (measured as the time to the complete loss of a hard crust or the time to normal skin). No previously published trials of episodic treatment of humans have shown a consistent influence of antiviral therapy on the incidence of lesions or the proportion of aborted lesions.

The objective of the present clinical trial was to provide a proof of concept as to whether a combination of an antiviral agent with an immunomodulatory agent can provide benefits to patients with recurrent HSV infections. To carefully control patient self-medication and lesion severity assessments, we exposed patients with a history of recurrent herpes labialis to experimental UV radiation (UVR) and treated the induced recurrences (7).

MATERIALS AND METHODS

Study medication. The clinical trial material consisted of 5% acyclovir and 1% hydrocortisone (ME-609) or a placebo. The appearances of the two creams were

* Corresponding author. Present address: Division of Infectious Diseases, University of California, Davis, 4150 V St., PSSB 500, Sacramento, CA. Phone: (916) 734-3741. Fax: (916) 734-7766. E-mail: tgevens@ucdavis.edu.

similar. Both creams were produced and packed in identical plastic containers by CCS, Borlänge, Sweden.

Patient population. The study was conducted at four major university clinics in North America. To be eligible, patients had to be ≥ 18 years of age and had to have a history of recurrent herpes labialis after exposure to sunlight in the previous 12 months or to have had two or more cold sores in the previous 12 months. In addition, women of childbearing age had a documented negative pregnancy test and used an acceptable method of birth control. All patients were generally healthy, had a Fitzpatrick skin type category of 1 to 4, and signed an informed consent form approved by the local institutional review board. The patient could not have participated in any herpes UVR reactivation study within the previous 3 months or have had an episode of herpes labialis within 30 days before enrollment in the study.

MED determination and UVR exposure. At the screening visit, the patient's sensitivity to UVR was evaluated by determination of the minimal erythema dose (MED), as described previously (8). In short, the forearm is irradiated with a FS20 T12 sunlamp (National Biologic Corp., Twinsburg, Ohio) at a distance of 19 cm for 1, 2, 3, 4, 5, or 6 min. The power at the irradiation site was measured with a handheld meter and averaged approximately 1 mW/cm²; the power did not differ between the two treatment groups. Patients who did not develop a reaction following 6 min of exposure were excluded from further study. The lips of the patients were exposed to UVR (study day 0) within 7 days of the initial reading. The half of the lips (either the lower lip, the upper lip, or the right or left portions of both the lower and upper lips) that was regarded as the usual site of recurrence was exposed to UVR as described above for a duration four times the MED, as described previously (3, 8, 11). The remainder of the lips and the perioral skin outside this zone were covered with a *para*-aminobenzoic acid-containing sunscreen with a sun protection factor of at least 30.

Study procedure and lesion evaluation. After the screening history, local examination, pregnancy test, signing of the informed consent, and MED determination, eligible patients were randomized 1:1 to the two treatment groups without stratification. The containers were dispensed by study personnel such that neither the patients nor the investigators were aware of the treatment assignments. On the morning of the second day after UVR exposure, patients were instructed to apply the study medication (ME-609 or the corresponding placebo) six times daily for 5 days to the whole area that was exposed to UVR. If patients developed a lesion, treatment was continued until healing (complete loss of the hard crust) or for a maximum of 5 days. Patients returned to the clinic on study day 1, 3, 7 or 8, and 15 and were evaluated for the development of lesions. "Immediate lesions" were defined as those that arose within 2 days of UVR, and "delayed lesions" were those that occurred 2 to 7 days after exposure to UVR. Immediate lesions are of uncertain etiology and pathophysiology and have not responded to antiviral drugs in previous studies (3, 7, 11). Therefore, only lesions that developed during the 2- to 7-day period following UVR exposure (delayed lesions) were evaluated. If a lesion that was deemed to be due to HSV developed, the patients were monitored daily until crusting of the lesion or the development of a hard crust and then every second day thereafter until the return of normal skin.

The first delayed lesion to develop was defined as the study lesion. Lesions other than the study lesion and other changes in the status of the skin or lip were noted but were not monitored in the present study. Only one lesion per patient was thus included in the evaluation presented here. Lesions were further categorized as aborted (those that did not progress beyond the papule stage) or classical (those that progressed to vesicles, ulcers, or hard-crust stages or a combination of such stages).

