Famciclovir for the Management of Genital Herpes Simplex

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Introduction

Treatment of herpes simplex virus (HSV) is currently based on the acyclic nucleoside analogues. In HSV-infected cells, these agents are monophosphorylated by viral-encoded thymidine kinase and then converted to their active triphosphate form by cellular enzymes. The triphosphate form, which lacks the 3-hydroxyl group necessary for elongation of the chain during DNA transcription, acts both as a competitive inhibitor for viral DNA polymerase and as a chain terminator, thereby blocking viral replication.

Aciclovir was the first such oral drug to be developed for the treatment of HSV infections.[1] In part because of its limited bioavailability, frequent administration may be required and efficacy may be limited in some patients.[2] Although the frequency of administration is reduced (from five times daily to twice daily) in patients receiving suppressive therapy with aciclovir, recurrences do occur.[3] These recurrences are associated with virus that remains susceptible to aciclovir.[4]

Penciclovir is another acyclic nucleoside analogue with anti-HSV activity that has similar potency and selectivity to aciclovir (reviewed by Boyd et al.[5]). An important distinction is that the active triphosphate form of this drug is more stable than that of aciclovir in HSV-infected cells, and its antiviral activity has been shown to be more persistent *in vitro* (half-life up to 20 hours in HSV-2-infected cells for penciclovir vs < 1 hour for aciclovir).[6,7] Famciclovir, the oral prodrug of penciclovir, was developed to improve the oral bioavailability of the parent compound. Bioavailability is high (77%) following oral administration of famciclovir, relative to intravenous (IV) administration of penciclovir.[8] A study in 20 volunteers demonstrated 60% recovery of penciclovir in urine after an oral dose of famciclovir and there was a higher and more consistent bioavailability than with aciclovir.[9] In addition, the high affinity of viral thymidine kinase for penciclovir results in high concentrations of penciclovir triphosphate (PCV-TP) and a long intracellular half-life in virus-infected cells (20 hours in HSV-2 *in vitro*), suggesting that the maintenance of high plasma concentrations of penciclovir may not be necessary in the clinical setting.[10]

Famciclovir at a dosage of 125–500mg twice daily is effective in treating genital herpes in immunocompetent and immunocompromised patients.[11-13] Long-term famciclovir therapy for 2–12 months has also been shown to be effective in suppressing recurrence of genital herpes.[14-16]

In light of the more persistent antiviral effects of penciclovir triphosphate (the active metabolite of famciclovir), the good oral bioavailability of penciclovir afforded by famciclovir, and the existence of anecdotal reports, we speculated that famciclovir may be useful in patients with HSV infections not responding to aciclovir and/or its oral prodrug valaciclovir. The aim of this study was to evaluate the efficacy of oral famciclovir 500mg three times daily in treating HSV infections in immunocompetent and immunocompromised patients with persistent or recurrent symptoms of genital herpes despite therapy with adequate doses of aciclovir and/or valaciclovir.

Materials and Methods

Patients aged ≥ 18 years with HSV culture-positive persistent (i.e. non-healing) herpetic lesions or who were experiencing culture-positive HSV recurrences (≥ 1 every other month) from seven centres in the US were included in this study. All patients had failed to respond to previous therapy with aciclovir ≥ 400mg five times daily and/or valaciclovir 500mg three times daily. Patients with persistent herpetic lesions were required to have been compliant with prior aciclovir/valaciclovir therapy for at least 7 days.

Patients had to have an active herpes outbreak at the time of the initial screening visit in order to be included in the study. Treatment with open-label famciclovir 500mg three times daily for 7 days was initiated within 1 week of the screening visit and could be extended by 3 days if the herpes outbreak was not adequately controlled during the first 7 days. There was an option to continue suppressive therapy with famciclovir 500mg three times daily for 16 weeks in patients who improved during the initial treatment phase. Complete healing was defined as the point at which all lesion crusts were lost and total re-epithelialisation occurred such that only erythema remained.

