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Single-day famciclovir for the treatment of genital herpes: follow-up results of time to next recurrence and assessment of antiviral resistance*

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Abstract

Background—Episodic therapy of genital herpes is usually recommended for patients with infrequent symptomatic recurrences and where transmission is not a concern. While shorter courses are as effective as standard 5-day regimens, it is unknown whether abbreviated therapy has detrimental effects on natural history and the development of antiviral resistance.

Objectives—To assess time to next recurrence and development of antiviral resistance in patients with recurrent genital herpes treated with either single-day famciclovir (1 g twice-daily) or 3-day valacyclovir (500 mg twice-daily).

Methods—Longer-term, follow-up data on the time to next recurrence and antiviral sensitivity were collected from a previously reported multicenter, multinational, double-blind, parallel group study in which 1179 immunocompetent adults were randomized 1:1 to receive either single-day famciclovir or 3-day valacyclovir. Treatment was self-initiated within 6 hours of a recurrence. Swabs for viral culture and sensitivity testing were collected for two sequential recurrences.

Results—The median time to next recurrence from treatment initiation was 33.5 days for famciclovir and 38.0 days for valacyclovir. No drug resistance to penciclovir, the active metabolite of famciclovir, was observed at baseline nor did any develop by the time of the next recurrence.

Limitations—The study had no placebo arm, typing of viral isolates was not performed and viral resistance testing was restricted to penciclovir only.

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Conclusion—Treatment with single-day famciclovir for recurrent genital herpes did not shorten the time to the next recurrence. Drug resistance to penciclovir continues to be a rare event in immunocompetent patients.

Keywords

Drug resistance; Famciclovir; Genital herpes; Single-day therapy; Time to next recurrence

Introduction

Genital herpes is highly prevalent worldwide and a significant cause of genital ulcer disease¹. Following an initial symptomatic outbreak with herpes simplex virus type 2, most patients (> 90%) have at least one lifetime recurrence with frequent episodes (6/year) occurring in approximately one-third of patients^{2,3}. In patients with intact immune function, recurrent episodes are associated with a rapid burst of viral replication, with viral loads peaking within the first 24 hours of an outbreak^{4,5}. Prompt patient-initiated therapy is recommended to take advantage of this brief therapeutic window, so identification of early prodromal symptoms (e.g., burning, pain, itching) prior to the appearance of lesions is important.

Episodic therapy may be most appropriate for patients whose symptomatic genital herpes recurrences are relatively infrequent and where transmission is not a concern. The benefits of short-course episodic therapy include convenience, reduced cost and improved compliance. Several abbreviated short-course regimens have been shown to be as effective as traditional 5-day regimens for recurrent episodes, including 3-day therapy with valacyclovir (500mg twice-daily)⁷, 2-day therapy with higher dose acyclovir (800mg 3 times daily), 2-day therapy with famciclovir (500mg initial dose, followed by 250mg twice-daily)⁹, and higher dose single-day famciclovir therapy (1 g for two doses)¹⁰ (Table 1). While a small, uncontrolled observational study of valacyclovir 2 g twice-daily for 1 day reported median lesion duration of 5 days, randomized controlled studies with this regimen have yet to be performed¹¹. Famciclovir is currently the only single-day regimen approved in the United States for treatment of recurrent genital herpes.

However, shorter treatment courses may adversely affect the natural history of subsequent recurrences and/or encourage the development of antiviral resistance. The aim of the current report is to assess the time to next recurrence and the development of antiviral resistance among participants of a previously reported study that compared single-day famciclovir (1 g twice-daily) with 3-day valacyclovir (500mg twice-daily) as patient-initiated episodic treatment of recurrent genital herpes¹².

Methods

In this paper previously unreported data from the single-day comparative famciclovir clinical trial are presented. The design of this study is reported in detail elsewhere¹². Briefly, 1179 immunocompetent adults with a history of at least 4 recurrences of genital herpes in the preceding year were randomized 1:1 to receive either single-day famciclovir (1 g twice-daily) or 3-day valacyclovir (500mg twice-daily). Treatment was self-initiated within 6 hours after the onset of prodromal symptoms and/or genital herpes lesions by 751 patients who developed a recurrence during the acute phase of the study. Lesions were investigator assessed daily for 3 days then every other day until healed or day 14. The primary efficacy endpoint was time to healing, defined as loss of crust plus re-epithelialization, of all non-aborted lesions. Secondary endpoints included the proportion of patients with aborted lesions and patient-reported time to resolution of genital herpes-associated symptoms. At

baseline, nearly half (46.7%) of the patients were seropositive for herpes simplex virus type 2 (HSV-2) only and 45.5% were seropositive for both HSV-2 and herpes simplex virus type 1 (HSV-1); 7.7% of patients were seropositive for HSV-1 only. The study was conducted at 66 centers in the United States, Canada, Germany, and Australia.

