

# Valacyclovir for Prevention of Recurrent Herpes Labialis: 2 Double-Blind, Placebo-Controlled Studies

David Baker, MD; Drove Eisen, MD, DDS

*The oral antiviral valacyclovir, which is 3 to 5 times more bioavailable than its parent compound acyclovir, is a good candidate for effective therapy to suppress recurrent herpes labialis lesions. The efficacy of oral valacyclovir in the suppression of herpes labialis has not previously been reported. Two identical, randomized, double-blind, parallel-group studies were conducted to evaluate the efficacy of oral valacyclovir 500 mg (n=49) versus placebo (n=49) once daily for 16 weeks in the suppression of herpes labialis among patients with a history of 4 or more recurrent lesions in the previous year. Data from the studies were pooled for analysis. Twenty-eight patients (60%) in the valacyclovir group compared with only 18 patients (38%) in the placebo group were recurrence-free throughout the 4-month treatment period (P=.041). The mean time to first recurrence was significantly longer with valacyclovir (13.1 weeks) compared with placebo (9.6 weeks)(P=.016). The total number of recurrences in patients using valacyclovir was 24 compared with 41 in patients using placebo. The incidence of adverse events during the*

*4-month treatment period was slightly lower in the valacyclovir group (22 events, 33% of patients) compared with the placebo group (29 events, 39% of patients). The results of these small double-blind, placebo-controlled studies suggest that oral valacyclovir 500 mg once daily for 4 months is effective and well tolerated for the prevention of recurrent herpes labialis. More research with larger patient numbers is warranted to corroborate and extend these findings.*

**R**ecurrent herpes labialis, or cold sores, affect approximately one third of the US population.<sup>1-4</sup> The frequency of recurrence among adults with herpes labialis varies from 1 to 12 episodes or more per year.<sup>5</sup> Several factors necessitate the treatment of recurrent herpes labialis lesions in some patients<sup>6</sup>: their frequency, duration, and/or painfulness; the disfigurement they cause; their interference with oral behaviors such as eating and speaking; and their psychosocial impact.

To date, oral acyclovir has been shown to be effective for the suppression of herpes labialis.<sup>7-9</sup> Oral valacyclovir, the leucine-valine ester prodrug of acyclovir, is 3 to 5 times more bioavailable than its parent compound.<sup>10,11</sup> For this reason, oral valacyclovir may be a good candidate for effective therapy for the episodic treatment and suppression of herpes labialis lesions.

## Methods

Men or women aged 18 years or older who tested seropositive for herpes simplex virus type 1 by Western blot test and had a history of at least 4 herpes simplex virus type 1 herpes labialis lesions in the previous year were eligible for the study.

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Dr. Baker is from the Division of Infectious Diseases, Department of Obstetrics/Gynecology, State University of New York at Stony Brook School of Medicine. Dr. Eisen is with Dermatology Associates, Cincinnati, Ohio.

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Reprints: David Baker, MD, Division of Infectious Diseases, Department of Obstetrics/Gynecology, State University of New York at Stony Brook, Stony Brook, NY 11794-8091 (e-mail: david.baker@stonybrook.edu).

Table 1.

**Demographics and Patient Characteristics**

	Valacyclovir (n=49)	Placebo (n=49)
Female, n (%)	41 (84)	40 (82)
Race, n (%)		
White	45 (92)	47 (96)
Black	1 (2)	0 (0)
Other	3 (6)	2 (4)
Mean age, y (range)	36.9 (22.8–54.6)	40.6 (21.0–55.4)
Median time since previous episode of herpes labialis, mo	0.9	1.1

Patients were excluded if they (1) had used any antiherpes medication in the month prior to enrollment; (2) showed evidence of active herpes labialis reactivation; (3) were immunosuppressed or taking immunosuppressant medication; or (4) were women who were breast-feeding or had a positive pregnancy test. All patients provided informed written consent.

Two randomized, double-blind, placebo-controlled, single-center studies approved by institutional review boards were conducted from 1999 to 2000. Patients were randomized on the day they enrolled to receive oral valacyclovir 500 mg once daily or placebo once daily for 4 months. Patients were instructed to contact their clinician within 8 hours of any sign of a recurrence of a herpes labialis lesion occurring at any time during the 4-month treatment period. Patients were to be examined at the clinic within 12 hours of onset of a suspected recurrent lesion and, if there was clinical evidence of a lesion, were to receive open-label oral valacyclovir 500 mg twice daily for 5 days. Patients resumed their assigned study medication at the end of the 5-day, open-label regimen.

At monthly clinic visits, physical examinations were performed, and accounts of compliance with study treatment and any adverse events occurring since the last clinic visit were obtained. All patients randomized to treatment who attended at

least 1 of the monthly clinic visits were included in the efficacy analyses.

