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A Review of Famciclovir in the Management of Genital Herpes

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ABSTRACT

The frequent occurrence of genital herpes continues to be a serious clinical problem. Although not life threatening, the physical symptoms of the disease, and the ensuing psychosocial complications, can be overwhelming to patients. The life cycle of the herpes simplex virus is complex, comprising multiple stages. Following infection, the virus establishes life-long latency in its host and can reactivate at any time as a recurrent infection. Successful management of genital herpes simplex infections involves patient education and psychological support, as well as antiviral agents. The antiviral agent famciclovir has been shown to shorten the course and decrease the severity of episodes of recurrent genital herpes. In addition, famciclovir has been shown to be effective in suppressing recurrent genital herpes. A review of the clinical experience with famciclovir in the treatment of genital herpes is presented. Infect. Dis. Obstet. Gynecol. 6:38–43, 1998. © 1998 Wiley-Liss, Inc.

KEY WORDS

genital herpes; herpes simplex infection; recurrent genital herpes; antiviral therapy

More than 45 million people in the United States are infected with the herpes simplex virus (HSV) type 2 (HSV-2), the primary causative agent of genital herpes; an additional 500,000 people become infected each year.[1,2] The predominance of HSV-2 antibodies among those over 12 years of age is almost 22%.[2] Although HSV type 1 (HSV-1) infection is associated primarily with oral herpes, it is being increasingly linked to genital disease.[3] The astounding prevalence of this sexually transmitted disease suggests the need for better clinical management of genital herpes, including appropriate treatment with antiviral agents.

The HSV life cycle is complex, consisting of five stages: primary mucocutaneous infection, acute infection of nerve ganglia, establishment of life-long latency, reactivation, and recurrent infection (Figure 1).[4] Exposure to HSV at mucosal surfaces or abraded skin permits entry of the virus into epidermal and dermal cells and the initiation of viral replication.[5] Following primary infection, which can be symptomatic or asymptomatic, the virus travels to the neuronal nuclei in the dorsal root ganglia, where it remains latent for indefinite periods.[4] The ability to persist in cells indefinitely, escaping elimination by the host's immune mechanisms, is one of the most perplexing aspects of the herpesviruses.[6]

Patients with a first episode of genital herpes may have either a true primary infection or an initial genital HSV-2 infection (nonprimary first episode). Symptomatic true primary infections are typically severe and occur in seronegative individuals. Patients with nonprimary, first-episode HSV-2 infection have preexisting HSV-1 antibodies and typically have a milder clinical presentation. Although the diagnosis of HSV infection is usually based on clinical signs and symptoms, most genital HSV infections are not clinically apparent. Patients can have atypical lesions or be asymptomatic. Pa-

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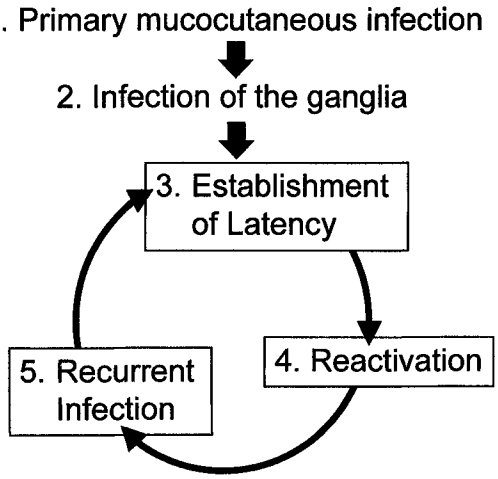

Fig. 1. Herpes simplex virus cycle. There are five stages to the herpes simplex virus life cycle. Stage 1: Primary mucocutaneous infection of a susceptible individual and onset of primary infection. Stage 2: After viral replication at the site of inoculation, HSV infects the terminal branches of sensory endings to the skin and is transported to the cell body of sensory ganglia. Stage 3: At resolution of primary infection viral replication is shut off and HSV establishes life-long latency. Stage 4: Reactivation from the latent stage is triggered and HSV is released from infected ganglia to reestablish active infection. Stage 5: Recurrent infection ensues.

tients may also experience the reactivation of a previously asymptomatic genital herpes infection.