During the study the patients were instructed to record on patient diary cards lesion stage, the presence or absence of pain and tenderness, and the severity of pain and tenderness three times daily. Clinical assessment of lesion severity was performed by the investigator after the patient was consulted and included observations of lesion stage, measurement of the lesion area (defined as the product of the length and the width), and assessment of pain and tenderness. Lesion stages were prodrome, erythema, papule, vesicle, ulcer or soft crust, hard crust, residual swelling or dry flaking, and normal skin, as described previously (7, 11). Two predefined definitions of healing were used: return to normal skin and loss of a hard crust. Pain and tenderness were recorded as mild, moderate, or severe. The duration of pain and tenderness was recorded from its first occurrence until its first recorded permanent absence. Tenderness was defined as unpleasant effects upon touching the affected region, while pain was used to describe the global unprovoked soreness. The patients were also asked to assess whether the current episode was better, the same, or worse than their usual recurrences.

Virus isolation. Specimens of the lesions for virus isolation were obtained during the vesicle and ulcer stages through the use of cotton swabs. The speci-

TABLE 1. Patient disposition and type of developed lesion

Patient disposition	No. of patients		
	ME-609 group	Placebo group	All
Randomized	209	208	417
Not exposed to UVR	19	18	37
Safety population	190	190	380
Did not develop lesion	123	112	235
ITT population	67	78	145
Delayed classical lesions	50	70	120
Delayed aborted lesions	3	1	4
Immediate lesions	14	7	21

mens were processed as described elsewhere (3). In short, the swabs were immediately placed into viral transport medium, inoculated onto tissue cultures at each study site, and observed for at least 7 days for evidence of a cytopathic effect.

Data analysis. The population of interest was the patients who developed delayed classical lesions. The lesion variables examined included development of delayed classical lesions, time to healing (defined as the time to the loss of a hard crust or the time to normal skin), maximum lesion area, pain, tenderness, duration of individual lesion stages including aborted lesions that did not progress past the papule stage, positive virus cultures, and patient assessment.

The time to the loss of a hard crust and the time to normal skin were analyzed by analysis of variance by adjusting for differences between study sites with log-transformed (*e*-log) data. Censored data were not observed in this analysis. The following other variables were also analyzed by analysis of variance, adjusting for differences between study sites: time to normal skin on square root-transformed data, maximum lesion size, and duration of pain and duration of tenderness with log-transformed (*e*-log) data. The incidence of delayed classical lesions, the frequency of pain, and the frequency of tenderness were analyzed by logistic regression. The severity of tenderness, the severity of pain, and the patient's opinion of the lesion were analyzed by use of a logit model. The transformation of all variables was followed by a check for the normality of the data. All tests were two sided, with significance being a *P* value of 0.05. The statistical analysis software used was STATISTICA (version 5.5; StatSoft Inc., Tulsa, Okla.).

RESULTS

Characteristics of the study population. In total, 417 patients were enrolled in the study. Thirty-seven patients underwent evaluation for determination of the MED but were not subsequently exposed to UVR (mainly due to failed determination of the MED) and thus were not treated with the study medication. A total of 380 patients were exposed to UVR and treated with at least one dose of study medication (safety population) (Table 1). A total of 145 (38.2%) of these patients developed a lesion. Twenty-one of the 145 patients (14.5%) developed lesions immediately before the start of administration of the study medication. These lesions were noted but were not monitored. One hundred twenty patients (31.6%) developed delayed classical lesions (intent-to-treat [ITT] population). All data shown are derived from the ITT population. Evaluation of the per-protocol population revealed similar results.

Overall, 80% of the patients were females. The average age was 39 years (age range, 18 to 76 years), and the mean number of herpes labialis episodes per year prior to the study was 5.3. The average duration of UVR exposure was 13 min (range, 4

FIG. 1. Start of lesions shown as time from UVR exposure in patients developing classical lesions, per treatment group. Day zero includes the first 24 h following UVR exposure. □, ME-609; ■, placebo.

to 24 min) in the two treatment groups. There were no notable differences between the two treatment groups.

