Famciclovir for Cutaneous Herpesvirus Infections: An Update and Review of New Single-Day Dosing Indications

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Infections with herpes simplex virus (HSV) types 1 and 2 and herpes zoster are common and a substantial public health issue. Famciclovir is an effective treatment for herpes simplex and herpes zoster. We review studies evaluating the efficacy of single-day doses of famciclovir for the treatment of recurrent herpes labialis (cold sores) and genital herpes. Famciclovir has received single-day dosing indications for both of these entities. The studies leading to these new indications are reviewed.

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It has been estimated that 90% of individuals aged 20 to 40 years have antibodies to herpes simplex virus (HSV) type 1, and HSV-2 is the most common sexually transmitted disease worldwide.[1] With the aging of the US population, the absolute number of herpes zoster cases is increasing dramatically. Lifetime incidence of herpes zoster is estimated to be 10% to 20% and up to 50% in individuals aged 85 years.[2] Infection with HSV initially can result in primary infection followed by an establishment of latency because the viral genome remains in the neuronal bodies indefinitely. Patients then may have recurrences that may be symptomatic or asymptomatic. Many individuals may experience frequent recurrences that may be symptomatic; oral antiviral agents are the first-line therapeutic options in these cases.

Penciclovir is a nucleoside analogue that is selectively phosphorylated to penciclovir monophosphate by viral thymidine kinase and then converted to the active triphosphate form by cellular enzymes.[3] Penciclovir triphosphate has a long intracellular half-life (10 hours in HSV-1–infected cells),[3] and famciclovir, the oral prodrug of penciclovir, has high bioavailability.[4] For several years, famciclovir has been approved for the treatment of acute herpes zoster, treatment or suppression of recurrent genital herpes in immunocompetent individuals, and treatment of mucocutaneous HSV infections in patients with human immunodeficiency virus infection. On July 31, 2006, the US Food and Drug Administration (FDA) approved famciclovir as a single-day treatment of immunocompetent individuals with recurrent genital herpes. Famciclovir also was approved as a single-dose treatment of recurrent herpes labialis in immunocompetent individuals.

Herpes Labialis

HSV-1 infects at least 40% of the US population by the time they reach adolescence. Infection usually is acquired during childhood. The incidence of HSV-1 increases with age; up to 90% of individuals older than 50 years are seropositive for HSV-1.[5] Approximately one third of individuals with HSV-1 infection will experience recurrent episodes of herpes labialis. Although most episodes are mild and self-limiting, patients report substantial irritation, pain, discomfort, and loss of self-esteem.

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Because of the prevalence of herpes labialis, effective therapy has the potential to affect the lives of many patients and presents a therapeutic challenge for clinicians. For the past several years, most of the focus of herpes research has been on the treatment of genital herpes. 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, clinical research has investigated the efficacy of therapies specifically for herpes labialis. Although the virus responsible for the disease is not eradicated, several oral and topical treatments are available for controlling and managing the disease

Three oral antiviral agents (acyclovir, valacyclovir hydrochloride, and famciclovir) are available for the treatment of herpes labialis (Table 1). However, until the recent approval of single-day famciclovir, only valacyclovir hydrochloride was specifically approved by the FDA for the episodic treatment of genital herpes. All 3 agents are acyclic guanosine analogues that competitively inhibit viral DNA polymerase after phosphorylation by the viral thymidine kinase and cellular kinases.

Spruance et al[5] recently demonstrated the efficacy of single-dose patient-initiated famciclovir for episodic treatment of herpes labialis. Because of the natural history of herpes labialis, the high bioavailability of famciclovir, and the long intracellular half-life of penciclovir triphosphate, the authors hypothesized that a single dose of patient-initiated oral famciclovir would be superior to placebo in shortening the duration of recurrent herpes labialis lesions. They chose a 1500-mg dose of famciclovir to achieve the maximum possible suppression of viral replication.[5]

This randomized, double-blind, parallel-controlled study examined the effectiveness of a single 1500-mg dose of famciclovir, two 750-mg doses of famciclovir twice daily for one day, and a matching placebo.[5] In the trial, 701 patients were randomized in a 1:1:1 ratio to receive either single-dose famciclovir (1500 mg), single-day famciclovir (750 mg twice daily for one day), or matching placebo to treat the subsequent recurrence of

Table 1.