Exclusion criteria included: recent history of unstable liver function tests; recent clinical history or evidence of severe renal dysfunction; known hypersensitivity to famciclovir or any other nucleoside analogue; pregnant or lactating females; of child-bearing potential not using an accepted method of contraception; clinical evidence of disseminated or visceral disease caused by HSV or any other herpes virus that would warrant anti-herpes virus therapy; known to have an isolate of HSV previously determined to be resistant *in vitro* to aciclovir or penciclovir.

Patients were not permitted concurrent use of any antiviral treatment other than the study drug during the course of the study. No systemic corticosteroids were to be used; no topical products such as corticosteroids, anti-infectives or anaesthetics were to be applied to the lesions. Antiretroviral medications were allowed during the course of the study.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines following approval by the appropriate institutional review boards of the participating study sites. Written informed consent was obtained from all participants prior to enrolment in the study.

Results

A total of 18 patients with active herpes lesions were enrolled in the study; 13 patients were immunocompetent and five were immunocompromised (HIV/AIDS; n = 4; cancer leukaemia; n = 1). Overall, five patients had a persistent episode of genital herpes (three immunocompetent and two immuno-compromised) and 13 had a history of recurrent episodes and were currently experiencing an active outbreak (ten immunocompetent and three immunocompromised). Patient characteristics at baseline are summarised in table I . One immunocompetent patient was not included in the efficacy analysis because of lack of post-baseline data. Fifteen patients (83%) took at least one concomitant medication during the study. The most common concomitant medications included fluconazole, lamivudine, ibuprofen and zidovudine.

In the immunocompetent group, two patients received episodic treatment only, while ten patients received both episodic and suppressive therapy, seven of whom completed 16 weeks' treatment. In the immunocompromised group, three patients received episodic treatment only, while the remaining two patients received both episodic and suppressive treatment, one of whom completed 16 weeks' treatment. Thus a total of eight patients received episodic treatment with famciclovir and completed 16 weeks of suppressive therapy. Ten patients (55.6%) withdrew from the study prematurely. Reasons for withdrawal were a significant adverse experience (n = 3), patient lost to followup (n = 2), investigator decision that further treatment was not necessary (n = 1), efficaand protocol violation (n = 2), including the immunocompetent patient who was not included in the efficacy analysis. Two immunocompromised patients were withdrawn from the study because of immunocomlack of efficacy: both patients had penciclovir-resistant virus isolates at screening and during subsequent treatment (see Immunocompromised Patients section). The majority of withdrawals occurred within the first 2 weeks of the study. Efficacy results from 17 patients who received at least one dose of famciclovir had at least one post-baseline efficaand cy evaluation are summarised in table II .

Immunocompetent Patients

Lesion healing occurred in all three immunocompetent patients enrolled with a non-healing episode of genital herpes (healing reported on days 6, 9 and 11). Two of these patients had no recurrences during the 102–122 days of suppressive therapy that followed lesion healing, while the third patient had a recurrence while on suppressive therapy 22 days after healing of the baseline lesion.

Lesion healing occurred in seven of nine immunocompetent patients who had a history of recurrent genital herpes and an active outbreak at enrolment. One patient each reported healing of the baseline lesion on days 5, 8, 11, 13 and 22 and two patients reported healing on day 6. Among these seven patients, four remained recurrence-free throughout the study period; these patients had experienced two to ten recurrences while on aciclovir/valaciclovir therapy in the 6 months leading up to the study. The remaining three patients reported one recurrence each.