Time to next recurrence

Patients who experienced a recurrence during the acute phase of the study were followed for up to 6 months after confirmed lesion healing to monitor the time to next recurrence. No suppressive anti-herpes therapy was to be taken in the interim. Patients were asked to present to the study center for clinical confirmation and to deliver a self-collected genital swab for viral culture.

Antiviral resistance

All patients were supplied with kits to self-collect swabs for HSV culture at the onset of the initial outbreak, the next three mornings before bathing, and at the time of the next recurrence. HSV isolates were evaluated in a blinded fashion (University of Alabama, Birmingham, AL, USA) for potential resistance to penciclovir, the active metabolite of famciclovir, by plaque reduction assays¹³. An isolate was considered sensitive to penciclovir if the 50% effective concentration (EC50) value was <5 mg/mL. Sensitive and drug resistant control strains were included to confirm the validity of the assay.

Statistics

The Hodges–Lehman shift model was used to estimate the difference in treatment effect for time to next recurrence without censoring or imputing any missing times to next recurrence. Descriptive statistics were used for the incidence of antiviral resistance.

Results

Original study findings (primary results)

The single-day famciclovir regimen (1 g twice-daily) was found to be non-inferior to 3-day valacyclovir therapy (500mg twice-daily) in reducing time to healing of non-aborted recurrent genital herpes lesions (4.25 vs. 4.08 days), with approximately one-third of patients in both treatment groups having aborted lesions (32.7 vs. 33.6%) and a similar time to resolution of common symptoms (3.04 vs. 3.00 days)¹². The results from the famciclovir arm of this study were very consistent with those of the famciclovir arm of Aoki's placebo-controlled study¹⁰.

Patient disposition

The majority of patients who experienced a genital herpes recurrence during the acute phase of the study (87.6% [324/370] in the famciclovir group and 89.8% [342/381] in the valacyclovir group) agreed to be monitored for a next recurrence over the following 6 months.

Time to next recurrence

The frequency of patients with next recurrence and the time to next recurrence was similar between those assigned the single-day famciclovir and 3-day valacyclovir regimen (Table 2). The median time to next recurrence from treatment initiation was 33.5 days in the famciclovir group and 38.0 days in the valacyclovir group.

Antiviral resistance

Susceptibility to penciclovir was evaluated in 573 viral isolates obtained before ($n=185$) and during ($n=230$) treatment of the initial outbreak, or before ($n=158$) treatment of the subsequent outbreak. None exhibited resistance to penciclovir.

Discussion

The finding that short-course antiviral therapy did not lead to a more rapid recurrence of signs or symptoms is consistent with reports by other groups^{8,9}, although direct comparisons between regimens are impossible as the study populations and methodology differ between the studies. Nonetheless, for the nearly 61% of patients in each treatment group who experienced a recurrence during the 6-month follow-up, the median time to next recurrence was approximately 1 month after completing either the single-day famciclovir or 3-day valacyclovir regimen. At enrollment participants had a historical median of 5–6 recurrences in the preceding year¹², which is consistent with an average of approximately 1 month until next recurrence. However, many patients with this frequency of recurrences will prefer suppressive therapy. Accordingly, the findings from this study may not apply to a more typical candidate for episodic therapy whose recurrences are less frequent.

No evidence of reduced penciclovir sensitivity in viral isolates was observed in immunocompetent patients before, during or after the brief treatment used in this study. These findings support previous observations that HSV resistance to penciclovir and other antiviral nucleoside analogues continues to be rare accounting for just 0.1–0.7% of isolates from immunocompetent patients even following prolonged therapy^{14–18}. In a longitudinal susceptibility program involving 11 multinational clinical trials using chronic suppressive treatment with penciclovir or famciclovir in immunocompetent and immunocompromised patients, there was no evidence of reduced penciclovir sensitivity in viral isolates obtained during or after treatment¹⁶. Sensitivity monitoring of HSV isolates during an extensive clinical program and a 5-year post-marketing period with valacyclovir confirmed a low rate of acyclovir resistance in immunocompetent patients (<0.5%) and immunocompromised patients (approximately 5%)¹⁷.

