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Treating Recurrent Herpes Simplex Labialis:
A New Modality With
a Novel Formulation Technology

TREATING RECURRENT HERPES SIMPLEX LABIALIS: A NEW MODALITY WITH A NOVEL FORMULATION TECHNOLOGY

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Delivery Technologies Matter: Maximizing Efficacy and Minimizing Side Effects



Leon H. Kircik MD

For the millions of Americans with herpes labialis, the recurrent cutaneous manifestations of the viral infection are an unwelcome part of life. Once an individual is infected with Herpes Simplex Virus (HSV), the virus remains latent in the trigeminal ganglion and in the oral mucosa, and up to 40 percent of affected individuals develop cutaneous manifestations of the infection.¹

Although there are known triggers, outbreaks of cold sores are rarely predictable. The development of vesicles precedes a prodromal phase in which many patients experience symptoms such as tingling or burning. Ironically, cold sores can be both a cause of and a consequence of stress for affected patients. This is because, in addition to pain and discomfort, cold sores may be associated with social stigma.

While oral antivirals can be used to treat, or prevent outbreaks of herpes labialis, treatment is often protracted, requiring multiple doses over several days. Furthermore, it typically takes several days for lesions under treatment to resolve.

Relatively new to the treatment field is Sitavig® (Cipher Pharmaceuticals) 50 mg acyclovir mucoadhesive buccal tablet, using Lauriad® technology. This novel delivery system provides a sustained release of active drug within the oral cavity when the tablet is applied onto the gum. Drug levels are rapidly detectable in the saliva and oral mucosa within minutes and sustained for more than 24 hours.

In studies, described ahead, use of Sitavig was associated with a shorter duration of cold sore episodes compared to placebo. In fact, duration of cold sores was reduced by nearly a full day. Of note, subjects using Sitavig also had a lower incidence of secondary lesions, compared to placebo. Data analysis from the studies also showed that subjects treated with Sitavig had statistically significantly fewer recurrences in a nine-month follow-up period, compared to controls.²

Sitavig represents a convenient option for the management of herpes labialis, requiring a single dose to reduce the duration of cold sores. While this reduction of outbreak duration is welcome by patients, the potential reduction of recurrences is also compelling. Carrying a single tablet may be both more convenient and discreet for patients, allowing them to apply the medication with the first signs and symptoms of vesicle formation. As clinicians, we must be sensitive to the needs of patients with herpes labialis. Given both the physical and personal discomfort associated with cold sores, the ability to reduce the duration of an outbreak and perhaps reduce the risk for future outbreaks with a single dose regimen is a great addition to our treatment armamentarium of herpes labialis.

Finally, we have another example of a unique delivery system, in this case, Lauriad technology, where the active agent targets the site of the disease activity like “a smart bomb” with maximum efficacy and minimal adverse events. For years, we have recognized the significant impact that formulation has on therapeutic efficacy—we know that vehicles matter. Experience with Sitavig 50 mg acyclovir mucoadhesive buccal tablet demonstrates the importance of a scientifically engineered delivery technology

further enhancing patient experience with an established drug.

“Delivery Technologies Matter” just like “Vehicles Matter”.

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Recurrent Herpes Labialis in Adults: New Tricks for an Old Dog

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ABSTRACT

Herpes labialis remains a common worldwide affliction. Recent advances in understanding the basic pathogenesis have led to new therapeutic intervention, both on-label and off-label. Aside from reducing the duration and symptomatology of acute outbreaks, another goal of treatment is to decrease the frequency of future episodes. Oral and topical acyclovir and its analogues are the mainstay of both chronic suppressive and episodic therapy. A new muco-adhesive formulation of acyclovir provides a decrease in outbreaks, probably due to a diminution of herpesvirus load in all reservoir sites. Acyclovir-resistant strains are rare in immunocompetent hosts; parenteral foscarnet and cidofovir are administered in this situation. Parenteral acyclovir is the drug of choice for eczema herpeticum, which may begin as herpes labialis in an atopic dermatitis patient. Thermotherapy may be beneficial, and a certified device to deliver heat is available outside the United States.