Immunocompromised Patients

Two immunocompromised patients enrolled with a non-healing herpes lesion were withdrawn because of lack of efficacy on days 10 and 12, respectively. Virus isolates obtained from these patients at screening and during treatment required penciclovir concentrations that produce 50% inhibition (IC_{50}s) ≥ 30 μg/mL and were considered to be penciclovir-resistant (Sarisky et al., personal communication). Both patients had previously failed to respond to at least 32 days of treatment with valaciclovir. Of the three immunocompromised patients enrolled with a history of recurrent genital herpes and an active outbreak at baseline, two reported lesion healing on days 6 and 8, respectively, and both remained recurrence-free on suppressive therapy. These two patients had experienced three and six recurrences, respectively, while on suppressive aciclovir/valaciclovir therapy in the 6 months prior to study entry. The remaining immunocompromised patient with recurrent genital herpes was withdrawn after 8 days of famciclovir therapy because of moderate nausea and vomiting considered by the investigator to be probably related to study medication. In this patient, the baseline lesion had shown partial response (25–49% decrease in lesion surface area) prior to the patient's withdrawal. The virus isolates from all three patients were considered to be susceptible to penciclovir (Sarisky et al., personal communication).

Patients' Evalutation

The majority of patients (3/5 immunocompromised patients and 9/12 immunocompetent patients) felt that famciclovir was better than their usual medication, while the remaining patients (2/5 immunocompromised patients and 3/12 immunocompetent patients) rated famciclovir as being the same as their previous medication.

Tolerability

No serious adverse events or deaths were reported over the course of this study. At least one adverse event was reported in 6/13 (46.2%) immunocompetent patients and 4/5 (80.0%) immunocompromised patients while receiving famciclovir therapy. The most common adverse events were diarrhoea in immunocompetent patients (n = 2) and nausea and vomiting (two patients each) in immunocompromised patients. Three patients withdrew from the study prematurely because of adverse events. As mentioned previously, one of these patients experienced nausea and vomiting, while a second experienced itching and maculopapular rash; these events were reversible after stopping treatment and were rated by the investigator as moderate and probably related to study medication. The third patient experienced teeth sensitivity that was considered moderate and probably unrelated to study medication.

Discussion

The management of genital HSV infection, particularly in immunocompromised patients, can present problems

to the clinician as such patients may develop severe herpes disease relatively refractory to antiviral drug therapy because of the emergence of drug-resistant strains of HSV. Aciclovir-resistant strains of HSV have rarely been reported in immunocompetent patients.[17-20] They are more common in immunocompromised patients; Englund et al. recovered aciclovir-resistant HSV from 7/148 immunocompromised patients (4.7%), but none from 59 immunocompetent patients.[21] Aciclovir-resistant strains of HSV in immunocompromised patients have been associated with clinical disease progression.[21-25] Fatal herpetic encephalitis or disseminated HSV infection may result from frequent and severe reactivations.[26] The successful treatment of resistant HSV in this patient population has previously been demonstrated with high-dose, continuous-infusion aciclovir given for a prolonged period of time.[27] Engel et al. successfully treated two AIDS patients with mucocutaneous infection caused by aciclovir-resistant thymidine kinase-negative HSV (TK- HSV) infection that had responded incompletely or not at all to oral and IV aciclovir in traditional divided doses.[27] Both patients improved clinically within a week of beginning therapy with continuous IV aciclovir at 1.5–2 mg/kg/h, and healed completely during the 6 weeks of therapy. Similar results have been reported in three immunocompromised patients with aciclovir-resistant HSV infection.[28] These data suggest that, notwithstanding its excellent oral bioavailability and the long intracellular half-life of penciclovir, famciclovir utility will be limited in immunocompromised patients with TK- HSV aciclovir-resistance phenotype, whereas continuous IV aciclovir may be an alternative to IV foscarnet, the generally accepted standard treatment for such patients.[29] However, aciclovir-resistant HSV is being observed more frequently in immunocompromised patients.[30]

Unsuccessful treatment of infection caused by aciclovir-resistant HSV in an immunocompetent patient with oral aciclovir, valaciclovir and famciclovir has recently been reported.[20] Neither IV aciclovir nor higher dosage famciclovir (500mg three times daily) was used in this report and may be worth considering given their safety and the reports of efficacy[23,24]and the data from this study, respectively.