Oral Therapies for Herpes Labialis*

Drug	FDA-Approved Indications	Dosage for Herpes Labialis
Acyclovir	Herpes zoster	Recurrent: 200−400 mg 5× daily for 5 d†
	Genital herpes	Suppression: 400 mg 2× daily for 4 mo†
	Varicella	
Valacyclovir hydrochloride	Herpes zoster	Recurrent: 2 g 2× daily for 1 d taken about 12 h apart‡
	Genital herpes	
	Herpes labialis	Suppression: 500 mg 1× for 4 mo†
Famciclovir	Herpes zoster	Recurrent: 1500 mg single dose‡
	Herpes simplex infections	Recurrent in HIV-infected patients: 500 mg 2× daily for 7 d‡
	Treatment or suppression of recurrent genital herpes	
	Recurrent herpes labialis	
	Recurrent mucocutaneous herpes simplex infections in HIV-infected individuals	

*FDA indicates US Food and Drug Administration; HIV, human immunodeficiency virus.
†Off-label use.
‡FDA-approved dosage for orolabial herpes simplex virus (herpes labialis).

herpes labialis. The primary efficacy variable was the investigator-assessed time to healing of the primary vesicular lesions. The secondary efficacy variables included time to return to healthy skin for all lesions (vesicular, aborted) and duration of lesion pain and tenderness.[5]

Lesion healing was monitored by patient diaries and frequent clinic visits.[5] The authors found that median healing times of primary (first to appear) vesicular lesions in the famciclovir single-dose, famciclovir single-day, and placebo groups were 4.4, 4.0, and 6.2 days, respectively. There was no significant difference between the famciclovir therapeutic regimens. Single-dose famciclovir reduced the time to healing (loss of crust, reepithelialization) of vesicular herpes labialis lesions by approximately 2 days compared with placebo. The time to return to healthy skin for all lesions also was reduced by approximately 2 days compared with placebo. In addition, single-dose famciclovir resolved the pain and tenderness associated with a herpes labialis outbreak approximately one day faster compared with placebo. Adverse events in both famciclovir groups were similar to the placebo group. Overall, adverse events were infrequent and of mild to moderate severity.[5]

Genital Herpes

HSV-2 is the etiologic agent of genital herpes, one of the most prevalent sexually transmitted diseases. In 2000, 22% of adults in the United States were seropositive for HSV-2, and prevalence rates may be as high as 30% worldwide.[6] In addition, genital lesions caused by HSV-1 are increasingly common, likely because of the increase in oral-genital sexual behavior.

Traditional episodic therapy for recurrence of genital herpes was twice-daily dosing for 5 days. However, 2 studies have demonstrated that shorter courses of antiviral therapy are as effective. Leone et al[7] compared the efficacy of a 5-day treatment course of valacyclovir hydrochloride with a shorter 3-day treatment course for subjects with frequent recurrence of genital herpes. No significant differences were detected between the 2 dosing schedules for any of the end points measured. Median times to lesion healing, pain duration, and episode length for the 5-day versus 3-day treatment were 4.7 versus 4.4 days, 2.5 versus 2.9 days, and 4.4 versus 4.3 days, respectively. The authors concluded that a 3-day course of 500 mg of valacyclovir hydrochloride administered twice daily as episodic treatment of recurrent genital herpes was equivalent to a 5-day treatment course with regard to major efficacy end points.[7]

Famciclovir previously was approved for treatment of recurrent genital herpes at a twice-daily 125-mg dosage for 5 days. Aoki et al[8] conducted a study to assess the efficacy and safety of a patient-initiated single-day regimen of famciclovir therapy compared with placebo in immunocompetent adults with recurrent genital herpes. In a multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled study, patient-initiated single-day oral famciclovir dosed at 1000 mg twice daily was compared with placebo for the treatment of recurrent genital herpes. Patients were instructed to initiate therapy within 6 hours after onset of prodromal symptoms or genital herpes lesions.[8]

