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Q/ Which drugs are most effective for recurrent herpes labialis?

EVIDENCE-BASED ANSWER

A/ DAILY ORAL ACYCLOVIR OR VALACYCLOVIR may help prevent herpes simplex labialis (HSL) recurrences (strength of recommendation [SOR]: **B,** meta-analysis of randomized controlled trials [RCTs] with heterogeneous results).

No trials compare oral or topical treatments for HSL outbreaks against each other. Oral antivirals modestly reduce healing time and duration of pain, varying according to the agent used: valacyclovir reduces both healing time and duration of pain, famciclovir reduces both in one dosage form but not another, and acyclovir reduces only pain duration (SOR: **B,** single RCTs).

Several topical medications (acyclovir, penciclovir, docosanol) modestly decrease healing time and pain duration—typically by less than a day—and require multiple doses per day (SOR: **B,** multiple RCTs).

Evidence summary

A systematic review and meta-analysis of the effectiveness of oral and topical nucleoside antiviral agents to prevent recurrent HSL in immunocompetent people found 11 RCTs with a total of 1250 patients that compared an active drug against placebo.[1] The medications were topical 5% acyclovir, topical 1% penciclovir, and oral acyclovir, valacyclovir, or famciclovir in various doses. The primary outcome was recurrence of herpes simplex virus type 1 lesions during the treatment period. The relative risk (RR) of recurrence ranged from 0.22 to 1.22. Pooled results found a benefit favoring antiviral agents (RR of recurrence=0.70; 95% confidence interval [CI], 0.55-0.89).

Seven of the trials looked at acyclovir (5 oral, 2 topical). A subgroup analysis demonstrated that oral acyclovir (800-1000 mg/d) was more effective than placebo (RR=0.51; 95% CI, 0.29-0.88), whereas topical acyclovir wasn't. Oral valacyclovir (2 studies; 500 mg/d for 4 months) also reduced recurrence (RR=0.65; 95% CI, 0.43-0.91).

The authors of the meta-analysis noted that although 9 studies favored the use of an antiviral drug, only 4 showed statistically significant differences when compared with placebo, and none of them had a low risk of bias. They concluded that the review supported using oral acyclovir and valacyclovir to prevent recurrent HSL.[1]

Oral antivirals produce variable treatment results

Three RCTs evaluated oral antiviral medications against placebo to treat recurrent HSL, with mixed results. The largest RCT found that valacyclovir (2000 mg twice in 24 hours, with or without an additional 1000 mg twice in another 24 hours) modestly but significantly reduced both healing time and duration of pain (by 0.5-0.8 day).[2] The second RCT showed that a higher, single dose of famciclovir (1500 mg) reduced healing time (by 1.8 days) and pain duration (by 1.2 days) and that a smaller, repeated dose (750 mg twice in 24 hours) reduced healing time alone (by 2.2 days).[3]

The third RCT demonstrated that acyclovir (400 mg 5 times a day for 5 days) reduced pain duration (by 0.9 day) but didn't shorten healing time. If acyclovir was started during the prodrome, it decreased the time to disappearance of the lesion's hard crust (2.1 days' less time; *P*=.03), but the clinical significance of this finding is unclear.[4]

Topical treatment shows modest success

Two trials demonstrated that topical acyclovir (5% cream) modestly improved healing time and duration of pain (by as much as half a day). Patients in the first trial (paired RCTs reported together) began treatment within an hour of prodromal symptoms or signs, applying the medication 5 times daily for 4 days.[5]

Patients in the second trial used ME-609 cream (5% acyclovir plus 1% hydrocortisone), 5% acyclovir cream, or placebo, all applied 5 times daily for 5 days.[6] Although the cream with acyclovir and hydrocortisone showed a slight benefit compared with placebo (lessening healing time by 0.8 day and pain duration by 1 day), it didn't improve healing more than acyclovir alone. Other topical agents (penciclovir 1%; docosanol 10%) produced results similar to topical acyclovir.[7,8]

Recommendations

No national guidelines on this topic exist. An online resource notes that most patients don't require treatment for mild self-limited HSL.[9] For patients with prodromal symptoms, the authors recommend episodic oral antiviral therapy. Patients who have no prodome but multiple painful or disfiguring lesions may choose to use chronic suppressive therapy with an oral antiviral drug. JFP

Topical acyclovir, penciclovir, and docosanol modestly decrease healing time and pain duration—typically by less than a day—and require multiple doses per day.

References

1. Rahimi H, Mara T, Costella J, et al. Effectiveness of antiviral agents for the prevention of recurrent herpes labialis: a systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012;113:618-627.
2. Spruance SL, Jones TM, Blatter MM, et al. High-dose, short-duration, early valacyclovir therapy for episodic treatment of cold sores: results of two randomized, placebo-controlled, multicenter studies. *Antimicrob Agents Chemother.* 2003;47:1072-1080.
3. Spruance SL, Bodsworth N, Resnick H, et al. Single-dose, patient-initiated famciclovir: a randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. *J Am Acad Dermatol.* 2006;55:47-53.
4. Spruance SL, Stewart JC, Rowe NH, et al. Treatment of recurrent herpes simplex labialis with oral acyclovir. *J Infect Dis.* 1990;161:185-190.
5. Spruance SL, Nett R, Marbury T, et al. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother.* 2002;46:2238-2243.
6. Hull CM, Harmenberg J, Arlander E, et al; ME-609 Studt Group. Early treatment of cold sores with topical ME-609 decreases the frequency of ulcerative lesions: a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. *J Am Acad Dermatol.* 2011;64:696.e1-696.e11.
7. Raborn GW, Martel AY, Lassonde M, et al; Worldwide Topical Penciclovir Collaborative Study Group. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc.* 2002;133:303-309.
8. Sacks SL, Thisted RA, Jones TM, et al; Docosanol 10% Cream Study Group. Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol.* 2001;45:222-230.
9. Klein RS. Treatment of herpes simplex virus type 1 infection in immunocompetent patients. Waltham, MA: UpToDate; 2012. Available at: www.uptodate.com/contents/treatment-of-herpes-simplex-virus-type-1-infection-in-immunocompetent-patients. Accessed January 19, 2012.