Factors responsible for the reactivation of the herpesvirus and the onset of recurrent genital herpes infection are not well understood, although emotional stress, sexual intercourse, menstruation, and pregnancy may play a role.[4–6] When reactivation is triggered, the virus is released from infected dorsal root ganglia to reestablish active infection.[7] Recurrences are shorter and less intense than primary infections and are generally more severe in women than in men.[7,8] In addition, while men appear to have a higher rate of symptomatic recurrence, asymptomatic recurrence is more frequent in women.[8,9] Women infected with HSV-2 also require careful gynecological management, including frequent Pap tests, for the remainder of their lives because HSV-2 antibodies have been associated with cytological abnormalities of the cervix.[2,4,6]

Recurrence rates of HSV infections vary among individuals and within the same individual.[5] Immune competence appears to be crucial in the balance between latency and reactivation of the virus.[5,7] In patients with symptomatic, first-episode genital HSV-2, recurrence rates are high: four or more per year in about 89% of patients within one year of a first-episode HSV-2 infection.[8]

Although not life threatening in the immunocompetent patient, genital herpes is associated with long-term negative sequelae. Psychological and emotional complications are important aspects of the long-term morbidity of HSV infections.[6] The unpredictability of recurrent episodes and their effect on interpersonal relationships can have a substantial negative impact on a patient's quality of life. Palliative and supportive measures remain the cornerstone of therapy for genital herpes, with psychological support and patient education being key elements of disease management. However, these supportive measures do not treat the infection.[4]

In recent years, the development of safe and effective antiviral agents has improved the management of HSV. Although there is no drug that permanently destroys HSV, antiviral agents inhibit the virus by interacting with the viral-coded DNA polymerase, ending subsequent viral replication.[4,7] The challenge of antiviral therapy lies not only in treatment of symptoms during first and recurrent episodes, but also in the long-term suppression of the herpesvirus for patients with frequent recurrences.

PHARMACOKINETICS OF ANTIVIRAL THERAPIES

Acyclovir (Zovirax®, Glaxo Wellcome, Inc., Research Triangle Park, NC) has been the drug of choice for HSV infections for well over a decade. A large number of clinical trials have documented its safety and efficacy in various patient populations.[10]

Acyclovir is an acyclic nucleoside analog that inhibits DNA replication. It is activated to its triphosphate form, incorporates into viral DNA, and terminates viral DNA synthesis. Acyclovir triphosphate has limited stability when acyclovir is removed from the culture medium and a short intracellular half-life in vitro (less than one hour).[11] In addition, the bioavailability of acyclovir administered orally is 10% to 20%.[12]

Valacyclovir (Valtrex®, Glaxo Wellcome, Inc.), the L-valyl ester and prodrug of acyclovir, has more recently been developed for the treatment of acute recurrent genital herpes. It has a bioavailability of 55%;[12] however, since valacyclovir is the prodrug, once absorbed it has the same pharmacokinetic