Famciclovir significantly reduced ($P<.001$) the time to healing of nonaborted lesions (ie, those that progressed beyond the papule stage) compared with placebo (median time, 4.3 vs 6.1 days, respectively) and all aborted lesions compared with placebo (median time, 3.5 vs 5.0 days, respectively). The percentage of patients with aborted lesions was higher in the famciclovir group than the placebo group (23.3% vs 12.7%, respectively; $P=.003$). In addition, the time to resolution of symptoms such as burning, tingling, itching, tenderness, and pain was reduced. Adverse events in the famciclovir group were infrequent. Most of the events were mild to moderate and were observed to be similar to the placebo group. The authors concluded that a single-day treatment regimen of famciclovir was well-tolerated and safe, and the healing of recurrent genital herpes lesions occurred approximately 2 days faster than placebo. In addition, single-day famciclovir treatment aborted the development or progression of lesions beyond the papule stage. The authors further noted that this single-day regimen has the potential to improve patient compliance and satisfaction.[8]

Table 2 summarizes the current FDA-approved regimens for recurrent genital herpes.

Comment

The new single-day doses of famciclovir for recurrent herpes labialis and genital herpes offer both efficacy and convenience. For herpes labialis, the single dose (1500 mg) of famciclovir reduced the time to healing by approximately 2 days compared with placebo.[5] Although not directly compared with other therapies for herpes labialis, the magnitude of the benefit of this therapeutic regimen compared favorably with other therapies. Topical therapies and their reductions in time

Table 2.

Oral Therapies for Recurrent Genital Herpes*

Drug	FDA-Approved Dosage for Recurrent Genital Herpes
Acyclovir	200 mg every 4 h 5× daily for 5 d
Valacyclovir hydrochloride	500 mg 2× daily for 3 d
Famciclovir	1000 mg 2× daily for 1 d

*FDA indicates US Food and Drug Administration.

to healing were 0.5 to 0.6 days for acyclovir cream,[9] 0.7 to 1.0 days for penciclovir cream,[10] and 18 hours for docosanol cream.[11] In addition, treatment with an oral agent potentially could impact the frequency and severity of secondary lesions, whereas the site of activity of topical agents is limited to the lesion area where applied.[5] In the study by Spruance et al,[5] the frequency of secondary lesions in both famciclovir groups was almost half that of the placebo group.

A 2003 study by Spruance et al[12] evaluated short-course oral valacyclovir hydrochloride dosed at 2000 mg twice daily in a single day. This therapeutic regimen reduced the healing time of herpes labialis lesions by one day compared with placebo.[12] Of note, the results from the 2006 famciclovir study by Spruance et al[5] demonstrated that a single dose (1500 mg) of patient-initiated famciclovir therapy led to healing of herpes labialis lesions 2 days faster than placebo. The authors speculated that a potential explanation for the increased benefit of single-dose famciclovir compared with short-course valacyclovir hydrochloride may be due to the more prolonged duration of the intracellular concentrations of the famciclovir metabolite.[3] However, a clinical trial comparing the 2 agents directly will be necessary to further elucidate this issue.

In the treatment of recurrent genital herpes, episodic treatment with oral antiviral agents for 3 to 5 days has been the most common treatment regimen. However, because the maximum viral replication occurs within 24 hours after the onset of symptoms, single-day patient-initiated episodic treatment may provide a superior option.[13] A recent study by Aoki et al[8] demonstrated that single-day famciclovir reduced healing time and the duration of pain and other symptoms, and increased the proportion of subjects who did not progress to a full outbreak. Compared with previous studies, the results of single-day therapy were similar to or better than the results of conventional therapies of 2 to 5 days' duration.[13] In addition, the convenience of single-day treatment may lead to greater compliance and improved management of recurrent herpes outbreaks.

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