

THERAPEUTIC UPDATE



Treatment of Recurrent Herpes Labialis

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Cold sores, also known as herpes simplex labialis (HSL) affect millions of Americans. While evidence of serologic infection with herpes simplex virus type 1 (HSV-1) approaches 80% in the general adult population, only about 30% of people have clinically apparent outbreaks. The painful cluster of vesicles on an erythematous base is caused by the herpes simplex virus. Herpes labialis is the most common infection caused by HSV-1, whereas genital herpes is usually caused by herpes simplex virus type 2 (HSV-2). However, oral/genital sexual relations can allow the viruses to cross-infect; consequently, HSV-2 is responsible for herpes simplex labialis in 10-15% of cases. Intimate contact between a person who is actively shedding the virus (or with body fluids containing the virus) and an individual who is susceptible (who lacks antibodies against the virus) is necessary for HSV infection to occur.¹

The contact must involve abraded skin or mucous membranes. HSV invades the epidermal and dermal cells and travels to the sensory neurons (dorsal root ganglion) where latency is established. The virus replicates in the neurons, leading to recurrent outbreaks. The outbreaks are often induced by exposure to ultraviolet light (sunlight and/or tanning beds), stress, immunosuppression, the common cold, fatigue, fever (hence the term "cold sore" or "fever blister"), overexposure to the wind, extremes in temperature, menstrual periods, pregnancy, dental work, or lip trauma. Perioral laser resurfacing or injection of perioral botulinum toxin or fillers can stimulate an outbreak. Transmission of the virus can occur during primary infection, during subsequent recurrent infections, and even during periods of asymptomatic viral shedding.

At present, there is no cure for HSL, so theoretically, once contracted, the infection remains for life. The initial HSV-1 infection is often asymptomatic and may not be noticed, or a fever may be the only symptom. When perioral lesions do occur with the primary infection, the initial outbreak is often the most severe;

recurrences are typically more attenuated as a result of antibody production.² Approximately one-third of patients who experience the initial HSV-1 infection go on to have recurrent herpes labialis (RHL). Most patients with RHL have less than two episodes per year but 5-10% experience six or more recurrences per year.³ The pain, embarrassment, and temporary disfigurement of herpes lesions can be reduced by taking medication at the first sign of prodromal symptoms, such as itching, tingling, and burning, or by taking daily suppressive therapy. Most HSV infections are self-limited. However, antiviral therapy shortens the course of symptoms and may prevent transmission and dissemination.

Commercially available topical treatments are much less effective than IV or oral systemic therapy. All treatments are most effective if used at the first onset of symptoms.

I. Topical Antiviral Agents

1. *Docosanol 10% Cream (Abreva®)*

N-docosanol is a 22-carbon alcohol that has been FDA approved as an OTC agent for treating RHL. Applying the cream five times per day prevents fusion between plasma membranes and the HSV-1 virus envelope, reducing the risk of intracellular entry with subsequent viral replication. Ideally, docosanol is applied during the prodromal stage, but it is still useful, even at a later stage at shortening healing time and duration of symptoms.⁴

2. *Acyclovir 5% Cream or Ointment (Zovirax®)*

Acyclovir cream, FDA approved for RHL, has been shown to reduce lesion healing time by 0.5-0.6 days and the duration of pain by 0.3-0.4 days.⁵

3. *Penciclovir 1% Cream (Denavir®)*

Penciclovir cream, FDA approved for RHL, has been shown to reduce healing time in two studies by 0.7 and by two days, respectively, when compared with placebo controls.^{6,7} When compared directly with topical acyclovir cream in a randomized controlled trial with 124 subjects in each treatment group, there was no statistical difference between the two agents with respect to clinical healing time of herpetic lesions.²

4. *Acyclovir 5% and Hydrocortisone 1% Cream (Xerese®)*

This combination cream is FDA approved to treat RHL. In one study of 120 subjects with lesions of HSL, 50 subjects received the treatment combination cream and 70 subjects received the

placebo vehicle. While there was no statistically significant effect on pain, observed differences in healing time (nine days for those treated with the active drug vs 10.1 days for control subjects), on average, was statistically significant.⁸