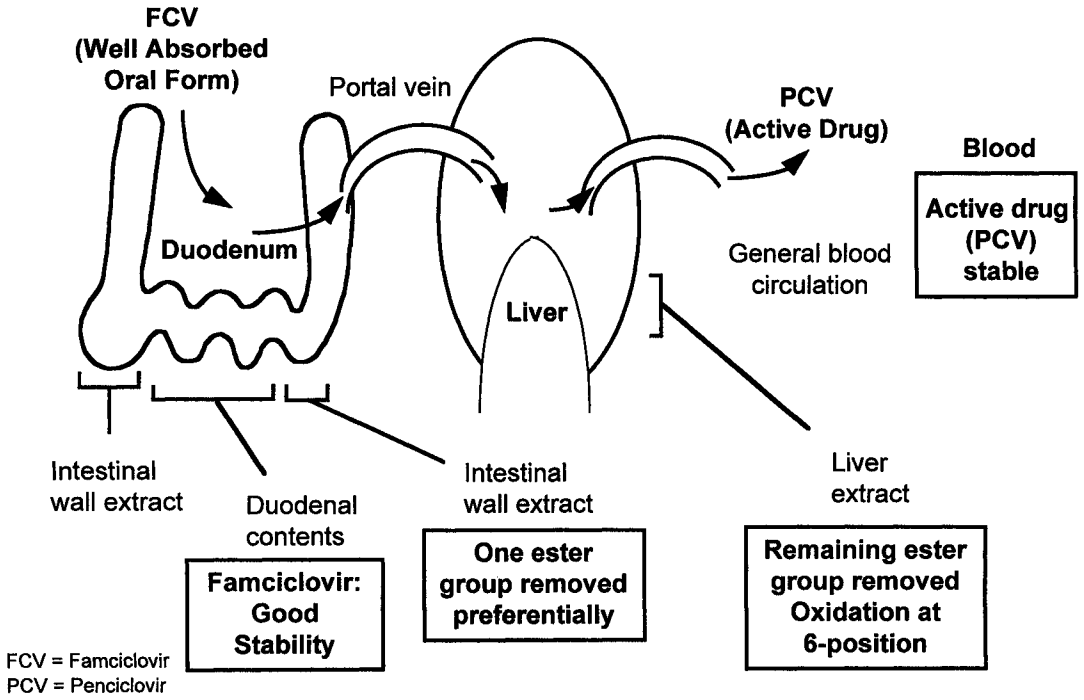

Fig. 2. Absorption of famciclovir. After ingestion, famciclovir has good stability in duodenal contents. Enzymes in the intestinal wall begin converting famciclovir to the pharmacologically active penciclovir, with most of the process occurring and completing in the liver. Once conversion is complete, penciclovir is rapidly circulated through the body via the bloodstream. (Figure from Vere Hodge et al.,[15] with permission.)

characteristics as acyclovir. Thus, the active form of valacyclovir also has limited stability and a short intracellular half-life in vitro (less than one hour in HSV-2-infected cells).[11]

Famciclovir (Famvir®, SmithKline Beecham Pharmaceuticals, Philadelphia, PA), the oral form of penciclovir, a guanosine nucleoside analog, has been introduced into clinical use for the management of acute herpes zoster and more recently for the treatment or suppression of recurrent episodes of genital herpes.[13,14] Famciclovir is well absorbed and rapidly converted to penciclovir by a series of metabolic steps in the intestinal wall and liver (Figure 2).[15–17] Once penciclovir enters herpesvirus-infected cells, it is rapidly converted to its active metabolite, penciclovir triphosphate, which is, in part, dependent on the viral enzyme thymidine kinase, and stops subsequent replication of the virus.[11,17–20] The intracellular half-life of penciclovir triphosphate in vitro is 20 hours in HSV-2-infected cells (Table 1).[11,16]

Little unchanged famciclovir is found in the plasma, and the overall bioavailability of penciclovir from oral famciclovir is approximately 77% (Table 1).[21] The bioavailability of penciclovir is not affected by the presence of food.[22,23] No clinically significant alterations in pharmacokinetics of penciclovir were observed following single versus repeat doses of 500 mg of famciclovir or single-dose administration of 500 mg of famciclovir after pretreatment with multiple doses of drugs known to inhibit hepatic oxidative enzymes (cimetidine and allopurinol) or to have narrow therapeutic ranges (theophylline and digoxin).[24] In addition, no clinically significant pharmacokinetic interactions be-

TABLE 1. Pharmacokinetic overview of famciclovir

	Penciclovir[a]
Bioavailability (%)	77
Dose proportionality	Yes
Plasma half-life (hr)	2–3
Rate of phosphorylation[b]	High
Intracellular half-life[c] (hr)	
HSV-1 infected cells	10
HSV-2 infected cells	20
Excretion	Renal

[a]Oral formulation of famciclovir.
[b]In vitro data.
[c]Measured in vitro as the triphosphate metabolites.

tween 500-mg, single-dose therapy with famciclovir and 200-mg of zidovudine (Retrovir®, Glaxo Wellcome, Inc.) were found when these agents were coadministered to immunocompromised patients.[25]

CLINICAL EXPERIENCE WITH FAMCICLOVIR

Safety

Since its introduction, famciclovir has been prescribed more than 2.7 million times worldwide (Data on file at SmithKline Beecham Pharmaceuticals). In integrated safety evaluations of more than 5,000 patients participating in clinical trials with famciclovir, the most common adverse experiences observed in a similar proportion of patients receiving either famciclovir or placebo were headache (~10%), nausea (~5%), and diarrhea (~3%).[26,27] Withdrawal from famciclovir treatment due to an adverse event has occurred in less than 1% of patients.[26,27] In addition, no consistent association has been observed between famciclovir treatment and any abnormal laboratory test.[26,27]

Efficacy

The efficacy of famciclovir in patients with recurrent genital herpes was evaluated in two dose-ranging, randomized, double-blind studies.[14,28] In these studies, 1,000 patients received famciclovir in 125-mg, 250-mg, or 500-mg doses or a placebo twice daily for five days beginning within six hours of lesion onset (clinic initiated) or prodromal/other signs or symptoms of an outbreak (patient initiated). The duration of viral shedding, cessation of all symptoms (collectively defined as lesion tenderness, pain, itching, burning, and tingling), and time to lesion healing was significantly improved at each dose of famciclovir, compared with placebo.[14,28]