Development and evaluation of lesions. Only 50 of 190 patients (26%) developed delayed classical lesions (lesions that developed between 46 h and 7 days following UVR exposure) during treatment with ME-609, whereas 70 of 190 patients (37%) treated with placebo cream developed delayed classical lesions, a reduction of 29% ($P = 0.022$). In addition, three patients in the ME-609 group and one patient in the placebo group experienced delayed lesions that did not progress beyond the papule stage (delayed aborted lesion). As shown in Fig. 1, 101 of the 120 patients in the study (84%) with delayed classical lesions exhibited lesions that appeared on the first or second day after the initiation of therapy (2 to 3 days after UVR exposure). Only 17 patients treated with ME-609 reported the occurrence of a delayed classical lesion during the first day of treatment, whereas 40 patients treated with placebo reported the occurrence of a delayed classical lesion during the first day of treatment, a reduction of 58%. The reduction in the incidence of a delayed classical lesion during the first day of treatment with ME-609 thus explains the overall reduction of incidence in the entire study.

The 50 patients in the ME-609 treatment group who devel-

FIG. 2. The Kaplan-Meier curve (ITT population) for time to normal skin in patients with delayed classical lesions, per treatment group. Cum. prop., cumulative proportion; thick line, ME-609; thin line, placebo.

oped delayed classical lesions had a median time to healing to normal skin of 9.0 days, whereas the time was 10.1 days ($P = 0.037$) for the 70 placebo-treated patients who developed delayed classical lesions (Table 2). Similarly, the healing time measured as the time to the loss of the hard crust was reduced 19% by ME-609 treatment, from 6.8 to 5.4 days, although this reduction did not reach statistical significance ($P = 0.084$). The Kaplan-Meier curves of time to normal skin are shown in Fig. 2.

ME-609 treatment also reduced the median maximal lesion area of the delayed classical lesions by 28% ($P = 0.072$). The mean durations of the lesion stages in patients with delayed classical lesions are shown in Fig. 3. The major effect of ME-609 treatment was on the vesicle and crusting stage, whose durations were reduced by a total of 1.6 days (25%) compared with the durations in patients who received the placebo treatment.

The present study is the first study of herpes labialis to divide unpleasant sensations into pain, which was an overall measure of unprovoked soreness, and tenderness, which described unpleasantness upon touch of the region of a lesion. Pain was evaluated as the proportion of patients who developed classical delayed lesions and who reported pain. In addition, the severity of pain and the duration of pain were also studied. No statistically significant treatment effects with respect to pain were observed in the study. Eighty-one percent of placebo recipients and 76% of those receiving ME-609 developed pain. Moderate pain developed in 26 and 36% of the placebo and

TABLE 2. Treatment effects (ITT population) with respect to development of delayed classical lesions and all lesions

Variable	ME-609 group	Placebo group	Improvement (%)	P value
Incidence of delayed classical lesions (no. of patients with lesions/total no. evaluated)	50/190	70/190	28.6 (1.69 ^a)	0.022
Median time to loss of hard crust (days [range])	5.4 (1.6–13.2)	6.8 (1.9–19.6)	19.2	0.084
Median time to normal skin (days [range])	9.0 (4.0–19.1)	10.1 (1.9–24.3)	11.2	0.037
Median maximum lesion area (mm ² [range])	43.5 (6–450)	60.0 (4–364)	27.5	0.072

^a Odds ratio.

FIG. 3. Median durations of lesion stages in patients (ITT population) with delayed classical lesions. The papule stage (■) is the time from the start of a lesion (papule) to the time of observation of the first vesicle. The vesicle stage (▤) is the time of observation of the first vesicle to the time of the first sign of crusting. The crusting stage (▥) is the time from the first sign of crusting to the time of the loss of the hard crust. The healing stage (□) is the time from the loss of the hard crust to normal skin.

the ME-609 groups, respectively, and severe pain developed in 11 and 4% of the placebo and the ME-609 groups, respectively.