5. Topical Mucoadhesive Acyclovir (Lauriad®)

Acyclovir Lauriad is a new topical agent approved in 2013 for the treatment of RHL. A single buccal application of a mucoadhesive tablet is applied to the gum above the canine incisor at the onset of prodromal symptoms. Patients hold the tablet in place for 30 seconds and acyclovir is absorbed into the labial mucosa for the next six to eight hours. In a recent study, researchers enrolled 775 immunocompetent patients who had at least four episodes of RHL in the past year and who were able to recognize their prodromal symptoms. 378 patients were randomized to receive the acyclovir buccal tablet, while 397 were randomized to receive placebo. A total of 330 patients had recurrence of a primary vesicle, but significantly fewer, 149 (64.2%) in the treatment group vs. 181 (73.6%) in the control group. The time to the next recurrence in the treatment group was 304 days compared to 199 days for the placebo group. It is postulated that having a high salivary concentration and high mucosal concentration of acyclovir during the time of highest viral replication may modify the clinical course of labial herpes.^{9,10}

II. Oral Systemic Antiviral Agents

1. Acyclovir (Zovirax®)

Although not FDA approved for RHL, oral acyclovir (200mg-400mg, five times a day) used off-label is an effective treatment for RHL. Several studies have shown a reverse in healing time by 1 to 1.5 days compared to placebo.^{11,12}

2. Valacyclovir (Valtrex®)

Valacyclovir, the prodrug of acyclovir, is FDA approved for the treatment of RHL. It is associated with three to five times the bioavailability of acyclovir. A dosage of 2000 mg bid for one day has been shown to improve healing time compared to placebo (0.5 to 1 day reduction) and to decrease downtime of pain compared to placebo (0.5 to 0.7 day reduction).¹³

Valacyclovir also approved by the FDA for patients with frequent episodes of RHL. Two studies evaluated the efficacy of oral valacyclovir 500 mg daily compared with placebo for the suppression of herpes labialis in those who had four or more episodes in the antecedent year. Daily suppressive therapy was administered for four months. 60% of the subjects who took valacyclovir remained recurrence free during the four months, compared to 38% who were treated with the placebo.¹⁴

3. Famciclovir (Famvir®)

Famciclovir, the prodrug of penciclovir, is FDA approved for treating RHL, with a more convenient dosing schedule (1500 mg as a single dose). Famciclovir is also FDA cleared for use in episodic therapy as well as daily suppressive therapy in immunosuppressed patients.¹⁵

III. Antiviral Agents

Complicated HSV-1 infections, cutaneous and/or visceral dissemination, and severe infections in immunocompromised patients should be treated promptly with intravenous acyclovir. For those patients who have acyclovir-resistant HSV strains, IV foscarnet or cidofovir may be useful.¹

IV. Emerging Trends: Combination of Oral Antiviral with Topical Steroid

Treatment combining oral acyclovir with topical clobetasol gel may be synergistic. A recent pilot study combining valacyclovir 2000 mg bid for one day and clobetasol gel 0.05% bid for three days vs a combination of placebo pills and cream saw a mean healing time of 5.8 days compared to 9.3 days in placebo.¹⁶ Another study evaluated the combination of oral famciclovir and topical fluocinonide gel vs famciclovir plus placebo cream in 29 subjects. There was a 70% reduction in herpes lesions size when the combination treatment was administered after the onset of prodromal symptoms, but there was no difference in healing time between the two groups.¹⁷

Conclusion

The treatment of RHL remains a challenge in the 21st century. The herpes virus is ubiquitous, and no effective vaccine to protect against it has been developed thus far. Fortunately, there are many oral and topical treatments for RHL that provide some improvement in healing time and pain relief. Future research will undoubtedly lead to advances in the discovery of new, more effective therapeutic agents, combination of drugs and more efficient delivery systems.

Disclosure

Dr. Sarnoff has no relevant conflicts of interest to disclose.

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