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INTRODUCTION

The prevalence of common herpes viruses varies greatly by continent, country, and even region within a country, as well as by population subgroup (such as age, gender, and immune status). However, based upon recent evidence, HSV-1 is rather ubiquitous worldwide, typically reaching about 40% seroprevalence by age 15 and then rising to a seroprevalence of 60-90% among older adults.^{1,2} While some HSV-1 infections cause genital herpes, this virus is predominantly responsible for oro-labial disease, commonly referred to as “cold sores” or “fever blisters.” This disorder is most common in Caucasian women, although it certainly can affect both genders and individuals from any ethnic group.

Oro-labial herpes may occur as a singular event, or it may become a periodically recurrent disorder. Recurrent HSV-1 outbreaks are generally associated with mild morbidity, notably a low risk of scarring. However, outbreaks are also quite variable in both frequency and severity.³ For those who experience frequently recurrent oro-labial herpes, these often painful and usually unsightly lesions engender considerable stress and anxiety.⁴ It can be estimated that between 15-40% of those infected with HSV-1 involving the peri-oral region will develop bothersome recurrences.⁵⁻⁷ Factors that can lead to recurrences include, but are not limited to: emotional stress or physical fatigue, infection (most often upper respiratory), exposure to ultraviolet light, local trauma (including medical procedures in close proximity to the mouth), menses, and immunosuppression.⁸ On the other hand, some recurrences occur without any appreciable precipitating event. Interestingly, smoking tobacco products has been associated with both less frequent and less severe HSV-1, although it is doubtful

that any healthcare provider would offer this as a therapeutic intervention.⁹

Rationale for Treatment

It is certainly worth a short discussion about whether such a common and relatively banal disease warrants any treatment at all. The opinion of this author is that therapy is justified for many disparate reasons. Treatment may shorten the duration of an attack, thereby reducing the duration of cosmetically distressing lesions and associated emotional upset. In fact, “cold sore” sufferers’ emotional upset is actually quite justified. A recent survey study disclosed that oro-labial herpes simplex infections are among the two most stigmatizing of all cutaneous disorders; so much so, that a majority of those surveyed would be ashamed if they themselves had herpes labialis, would find another person unattractive if they had herpes labialis, and wouldn’t want to touch or share food/drink with someone afflicted with HSV-1.¹⁰ Treatment may also decrease the duration of pain (or discomfort) attendant to an outbreak. Therapy may encourage or hasten healing, which normally takes 12-17 days from the onset of the associated prodrome. Despite an overall low inherent risk, treatment should reduce the potential for residual scarring. As discussed below, select treatments may even alter the natural disease history by reducing the frequency of future recurrences. A more theoretical rationale for treatment is to reduce the ongoing asymptomatic shedding of virus, which occurs on the oral mucosa about 20-25% of days of the year.¹¹ Moreover, considering the high degree of safety of the current anti-viral therapeutic armamentarium directed toward HSV-1 infection, it appears that treatment is clearly warranted, especially if the patient desires therapy.

TABLE 1.

Treatments for Primary Oro-labial HSV-1		
Anti-viral drug	Dose	FDA Approved?
Acyclovir	15 mg/kg 5x daily for 7 days	Not for age < 12
Valacyclovir	1.0 g BID for 7 days	Not for age < 12
Famciclovir	500 mg BID for 7 days	Not for age < 12

Adopted from reference 12 and package inserts

Primary Herpetic Gingivo-Stomatitis

Although discussion of this entity, most often seen in the pediatric population, is beyond the scope and purpose of this paper, the typical treatment options are shown in Table 1. Please note that the safety and efficacy of the commonly used oral anti-herpes drugs (acyclovir and its analogues) have not been established in the population under 12 years of age; therefore, formal FDA approval does not exist.¹²

Recurrent Oro-Labial Herpes: Suppressive Therapy

In managing recurrent HSV-1, there are several key decisions. Most importantly, the clinician must decide between episodic treatment (only administered during an outbreak) or chronic suppressive treatment. Episodic therapy can be accomplished via topical, systemic, and mucosal routes of drug administration, whereas chronic suppressive therapy is primarily accomplished by oral anti-viral drug administration. Some possible reasons to choose episodic or suppressive therapy are enumerated in Table 2, with the caveats that therapeutic choices

TABLE 2.