Clinically significant HSV-2 antiviral resistance in immunocompetent patients is even rarer, including in patients who receive continuous antiviral prophylaxis for years. In fact, Kreisel and coworkers reported only the third case of recurrent disease caused by a resistant virus in an immunocompetent patient¹⁹. Drug-resistant strains are generally less virulent and less able to reactivate from latency and replicate, reducing their potential of transmission; wild-type susceptible virus typically causes relapses²⁰.

Mutations in two HSV genes are associated with drug resistance. The most common is diminished or absent HSV thymidine kinase (TK) accounting for some 95% of resistant isolates, with reduced nucleoside affinity for TK or HSV polymerase making up the remainder^{16,21}. Although isolates in the current study were only assayed for susceptibility to penciclovir, lack of resistance to acyclovir can be inferred, since all TK mutants and most of the polymerase mutants are typically resistant to both drugs^{22,23}.

This study has a few limitations. First, the lack of a placebo arm limits the assessment of any effect of short-course therapies on natural history. Similarly, typing of HSV isolates was not done, thereby, limiting the information regarding potential differences between HSV-2 and HSV-1. Finally, because no acyclovir susceptibility testing was performed it is possible that a very rare isolate resistant to acyclovir was missed but one that was still sensitive to penciclovir as a consequence of mutant HSV polymerase. Nevertheless, results from this

study are consistent with those published previously^{14–18} and confirm the low incidence of antiviral resistance in this patient population.

Conclusion

New findings from the single-day famciclovir vs. 3-day valacyclovir genital herpes study suggest that the desirable convenience of shorter treatment courses is not compromised by any detrimental effect on the natural history of recurrent genital herpes as measured by time to next outbreak or the development of antiviral resistance.

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Table 1
Episodic patient-initiated short-course antiviral therapy for recurrent genital herpes: contemporary controlled clinical trial findings*

Drug	Antiviral regimen	Median time (days) to lesion healing (treatment vs. control)	Percent of aborted episodes (treatment vs. control)	Median duration (days) of all symptoms (treatment vs. control)
Acyclovir ⁸	800 mg t.i.d. × 2 days vs. placebo	4.0 vs. 6.0 ($p = 0.001$)	27.0 vs. 10.6 ($p = 0.029$)	Not reported
Valacyclovir ⁷	500 mg b.i.d. × 3 days vs. 500 mg b.i.d. × 5 days	4.4 vs. 4.7 ($p = \text{NS}$)	25.4 vs. 26.6 ($p = \text{NS}$)	Pain: 2.9 vs. 2.5 ($p = 0.063$)
Famciclovir ^{9,10,12}	500 mg statim, then 250 mg b.i.d. × 2 days vs. 125 mg b.i.d. × 5 days	Not reported	7.6 vs. 9.5 ($p = \text{NS}$)	Not reported
	1 g b.i.d. × 1 day vs. placebo	4.3 vs. 6.1 ($p < 0.001$)	23.3 vs. 12.7 ($p = 0.003$)	All reported symptoms: 3.3 vs. 5.4 ($p < 0.001$)
	1 g b.i.d. × 1 day vs. valacyclovir 500 mg b.i.d. × 3 days	4.3 vs. 4.1 ($p = \text{NS}$)	32.7 vs. 33.6 ($p = \text{NS}$)	All reported symptoms: 3.0 vs. 3.0 ($p = \text{NS}$)

NS, not significant

*Those reported from 1998 to present

Table 2
Time to next recurrence within 6-month follow-up period (ITT population)

	Famciclovir N=370	Valacyclovir N=381
No. of patients who initiated the treatment and continued to the follow-up period, <i>n</i> (%)	324 (87.6)	342 (89.8)
No. of patients with next recurrence during follow-up period, <i>n</i> (%)	226 (61.1)	231 (60.6)
Median time to next recurrence from treatment initiation (Interquartile range Q1–Q3) (days)	33.5 (18–67)	38.0 (18–73)
Median of differences (days) (famciclovir – valacyclovir) Estimated Hodges–Lehman two-sided 95% CI (asymptotic)	–3.00 (–8.00, 2.00)	
Median time to next recurrence from the date of healing of non-aborted lesions or confirmation of aborted lesions (days)	27.5	32.0
Median of differences (days) (famciclovir – valacyclovir) Estimated Hodges–Lehman two-sided 95% CI (asymptotic)	–3.00 (–8.00, 2.00)	