Forty-two of the patients who were treated with ME-609 and who developed delayed classical lesions experienced tenderness, whereas 65 patients who were in the control group and who developed delayed classical lesions experienced tenderness (odds ratio, 2.94; $P = 0.11$) (Table 3). In addition, only 18 of the ME-609-treated patients experienced tenderness of moderate or severe intensity, whereas 38 patients in the placebo group experienced tenderness of moderate or severe intensity. The overall severity of tenderness was reduced by an odds ratio of 2.33 ($P = 0.018$). In addition, there was a trend toward a reduction in the median duration of tenderness in the ME-609-treated patients from 5.0 to 4.0 days ($P = 0.078$). Only

8 of the ME-609-treated patients who developed delayed classical lesions graded their current episode as "worse than their usual recurrences," whereas 24 patients in the placebo group gave their lesions such a grade. The overall patient opinion of the current episode was more favorable for the patients treated with ME-609 than for those treated with placebo, with an odds ratio of 2.78 ($P = 0.006$) (Table 3).

Virologic evaluations. Viral swabs from 34 of 49 (69%) ME-609-treated patients with delayed classical lesions and 54 of 70 (77%) of the placebo-treated patients with delayed classical lesions were positive for virus isolation at least once (P was not significant). The times to cessation of viral shedding were similar for both groups (data not shown).

Adverse events. The incidence and nature of adverse events were similar for both treatment groups. The treatment was well tolerated, and there were no serious adverse events.

DISCUSSION

A large number of individuals suffer from recurrent herpes labialis and seek treatment. A wide variety of treatment modalities have been used, including pain relievers, antivirals, moisturizers, or combinations of these agents. Therapy with topical acyclovir ointment alone has little to no benefit in the treatment of recurrent cold sores. Topical penciclovir cream and acyclovir cream have been shown to reduce the time to healing by less than 1 day (4, 10).

The signs and symptoms of herpes labialis are in part due to the inflammatory response that ensues following viral reactivation. Accordingly, combination therapy with drugs with immunomodulatory properties such as topical corticosteroids along with antiviral agents may have added clinical benefit compared to the use of antivirals alone. In the study reported here we have shown that the combination of an antiviral and an immunomodulatory cream (ME-609) reduced the severity of experimental UVR-induced herpes labialis, as defined by classical lesion incidence, healing time, lesion size, and lesion tenderness. In the present study, the incidence of delayed classical lesions was reduced by 29% when the ME-609 combination treatment was used compared with the incidence with the use of a placebo. Numerous previous studies have clearly shown that episodic treatment with antiviral drugs alone does not influence the incidence of the classical and aborted lesions that develop (3, 5, 8, 10, 11).

The prevention of classical cold sores was achieved in a clinical model of viral reactivation in which treatment was given from the morning of the second day following the UVR exposure, at a time just prior to the onset of the majority of lesions induced in this model. The events that follow UVR exposure and that lead to reactivation of virus in the trigeminal nerve are rapid (within hours in animal models), and treatment started on the morning of the second day would be unlikely to affect these early events. Treatment starting on the morning of the second day after UVR exposure may correspond to very early episodic treatment, similar to therapy initiated for the treatment of naturally occurring lesions during the prodromal symptom phase of disease.

The use of the antiviral properties of acyclovir in combination with the immunomodulatory properties of hydrocortisone in the treatment of recurrent HSV disease is a novel concept

TABLE 3. Treatment effects (ITT population) of secondary parameters with respect to delayed classical lesions

Variable	ME-609 group	Placebo group	Odds ratio	P value
No. of patients experiencing tenderness	42	65	2.94	0.110
Severity of tenderness (no. of patients)				
None	8	5		
Mild	24	27		
Moderate	14	29	2.33	0.018
Severe	4	9		
Patient opinion of the episode (no. of patients)				
Better than usual	32	29		
Same as usual	9	17	2.78	0.006
Worse than usual	8	24		

previously tested in a smaller pilot study (9). That study differs from the one reported here in terms of both the medications used and the timing of treatment. Spruance and McKeough (9) exposed 49 patients to UVR in order to induce herpes labialis. All patients were instructed to start treatment with study drugs for 5 days at the first sign or symptom of a recurrence and received high-dose famciclovir (500 mg three times daily orally) in conjunction with either a potent corticosteroid cream (0.05% Lidex gel three times daily) or a placebo cream. Because treatment was initiated at the start of the occurrence of a lesion in the pilot study, the incidence of recurrences could, by definition, not be altered by treatment. The most beneficial outcome in that study was an aborted lesion, which is a lesion that does not progress to the typical lesion stages of classical herpes labialis (vesicle, ulcer, crust). The investigators found that 41% of the patients treated with the combination therapy developed aborted lesions, whereas 8% of the patients in the arm that received famciclovir only developed aborted lesions. The results of the present study together with the results of the pilot study indicate that as many as one-third of the patients with herpes labialis have episodes that may be prevented or aborted by combination therapy.