Episodic versus Suppressive Therapy	
Episodic Therapy if....	Suppressive Therapy if....
Infrequent outbreaks	Frequent outbreaks
Mild-Moderate disease	Severe disease
Patient preference	Patient preference
No erythema multiforme	Associated with erythema multiforme
No eczema	Patient has eczema
Clearly defined prodrome	No prodrome
Suppression fails	Suppression works well

TABLE 3.

Chronic Suppression of HSV-1 Oro-labial Herpes			
Agent/Dose	Maximum decrease in number overt outbreaks	Time studied	FDA Approval
Acyclovir 400 mg BID-QID	53%	4 months	No
Valacyclovir 500-1000 mg daily or 500 mg BID	50%	4-6 months	No
Famciclovir 500 mg BID	Uncertain data	Very short term	No

Adopted from reference 12

must always be individualized and selected by the healthcare provider following thorough discussion with the patient. Anti-viral drug dosages frequently utilized in chronic suppression are shown in Table 3. However, none of these regimens are FDA approved, and chronic anti-viral drug suppression of HSV-1 with resultant reduction in clinical outbreaks is much more difficult to successfully achieve than with HSV-2-related genital herpes.^{12,13} As aptly summarized in a recent Cochrane Systematic Review: "The current evidence demonstrates that long-term use of oral antiviral agents can prevent HSL (herpes simplex labialis), but the clinical benefit is small."¹⁴ Acyclovir has also been associated with several different forms of nephrotoxicity; this problem is discussed below. A host of other potential interventions designed to prevent herpes labialis outbreaks (such as oral lysine, ingestion of various food supplements, low-level laser therapy, administration of gamma globulin, or yellow fever vaccine) have not proven successful.¹⁴ The use of topical imiquimod, when applied directly to the lesion as an attempt to meaningfully suppress herpes labialis, has largely been abandoned due to the potential for a severe local reaction.¹⁵ However, an intriguing case report detailed the once daily occlusive application of ¼ a standard sachet of 5% imiquimod to a distant skin site for three weeks, with the treatment starting during an active outbreak.¹⁶ This method resulted in a massive polarized Th-1 immune response with interferon-γ release, and notable clinical suppression: namely, a remission of one and a half years duration.¹⁶ Unfortunately, there have been no confirmatory or follow-up reports regarding this method of attaining disease suppression.

Recurrent Oro-Labial Herpes: Episodic Therapy

As noted previously, there exists a plethora of therapeutic choices for the episodic management of oro-labial herpes. It should be noted that all episodic interventions demonstrate optimal benefit when administered immediately upon onset of the outbreak prodrome. Topical therapies are listed in Table 4. Why might topical therapy be preferred by select patients? Some reasons include: few real or potential side effects in the short-term and no long-term health concerns; no drug-drug interactions to consider; easy portability and rapid initiation; application right to the site of cutaneous pathology giving the patient a feeling of empowerment; and cost-effectiveness. However, even a cursory glance at Table 4 shows that

TABLE 4.

