

Therapeutic Options for Herpes Labialis, I: Oral Agents

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GOAL

To review the oral agents available for the treatment of herpes labialis

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the available oral agents for the treatment of herpes labialis.
2. Explain the research supporting use of oral agents for herpes labialis.
3. Describe the dosage regimens for oral agents in the treatment of herpes labialis.

CME Test on page 50.

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Given the prevalence of herpes labialis, effective therapy has the potential to affect the lives of many and presents a challenge for clinicians. Over the last several years, most of the focus of herpes research has been on the treatment of genital herpes. Recently, however, several studies have been published examining the efficacy of therapies specifically for herpes labialis. Several

therapeutic agents, both prescription and over-the-counter, are available for controlling and managing the disease. In this series of articles, we review oral and topical therapeutic agents that are available in the treatment of herpes labialis and its associated symptoms. This article will review oral treatment options.

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Herpes labialis is a common condition characterized by recurrent vesicular eruptions primarily on the lips and perioral skin. Most commonly caused by herpes simplex virus type 1 (HSV-1), this condition can significantly affect quality of life in patients with multiple recurrences,

which may cause pain, embarrassment, and psychosocial distress. Oral HSV is the most easily acquired herpesvirus. Approximately 50% of Americans are seropositive for HSV-1 by the time they reach adolescence—by age 50 years, 80% to 90% carry the virus.¹

Over the last several years, most clinical investigation of herpes infection has concerned genital disease. Therefore, the treatment of orolabial disease with oral therapies often was extrapolated from this data rather than based on direct study of the condition itself. Recently, however, several studies have been conducted to evaluate the efficacy of therapies specifically for herpes labialis. Although the virus responsible for the disease is not eradicated, several therapeutic agents, both prescription and over-the-counter, are available for controlling and managing the disease. In the first of this series of articles, we review oral therapeutic agents that are available in the treatment of herpes labialis and its associated symptoms.

Oral Agents

Three oral antiviral agents, acyclovir, valacyclovir, and famciclovir, are available for the treatment of herpes labialis. However, only valacyclovir has been specifically approved by the US Food and Drug Administration (FDA) for the episodic treatment of this condition. All 3 agents are acyclic guanosine analogs that competitively inhibit viral DNA polymerase after phosphorylation by the viral thymidine kinase and by the cellular kinases. Unlike acyclovir and valacyclovir, penciclovir and famciclovir are not obligate DNA chain terminators and would be expected to have lower efficacy.

Acyclovir—Little literature exists for oral acyclovir in the treatment of herpes labialis. In a study by Raborn et al,² oral acyclovir (200 mg 5 times a day for 5 days) reduced the time to loss of crust by 1 day (7 vs 8 days) but did not alter the duration of pain or time to complete healing. When treatment is started during the prodrome or erythema stage at 400 mg 5 times a day for 5 days, the mean duration of pain is reduced by 36%, and the time to loss of crust is reduced by 27%.² Therefore, according to Vander Straten et al,³ oral acyclovir therapy has modest clinical benefit and cannot be recommended for routine therapy of herpes labialis. However, it may be helpful in patients whose recurrence is associated with protracted illness.

Oral acyclovir has been shown to alter the severity of sun-induced herpes labialis.⁴ Administration of acyclovir 200 mg 5 times a day in skiers resulted in a similar frequency of HSV reactivation in treatment and placebo recipients, but significantly fewer

lesions formed on days 5 to 7 among those on acyclovir.⁴ Although not approved by the FDA, long-term suppression of herpes labialis with oral acyclovir has been shown to result in a 53% reduction in the number of clinical recurrences.⁵

Long-term use of acyclovir (up to 10 years) for HSV suppression is effective and well tolerated.⁶ Acyclovir is approved for use in children and has been monitored in more than 1000 pregnant women. The incidence of acyclovir resistance is estimated to be less than 0.5% among immunocompetent patients and 5% among immunocompromised patients. Primary infection responds well to oral acyclovir.⁶ In infants and children, acyclovir tablets can be crushed easily and mixed with food or dispersed in water or juice.

Valacyclovir—Unlike the parent drug acyclovir, valacyclovir has greater bioavailability (3 to 5 times that of acyclovir) and rapidly metabolizes to acyclovir and L-valine after absorption.³ As such, both agents have identical mechanisms of action, efficacy, and safety profiles. In previous studies, valacyclovir has been shown to be as effective as acyclovir in the treatment of first-episode genital herpes, recurrent genital herpes, and long-term suppression of genital herpes.³

Chosidow and colleagues⁷ evaluated the efficacy of the administration of a single course of valacyclovir in the prodromal phase of herpes labialis. In a randomized, double-blind clinical trial, 249 patients with similar baseline characteristics and recurrent disease were randomized to receive a 500-, 1000-, or 2000-mg dose of valacyclovir. The major outcome variable measure, the rate of aborted lesions on day 3, was not significantly different among the treatment groups, and a dose response was not observed. Although a placebo group was not included in this study, it was concluded that a single dose of valacyclovir was not beneficial in patients with recurrent herpes facialis.⁷