In the clinic-initiated study, the duration of viral shedding was reduced by more than 50% (1.6 days for 125-mg of famciclovir versus 3.4 days for placebo [$P = 0.0001$]). Median time to complete healing was shorter for patients receiving 125-mg doses of famciclovir, compared with placebo-treated patients ($P = 0.0009$).[28] In the patient-initiated study, the duration of viral shedding was reduced by almost two days with famciclovir treatment, from a median of 3.3 days with placebo to a median of 1.7 days with 125 mg of famciclovir. Of the patients who were viral-culture-negative prior to initiation of therapy, 73% of those treated with famciclovir remained culture-negative, compared with 46% of patients receiving placebo.[14] The median time to loss of all symptoms was 3.2 days for patients treated with 125 mg of famciclovir, compared with 3.7 days for placebo-treated patients ($P < 0.01$ based on a hazard ratio of 1.6).[14] Median time to complete healing was 3.8 days for patients receiving 125 mg of famciclovir, compared with 4.8 days for placebo-treated patients.[14]

The efficacy of famciclovir has also been evaluated for the suppression of genital herpes. Women (n = 375) with a history of six or more episodes of recurrent genital herpes per year were treated with famciclovir (125 mg, once or twice daily; 250 mg, once or twice daily; or 500 mg, once daily) or placebo for four months.[29] All doses of famciclovir were effective in suppressing HSV recurrences; however, famciclovir in doses of 250 mg, twice daily, was clearly the most effective.[29] In addition, the proportion of patients who remained free of HSV recurrences during the 120-day study increased from 48% in the placebo-treated group to 90% in patients receiving famciclovir in doses of 250 mg, twice daily ($P < 0.001$).[29]

The meta-analysis of two year-long clinical trials, in which 369 patients were enrolled (236 receiving famciclovir, 250 mg, twice daily; 133 receiving placebo), showed that 80% fewer genital herpes outbreaks occurred in famciclovir-treated patients (median number of recurrences was 1) than in placebo-recipients (median number of recurrences was 4.9) (Data on file, SmithKline Beecham Pharmaceuticals). These and other studies show that once-daily dosing is less effective at preventing outbreaks than is multidosing.[29–31]

The efficacy of famciclovir for the treatment of first-episode genital herpes was evaluated in three studies, which enrolled a total of 951 patients. In two of these studies, famciclovir, 250 mg, 500 mg, and 750 mg, three times for a day for five days, was compared with acyclovir, 200 mg, five times a day for five days; in the third study, famciclovir, 125 mg, 250 mg, and 500 mg, three times a day for 10 days, was compared with acyclovir, 200 mg, five times a day for 10 days.[32] No significant differences between famciclovir and acyclovir were seen in the times to cessation of viral shedding, complete healing, or loss of all symptoms, suggesting that three times daily dosing of famciclovir is as effective as acyclovir five times daily in treatment of initial episodes of genital herpes.

Famciclovir may also impact HSV latency and/or subsequent reactivation. Preclinical studies have shown that treatment with famciclovir was more effective than valacyclovir in reducing the incidence of clinical manifestations of HSV-1 infections in mice.[33,34] In addition, the famciclovir-treated mice showed markedly reduced evidence of latent virus present in explanted ganglia.[33,34] Based on these results, as well as preliminary clinical data that support these observations, clinical trials have been initiated to further examine the effects of famciclovir on latency/reactivation after administration to patients with first-episode genital herpes.[35]

SUMMARY

Genital herpes, caused by HSV infection, is a chronic and often debilitating disease. Life-long persistence of the virus and unpredictability of clinical recurrences cause both physical and psychological sequelae that require long-term management. Educational and psychological support are important aspects in the management of genital herpes. However, advances in antiviral therapy have also played an important role.

Famciclovir represents a new advance in antiviral therapy. Its pharmacokinetic profile exceeds those of both acyclovir and valacyclovir. Studies have shown that treatment with famciclovir reduces viral shedding, provides rapid resolution of lesions, and relieves all symptoms of recurrent genital herpes.[14,28] Patients may have fewer psychological problems coping with the disease if the duration of viral shedding and uncomfortable symptoms associated with genital herpes are reduced. Famciclovir has also been shown to be effective in those patients who require long-term suppressive antiviral therapy. Finally, famciclovir is effective in relieving the acute signs and symptoms of first-episode genital herpes, and preclinical evidence suggests it has the potential to be effective in preventing life-long HSV latency or subsequent reactivation following treatment of first episodes.

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