Topical Episodic Therapies for Herpes Labialis

Agent	Decrease in resolution time	Decrease in pain duration	Miscellaneous
Acyclovir 5% Cream	0.5 – 2.0 days	Minimal	Ointment not as effective
Penciclovir 1% Cream	0.7-1.2 days	0.6-1.0 day	May be applied after the prodrome
Docosanol 10% Cream	0.75-1.6 days	0.5-0.6 day	Over-the-counter Increased aborted attacks
Acyclovir 5% Hydrocortisone 1% Cream	1.4 days	1.0 day	Fewer lesions progress to frank erosion

Adopted from reference 12 and package inserts

the clinical benefits from episodic topical therapy are modest. While topical drugs are quite safe, such agents are also very inconvenient, as they require frequent and prolonged application. Acyclovir cream approved use is five times daily for four days; penciclovir cream is to be applied every two hours while awake for four days; docosanol cream is five times daily “until healed”; and acyclovir-hydrocortisone cream indicated dosage is 5 times daily for 5 days. The newest of the approved topical agents, acyclovir 5%-hydrocortisone 1% cream, was first introduced in 2009, and theoretically uniquely addresses both symptomatic relief and healing by concurrently reducing inflammation while exerting direct anti-viral effects.¹⁷ Two unique benefits related to this agent compared to placebo are smaller ultimate mean lesional size and fewer outbreaks progressing to overt erosion.¹⁷

An interesting adaptation of the aforementioned steroid/anti-viral combination as episodic therapy was tested on 42 patients, wherein a placebo-placebo group was compared to subjects who received valacyclovir (2 g orally BID for 1 day) and topical clobetasol gel 0.05% (BID for 3 days applied to the affected area).¹⁸ Patients who received the combination therapy experienced more aborted lesions (50% versus 15.8%), a reduced the mean maximum lesion size (9.7 versus 54 mm) and most strikingly a lower mean healing time of classical lesions (5.8 versus 9.3 days).¹⁸ This regimen, while proving quite effective in a small randomized and controlled study, did not alter the long-term natural disease history. A different, similarly sized (n=49) study compared oral famciclovir 500 mg and topical

fluocinonide .05% gel, administered three times daily for five days, to oral famciclovir and gel vehicle dosed in the same manner. In this steroid/anti-viral comparison to an active anti-viral agent plus placebo, addition of the steroid proved beneficial on some efficacy parameters; namely, the topical steroid/oral anti-viral subjects experienced: more aborted lesions, reduced maximum lesion size, and non-statistically significant reduced duration of pain and reduced healing time.¹⁹ Based on just a few studies, it appears that the addition of a topical corticosteroid to antiviral therapy produces improvements in the clinical course of herpes labialis, compared to antiviral agent monotherapy, and that such combination therapy shows an even greater degree of benefit compared to no treatment.

What about episodic oral anti-viral therapy? The most typically utilized oral therapies are summarized in Table 5. For all these regimens to be successful, drug is best taken within one hour of the onset of a prodrome. In patients lacking a definable prodrome, drug should be taken within 48 hours of the onset of any sign or symptom (eg, erythema, papule, or vesicle formation). As is true of topical therapy, episodic treatment with oral anti-viral drugs provides modest improvements in time to lesion healing and duration of pain. It should be noted that acyclovir is relatively insoluble in urine, is rapidly filtered by glomeruli and secreted by renal tubules, thereby producing high urinary concentrations, especially in patients with pre-existing renal impairment.²⁰ In turn, this may lead to direct renal tubular toxicity, acute interstitial nephritis and/or crystal nephropathy.²¹ While the absolute risk is certainly small (<0.5%) and discontinuation

TABLE 5.

Oral Episodic Therapies for Herpes Labialis

Agent	Decrease in resolution time	Decrease in duration of pain	Increase in aborted episodes	Miscellaneous
Acyclovir 400mg 5 times daily for 5 days	1.0 day	1.3 days	14%	Oral suspension available Not FDA approved
Valacyclovir 2.0 grams twice, 12 hours apart	1.0 day	0.5 day	10-22%	FDA approved
Famciclovir 1.5 grams once or 750 mg BID	2.0 day	1.2 days	2.4-15.4%	FDA approved

Adopted from reference 12 and package inserts

of the offending drug usually results in a rapid return to normal renal function, oral acyclovir (or valacyclovir) may induce acute nephrotoxicity.²² This may be a realistic consideration – both during high dose episodic and chronic suppressive therapy – in those individuals with diabetes, hypertension, or any other reason for decreased creatinine clearance. Famciclovir is apparently not similarly linked to kidney damage.