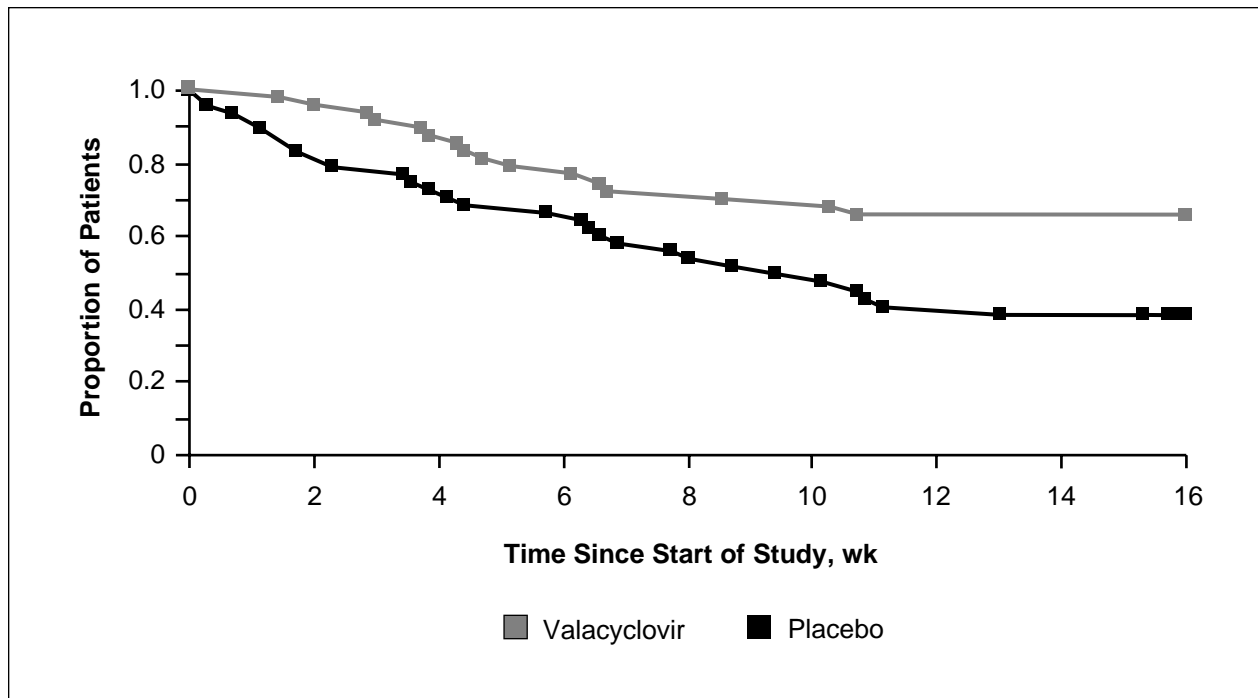
**Results**

Forty-nine patients were randomized to each treatment group; each patient was included in the safety data analyses. Two patients (1 in the valacyclovir group and 1 in the placebo group) who were lost to follow-up and 1 patient in the valacyclovir group who withdrew prior to the first clinic visit were not included in the efficacy analyses.

Demographic characteristics were similar between treatment groups (Table 1). The majority of patients were women with mean ages of 36.9 years and 40.6 years in the valacyclovir and placebo groups, respectively. At study entry, the median time since the previous episode of herpes labialis was 0.9 months in the valacyclovir group and 1.1 months in the placebo group.

*Efficacy*—Twenty-eight patients (60%) in the valacyclovir group compared with only 18 patients (38%) in the placebo group were recurrence-free throughout the 4-month treatment period ( $P=.041$ ) (Table 2). Correspondingly, 19 patients (40%) in the valacyclovir group compared with 30 patients (62%) in the placebo group experienced 1 or more recurrences ( $P=.041$ ).

The probability of remaining recurrence-free was consistently higher for the valacyclovir group than



Proportion of patients recurrence-free of herpes labialis as a function of time during the 4-month study period.

Table 2.

### Incidence and Frequency of Recurrences During the 4-Month Study Period

	Valacyclovir (n=47)	Placebo (n=48)
Patients recurrence-free, (n) %	28 (60)	18 (38)
Patients with recurrences, n (%)	19 (40)	30 (62)
Total number of recurrences	24	41
Number of recurrences per patient per month	0.12*	0.21

\* $P=.042$  valacyclovir versus placebo.

the placebo group throughout the 4-month treatment period (Figure). The mean time to first recurrence was significantly longer in the valacyclovir group (13.1 weeks) compared with the placebo group (9.6 weeks) ( $P=.016$ ).

The total number of recurrences in the valacyclovir group (24) was approximately half of that in the placebo group (41) (difference not statistically

tested). Likewise, the number of recurrences per patient per month in the valacyclovir group (0.12) was approximately half of that in the placebo group (0.21;  $P=.042$ ) (Table 2).

**Adverse Events**—The incidence of adverse events during the 4-month treatment period was slightly lower in the valacyclovir group (22 events; 33% of patients) compared with the placebo group (29 events;

39% of patients). The most common adverse event in both groups was headache, reported 5 times among 3 patients taking valacyclovir and twice in a placebo patient. All of the occurrences of headache were reported as being mild.

None of the adverse events occurring during valacyclovir therapy were assessed as being “certainly attributable” to study medication. Three adverse events occurring during placebo therapy (n=3; pinlike sensation on fingers and on toes, arthritis of toes) were assessed as being “attributable” to study medication. The 2 occurrences of headache in the placebo group were deemed “possibly attributable” to study medication as were 2 adverse events—1 occurrence of headache and 1 of constipation—in the valacyclovir group.

### Conclusion

These results demonstrate that valacyclovir 500 mg once daily for 4 months was effective in suppressing recurrent herpes labialis lesions. A higher percentage of patients receiving valacyclovir (60%) compared with placebo (38%) were lesion-free during the 4-month treatment period. When lesions did occur in the valacyclovir-treated patients, their onset was delayed and their frequency was reduced relative to placebo. Valacyclovir is thus the only oral antiviral medication dosed once daily for which efficacy for suppression of herpes labialis has been demonstrated. The data from these studies should be interpreted cautiously in the context of the small sample sizes of the studies.

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