Our study showed that famciclovir 500mg three times daily was not only effective in the majority of immunocompetent patients but also in some immunocompromised patients who had experienced non-healing or recurrent lesions while receiving aciclovir/valaciclovir therapy. Famciclovir healed baseline lesions in 10/12 (83.3%) immunocompetent patients and suppressed lesion recurrence in six (60%) of these ten patients. Among immuno-compromised patients, the healing rate was 2/5 (40%) and lesion recurrence was suppressed in two (100%) of these patients: if only those patients with penciclovir-susceptible virus isolates were considered, the healing rate increased to 2/3 (66%). These results may reflect a more sustained antiviral pressure exerted by famciclovir, relative to aciclovir/valaciclovir. Whether this is because of the higher and more consistent bioavailability of famciclovir, or possibly the increased intracellular half-life of its active triphosphate form, is still unknown. Information from virus isolate testing suggests that famciclovir was able to produce a response in some patients who had susceptible isolates but who had previously failed to respond to aciclovir or valaciclovir. However, famciclovir was unable to suppress replication of resistant HSV selected during aciclovir therapy. Viral sensitivity data on all patients are required for full interpretation of the results of our study.

The incidence of clinically important adverse drug reactions (ADRs) in this cohort appeared to be high: 3/18 (17%) patients withdrew because of ADRs (for nausea and vomiting, pruritic rash [both considered to be likely related to famciclovir] and teeth sensitivity [considered unrelated to famciclovir]). The most common ADRs were diarrhoea in immunocompetent patients (17%) and nausea and vomiting in 40% of immunocompromised patients.

These ADR data are in contrast to data on famciclovir tolerance in placebo-controlled trials in immunocompetent adults with genital herpes given treatment with 125, 250 or 500mg twice daily for 5 days.[11] Overall, 60% of patients reported at least one ADR and 2/376 famciclovir patients (0.5%) withdrew because of important symptomatic ADRs. Diarrhoea was not reported specifically, but nausea was reported by 9–14% of patients in all four treatment groups. Of note, no ADR occurred more often in famciclovir than in placebo recipients.

In healthy adults with ophthalmic zoster,[31] famciclovir 500mg three times daily as used in the current study

caused adverse event-related withdrawals in 9/251 patients (3.6%) compared with 6/246 patients (2.4%) treated with aciclovir 4 g/day. Nausea was observed in 10% of all patients, which was comparable to the effects described by Sacks et al.[11] The overall incidence of ADRs in this zoster trial was not provided. In another study in immunocompetent adults with zoster, 2% (6/300) of recipients of famciclovir 500mg three times daily for 3 days withdrew because of ADRs versus 1.7% (5/297) of valaciclovir recipients.[32] The incidence of nausea and diarrhoea in famciclovir recipients was 8% and 3%, respectively; this was similar to the rates in the valaciclovir recipients. The overall ADR rate was not provided.

In a study in 150 HIV-infected individuals with genital herpes treated with famciclovir 500mg twice daily for 7 days,[13] none withdrew because of an ADR considered related or probably related to therapy (three patients treated with aciclovir 400mg five times a day for 7 days withdrew but, again, not for reasons related to drug therapy). Nausea was reported by 10.7% of famciclovir-treated patients and 12.6% of those treated with aciclovir; diarrhoea was reported in 6.7% and 10.5%, respectively. The overall ADR rates were 54.0% and 57.3% in the famciclovir and aciclovir groups, respectively.