A recent (approved April, 2013) innovation in herpes labialis treatment is a muco-adhesive buccal tablet containing 50 mg of acyclovir. Large multinational pivotal trials included well over 700 patients. A milk derived protein functions as an adhesive that allows the tablet to stick to the ipsilateral upper canine fossa for the requisite 6 hours until dissolution. During the time the intact tablet adheres to the buccal mucosa and gradually dissolves, eating and drinking are permitted. If applied as studied (within one hour of prodrome onset), the drug hastens episode resolution by one day, reduces time to healing by about a half day, and leads to a greater number of aborted attacks (35%) compared to placebo.²³ What is rather unique about this drug is that it has been shown to actually reduce the number of future outbreaks and increase the time between subsequent outbreaks; muco-adhesive acyclovir tablets increased the time to next recurrence by 40 days (median) to 105 days (mean).²³ “Real world” utilization may lead to even better performance in this regard.²⁴ In short, acyclovir buccal tablet is the first antiviral drug that has demonstrated reduction in the number of fever blister outbreaks following an episodic treatment. Why can a single 50 mg tablet provide such benefit? Despite very low acyclovir plasma concentration, the buccal adhesive tablet provides extremely high concentrations in saliva and both oral and labial tissue.²⁵ In this manner, the overall viral load is likely reduced by addressing all the likely HSV-1 reservoirs, not only in the trigeminal ganglia but also within the peripheral nerves and oral soft tissues. The simple course of therapy (one tablet), a lack of significant plasma concentration, and the ability to alter the natural course of the disease all make this an exciting new modality for those with frequently recurrent herpes.

Role of Parenteral Acyclovir

Acyclovir Sodium Injection is a sterile, aqueous solution for intravenous infusion, containing 50 mg acyclovir per mL. This formulation is indicated for the following HSV-1 infections: herpetic encephalitis, neonatal herpes infection, and both initial and recurrent mucosal and cutaneous herpes simplex in immunocompromised patients. The standard dose is 5 mg/kg infused over one hour, every eight hours; higher doses may be utilized for encephalitis, in neonates, and for eczema herpeticum. Adequate hydration is essential and dosage adjustments are mandatory in the face of reduced renal function. Because herpes labialis in immunocompromised and immunosuppressed individuals can be devastating (Figure 1), parenteral acyclovir is often used. However, at least one meta-analysis suggested that

FIGURE 1. Severe HSV-1 associated with leukemia chemotherapy.



intravenous acyclovir and oral valacyclovir (1 gram BID) might well be equipotent.²⁶

Acyclovir Resistance

HSV-1 acyclovir resistance is rare in clinical isolates obtained from the general population (<1%), but is common among clinical isolates obtained from immunosuppressed and immunocompromised individuals (between 2.5% and 10.9%).²⁷ Acyclovir resistance is due to genetic mutations producing polymorphisms in the thymidine kinase and/or DNA polymerase genes. Luckily, many acyclovir-resistant mutants exhibit a reduction in their capacity to establish latency and to reactivate. Intravenous foscarnet or cidofovir are usually utilized. Details can be found elsewhere.^{27,28}

Thermotherapy

Short application of intense heat may be of benefit. A certified medical device which delivers a four second burst of 50-51°C heat through a small portal is in wide use in England, Europe, Canada, and Australia. When applied one to two times during the day of prodrome onset, the process may be aborted (no vesicles or erosions). If used on already active lesions, it may shorten the time to resolution by up to eight days. This device is not approved in the United States but is readily available on foreign versions of Amazon.

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