In a randomized, double-blind, placebo-controlled study, Spruance et al⁸ showed that a 1-day valacyclovir treatment regimen for cold sores is safe and effective. Treatment was administered in a 1-day regimen (2 g of valacyclovir twice a day for 1 day), 2-day regimen (2 g of valacyclovir twice a day for 1 day and then 1 g of valacyclovir twice a day for 1 day), or placebo. Patients were instructed to initiate treatment at the first symptoms of a cold sore. With a single day of treatment, median and mean durations of the episode were reduced by 1 and 1.1 days, respectively, compared with placebo. The 2-day treatment regimen led to a reduction in median and mean durations of the episode by 0.5 and 0.7 days, respectively, compared with placebo.

Oral Therapies for Herpes Labialis*

Drug	FDA-Approved Indications	Dosage for Orolabial HSV
Acyclovir (Zovirax [®])	Herpes zoster Genital herpes Varicella	Recurrent: 200–400 mg 5×/d for 5 d [†] Suppression: 400 mg 2×/d for 4 mo [†]
Valacyclovir (Valtrex [®])	Herpes zoster Genital herpes Herpes labialis	Recurrent: 2 g 2×/d for 1 d taken about 12 h apart Suppression: 500 mg/d for 4 mo [†]
Famciclovir (Famvir [®])	Herpes zoster Herpes simplex infections Genital herpes (immunocompetent) Mucocutaneous (HIV)	Recurrent: 500 mg 3×/d for 5 d [†] 500 mg 2×/d for 7 d (HIV)

*FDA indicates US Food and Drug Administration; HSV, herpes simplex virus; HIV, human immunodeficiency virus.

[†]Off-label dosage.

In addition, the suppression of cold sore development increased dose dependently by 6.4% ($P=.096$) and by 8.5% ($P=.061$) in the 1-day treatment and 2-day treatment groups, respectively, compared with placebo. Other variables evaluated in the study (eg, time to healing of lesion and cessation of pain or discomfort) also were reduced with valacyclovir compared with placebo. The authors concluded that a 1-day regimen of oral valacyclovir was efficacious against recurrent herpes labialis.⁸

Similarly, Baker and Eisen⁹ investigated the efficacy of oral valacyclovir in the suppression of herpes labialis. 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 a day for 16 weeks among patients with a history of 4 or more episodes of herpes labialis in the previous year. During the 4-month treatment period, 60% of patients in the valacyclovir group, compared with only 38% in the placebo group, were recurrence free. In addition, mean time to first recurrence was significantly longer with valacyclovir (13.1 weeks) compared with placebo (9.6 weeks). The authors concluded that oral valacyclovir 500 mg once a day for 4 months is effective and well tolerated in the prevention of recurrent herpes labialis. They suggested that additional research with larger numbers of patients be conducted to corroborate and extend these findings.⁹ The development of orofacial herpes labialis often is associated with

laser resurfacing. Gilbert and McBurney¹⁰ reported that valacyclovir is safe and effective as prophylaxis against such recurrences.

Famciclovir—This agent has been investigated in the treatment of herpes labialis in 2 small trials. In a double-blind, dose-ranging, placebo-controlled, multicenter trial, Spruance and McKeough¹¹ evaluated the efficacy of famciclovir in treating experimentally UV radiation (UVR)–induced herpes simplex labialis. In the study, patients received a 125-, 250-, or 500-mg dose of famciclovir or placebo 3 times a day for 5 days, beginning 48 hours after UVR exposure. Although there was no significant difference in the number of lesions between the famciclovir group and the placebo group, mean maximal lesion size was reduced dose dependently; the largest diameter was observed with the placebo, and the smallest was seen with a 500-mg dose of famciclovir. In addition, median time to healing was faster in the 500-mg famciclovir treatment group than in the placebo group.¹¹

In a second study with experimentally UVR-induced herpes simplex labialis, Spruance and McKeough¹² combined famciclovir 500 mg 3 times a day for 5 days with either topical fluocinonide 0.05% gel 3 times a day for 5 days or vehicle control gel. Patients using combination therapy experienced significantly reduced medium maximum lesion size, and the number of patients who had pain was reduced by approximately half compared with the control group (59% vs 100%).¹²

Famciclovir is not approved by the FDA for the treatment of herpes labialis. Although the drug has not been studied as suppressive therapy for this indication, Wall et al¹³ showed that famciclovir 125 or 250 mg twice a day, begun 1 to 2 days before laser resurfacing and continued for 5 days after surgery, reduced orofacial herpes outbreaks compared with placebo.

Several safe and effective therapeutic oral options exist in the treatment of herpes labialis (Table). Part II of this series will review topical therapies.

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