Overall, the ADR rate from our current controlled trial exceeds those reported by Saltzman et al. who reviewed ADR rates in the global experience with famciclovir.[33] Saltzman et al. reported that overall in an integrated safety analysis of 1607 patients, famciclovir was associated with withdrawal rates because of ADRs of 2.4% (placebo 1.6%).[33] Nausea was reported by 4.5% and 4.2% of famciclovir and placebo recipients, respectively, and diarrhoea by 2.4% and 2.3%, respectively. Overall, 24.6% of famciclovir patients reported at least one ADR compared with 19.9% of placebo recipients.[33]

Therefore, these data from several controlled trials indicate that famciclovir, over a range of dosages including 500mg three times daily as administered in this study, causes adverse reactions at rates no different from placebo. Overall, adverse reaction rates for famciclovir range from 24.6% in a pooled safety analysis[33] up to 60% in individual studies,[11,13]with no differences from placebo or control treatment rates being observed.

In this current study, the overall ADR rate was 46.2% in immunocompetent patients and 80% in immunocompromised ones, with an overall withdrawal rate because of ADRs of 11%. Withdrawal rates in large controlled trials of famciclovir range from 3% to 3.6%.[31] Similarly, the incidences of nausea and vomiting (2/5; 40%) and diarrhoea (2/13; 15%) in immunocompromised patients are also higher than in controlled trials of famciclovir therapy in immunocompromised patients: 9–14%[11] for nausea and 6.7% for diarrhoea in the trial by Romanowski et al.[13] The rates in these controlled trials were comparable to the control groups. It would be reasonable to ascribe the differences between the published famciclovir experience and the current trial in terms of ADRs and withdrawal resulting from ADRs to the small sample size in this study.

In conclusion, famciclovir may be effective in patients with susceptible HSV infections that are refractory to aciclovir/valaciclovir. Future studies, involving larger numbers of patients, are required in order to confirm the findings of the present study.

Table I. Patient Demographics, Immune Status and Reason for Enrolment in Study

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Characteristic	All patients (n = 18)	Immunocompetent (n = 13)	Immunocompromised (n = 5)
Age (y) [mean ± SD (range)]	38.6 ± 10.7 (22–62)		
Sex (male/female)	13/5		
Reason for enrolment [n (%)]			
non-healing episode	5 (27.8)	3 (23.1)	2 (40.0)
recurrent outbreaks	13 (72.2)	10 (76.9)	3 (60.0)
Mean duration (y) of genital herpes (range)		1.7 (0.3–11)	2.7 (0.2–11)
Mean no. of episodes per year (range)		8.6 (3–15)	6.4 (2–12)
Mean duration of typical episode (d)		8.1	16.4
Duration of previous aciclovir/valaciclovir therapy (d)			
non-healing episode		4–28 (n = 3)[a]	32–45 (n = 2)[a]
recurrent outbreaks		6–15 (n = 10)	3–12 (n = 3)
Pre-study herpes simplex virus (HSV) culture [n (%)]			
HSV II	7 (38.9)	5 (38.5)	2 (40.0)
HSV type unknown	3 (16.7)	2 (15.4)	1 (20.0)
unknown	8 (44.4)	6 (46.2)	2 (40.0)
Baseline lesion HSV culture results [n (%)]			
positive	10 (55.6)	5 (38.5)	5 (100)
negative[b]	8 (44.4)	8 (61.5)	0

a Days on aciclovir/valaciclovir for a previous non-healing episode (not the current episode prompting enrolment).

b Patients with a documented history of culture-positive HSV infection.

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Table II. Efficacy of Famciclovir in Immunocompetent and Immunocompromised Patients

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Outcome	Immunocompetent patients		Immunocompromised patients	
	non-healing lesion (n = 3)	recurrent lesions (n = 9)	non-healing lesion (n = 2)	recurrent lesions (n = 3)
Healing				
episodic therapy (day 1–10)	2	4	0	2
suppressive therapy (day 11 onwards)	1	3	0	0
Recurrence				
no	2	4	NA	2
yes	1	3	NA	0
Withdrawal because of lack of efficacy	0	0	2	0

NA = not applicable.

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