The combination treatment (ME-609) used in our study reduced the healing times for the 50 patients who developed delayed classical lesions approximately 11 to 19% compared with the healing times for the 70 placebo-treated patients. In addition to the benefit provided by the 29% decrease in the incidence of delayed classical lesions, ME-609 thus also reduced the healing times and maximal lesion sizes in the patients who did develop lesions, notwithstanding treatment. The reduction in healing times found in the present study is similar to the reduction in healing times found in large-scale field trials of the treatment of herpes labialis with topical formulations of antiviral compounds such as acyclovir and penciclovir (4, 10). Corticosteroids would not be expected to accelerate wound healing, and indeed, this was the outcome in both the present study and the pilot study with famciclovir-corticosteroid cream

(Lidex gel). The results of efficacy in a presumptive treatment trial with the UVR model do not necessarily imply efficacy in a natural history study. Nevertheless, because of the promising results obtained with the UVR model described here, a study evaluating early treatment of naturally occurring recurrent herpes simplex infections is warranted.

REFERENCES

1. Awan, A. R., J. Harmenberg, O. Flink, and H. J. Field. 1998. Combinations of antiviral and anti-inflammatory preparations for the topical treatment of herpes simplex virus assessed using a murine zosteriform infection model. *Antivir. Chem. Chemother.* **9**:19–24.
2. Awan, A. R., J. Harmenberg, A. Kristofferson, and H. J. Field. 1998. Herpes simplex virus zosteriform lesions with adoptive transfer of immune cells: a murine model which mimics human recurrent disease. *Antivir. Res.* **38**:43–53.
3. Bernstein, D. I., C. J. Schleupner, T. G. Evans, D. A. Blumberg, Y. Bryson, K. Grafford, P. Broberg, S. Martin-Munley, and S. L. Spruance. 1997. Effect of foscarnet cream on experimental UV radiation-induced herpes labialis. *Antimicrob. Agents Chemother.* **41**:1961–1964.
4. Raborn, G. W., W. T. McGaw, M. Grace, and J. Percy. 1988. Treatment of herpes labialis with acyclovir. Review of three clinical trials. *Am. J. Med.* **85**:39–42.
5. Spruance, S. L. 1992. The natural history of recurrent oral-facial herpes simplex virus infection. *Semin. Dermatol.* **11**:200–206.
6. Spruance, S. L., T. G. Evans, M. B. McKeough, L. Thai, B. A. Araneo, R. A. Daynes, E. M. Mishkin, and A. S. Abramovitz. 1995. Th1/Th2-like immunity and resistance to herpes simplex labialis. *Antivir. Res.* **28**:39–55.
7. Spruance, S. L., D. J. Freeman, J. C. Stewart, M. B. McKeough, L. G. Wenerstrom, G. G. Krueger, M. W. Piepkorn, W. G. Stroop, and N. H. Rowe. 1991. The natural history of ultraviolet radiation-induced herpes simplex labialis and response to therapy with peroral and topical formulations of acyclovir. *J. Infect. Dis.* **163**:728–734.
8. Spruance, S. L., J. D. Kriesel, T. G. Evans, and M. B. McKeough. 1995. Susceptibility to herpes labialis following multiple experimental exposures to ultraviolet radiation. *Antivir. Res.* **28**:57–67.
9. Spruance, S. L., and M. B. McKeough. 2000. 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.* **181**:1906–1910.
10. Spruance, S. L., T. L. Rea, C. Thoming, R. Tucker, R. Saltzman, R. Boon, et al. 1997. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. *JAMA* **277**:1374–1379.
11. Spruance, S. L., N. H. Rowe, G. W. Raborn, E. A. Thibodeau, J. A. D'Ambrosio, and D. I. Bernstein. 1999. Peroral famciclovir in the treatment of experimental ultraviolet radiation-induced herpes simplex labialis: a double-blind, dose-ranging, placebo-controlled, multicenter trial. *J. Infect. Dis.* **179**:303–310.